Pharmaco-epidemiology of sumatriptan

Cardiovascular adverse reactions to a new antimigrainous drug

Jan Paul Ottervanger

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CARDIOVASCULAR ADVERSE REACTIONS TO A NEW ANTIMIGRAINOUS DRUG

Farmaco-epidemiologie van sumatriptan

Cardiovasculaire bijwerkingen van een nieuw anti-migrainemiddel

Proefschrift

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Ter nagedachtenis van mijn ouders,

D.G. Ottervanger (maart 1937 - februari 1971)
D.W. Ottervanger-Gerritsen (januari 1937 - februari 1971)

Voor Annette en Wendy

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PART I

BACKGROUND

CHAPTER 1

INTRODUCTION AND OUTLINE OF THE PROJECT

To expect ever to treat the head by itself, apart from the body as a whole, is utter folly.

(Plato, Charmides)

The rationale to study a potential adverse reaction of a specific drug mainly depends on three questions: 1) how serious is the adverse reaction? 2) what is the incidence of the adverse reaction among users of the drug?, and 3) what is the frequency of consumption of the specific drug in the population? Especially drugs which are frequently prescribed and used, also rare serious adverse reactions may be important, such as thromboembolism in users of oral contraceptives.

The present thesis summarizes our studies of a potential serious adverse reaction of sumatriptan, which turned out to be relatively frequent among users. This new drug, used in the treatment of acute attacks of migraine, appears to have more actions outside the head than was initially thought.

Migraine

The word *migraine* is derived from Galen's term *hemicrania*. Indeed, the condition is characterized by attacks of one-sided headache. The pain pulsates, is aggravated by routine physical activity, and associated with nausea and photo- and phonophobia (1). By definition, migraine attacks last between 4 and 72 hours. The attacks may or may not be accompanied by preceding symptoms, the aura.

Migraine has probably always affected mankind. In ancient Egypt, the gods themselves had headache (2). In the book on neurology by the Dutch physician Iason Pratensis (1486-1558), entitled 'De cerebri morbis', one chapter is about migraine. He concluded that the causes of migraine include warmth, too much working, too frequent use of hot baths and long physical exercise (3). In the 17th century, Charles Le Pois noted that 'it has to be absolutely stated that sleep is a relative of migraine, and migraine itself arises from the same cause, namely an aqueous humour that flows over in the head, but is agitated and fermented by some sudden aerial storm and perturbation' (2).

Migraine is a common condition (4), which is often incapacitating, causes a substantial loss of working days, and is an important public health problem (5). Migraine is more common among females than among males. It has been estimated that it affects 4 to 19 percent of adult men and 8 to 29 percent of adult women (4). The prevalence tends to decrease slowly with age, beginning in females in their forties. It has been noted that over time the severity of headaches does not change in males but decreases in women, and headaches, among those who continue to have headaches, become more frequent with age in females but not in males (6).

Treatment of migraine

The treatment of migraine can be divided into treatment of acute attacks, and prophylactic treatment. Non-drug treatment should be the first choice. For prophylaxis, this concerns identification and avoidance of provoking factors. For acute attacks, this consists of bed rest in a dark, quite, cool room.

Drug treatment of acute attacks (7) includes analgesics such as aspirin and acetaminophen, other non steroidal antiinflammatory drugs, and serotonin agonists such as ergotamine, dihydroergotamine and, since 1991, sumatriptan. Prophylactic drug treatment includes (7) serotonin influencing drugs such as methysergide, amitriptyline or phenelzine, β-adrenergic antagonists such as propranolol and metoprolol, and calcium-channel blockers such as nifedipine and analgesics.

Sumatriptan: potential problems

In May 1991, The Netherlands was the first country in the world to register sumatriptan. Within one year after registration, the Netherlands Centre for Monitoring of Adverse Reactions to Drugs received several reports concerning chest pain attributed to use of sumatriptan. A few months later, the Centre received a report on a middle-aged female, who experienced an acute myocardial infarction shortly after subcutaneous administration of sumatriptan. These reports on (potential) serious adverse reactions to a new drug made us decide to perform a pharmaco-epidemiologic study on the adverse reactions of sumatriptan which is described in this thesis.

Outline of the project

The thesis comprises three parts. In part 1, the general background of the project is given. In part 2, the emergence of the potential problem is described as observed by the Netherlands Centre for Monitoring of Adverse Reactions to Drugs. In part 3, the exploration of the potential problem is described.

There is no doubt that premarketing randomized clinical trials supply us with a lot of information about new drugs. However, these trials also have their limitations, and after marketing of a drug continuous post marketing surveillance is necessary (chapter 2).

One method for post marketing surveillance makes use of spontaneous reporting schemes. In chapter 3, some characteristics of the Netherlands Centre for Monitoring of Adverse Reactions to Drugs are given. One group of adverse reactions concerns

drug-induced chest pain and myocardial infarction. Spontaneous reports of drug-induced chest pain or myocardial infarction to the Dutch Centre between 1975 and 1995 are described in chapter 4. In particular, many reports concerned sumatriptan-induced chest pain or myocardial infarction (33 reports). Some of the sumatriptan-associated cardiovascular adverse reactions are described in more detail in chapter 5. Since the association between use of sumatriptan and cardiac events was confirmed by case reports in the literature, the question whether there was cause for concern seemed to be justified (chapter 6).

In chapter 7, details on the design and enrolment of a cohort study on sumatriptan related chest pain are given. In particular, the frequency and character of adverse reactions to sumatriptan as reported by drug-dispensing general practitioners and patients are discussed. In chapter 8, the pattern of use and overuse as reported by the patients in the pharmaco-epidemiologic study is described. In chapter 9, determinants and characteristics of chest pain to sumatriptan are assessed, whereas in chapter 10 differences in exercise testing between patients with and without chest pain after use of sumatriptan are studied.

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CHAPTER 2

POST MARKETING SURVEILLANCE

2.1 Introduction

Drugs are being used by more and more people, and drug use has become a factor of increasing economical importance in health expenditure. The most consistent finding in utilization studies is that use of prescribed drugs increases with age and is higher in females (1). Use of drugs has decreased the mortality and morbidity of several diseases, as well as improved the quality of life of many patients. In comparison with other therapeutic interventions, medications are remarkably effective, cost-effective, and safe (2, 3). And although some people are worried about the growing consumption of drugs, results from some studies have suggested that several specific drugs are less used than may be necessary (4, 5). In this chapter on postmarketing surveillance, several aspects of safe and appropriate drug use will be discussed.

In chapter 2.2 the most important definitions used in post marketing surveillance will be given. In chapter 2.3, some details will be given on the premarketing and the marketing stages. In chapter 2.4, the history of postmarketing surveillance of adverse reactions will be reviewed. In chapter 2.5, several limitations of premarketing studies are discussed, whereas in chapter 2.6 methods and systems for postmarketing surveillance will be explored.

2.2 Definitions

The Dutch Health Council defined postmarketing surveillance as 'the systematic surveillance of and research on all intended and unintended effects (beneficial and adverse) caused by drugs after marketing' (6). A shorter definition is 'the close observation of drug effects following marketing' (7). According to these definitions postmarketing surveillance is more than adverse reaction monitoring. This chapter, however, will almost entirely focus on unintended effects of drugs after marketing. Directive 93/39/EEC of the European Community was published in June 1993, and defined *pharmacovigilance* as the 'collection of relevant information for the surveillance of medicinal products, particularly their undesirable effect on humans, and the scientific evaluation of this information. Pharmacovigilance concerns also the collection of information on frequently observed misuses and serious abuses of medicinal products.'

Pharmacoepidemiology can be defined as the study of drugs as determinants of health and disease in the general unselected population (8). The term 'pharmacoepidemiology' first appeared in the medical literature in a British Medical Journal editorial in 1984 (9).

The following definitions are mainly based on those used in the Directives and Regulations of the European Union and the definitions of the WHO. An *adverse reaction* means a reaction which is harmful and unintended and which occurs at doses normally used in man for the prophylaxis, diagnosis or treatment of disease or the modification of physiological function. A *serious* adverse drug reaction is defined as an adverse drug reaction which is fatal, life-threatening, disabling, incapacitating or which results in or prolongs hospitalisation. An *unexpected* adverse reaction is an adverse reaction which is not mentioned in the summary of product characteristics. Adverse reactions to drugs can be classified into *type A and type B reactions* (10). Type A adverse reactions are the result of the pharmacological activity of a drug, and are largely predictable and usually dose-dependent. Examples of type A reactions include bradycardia by beta-blockers and hypoglycaemia by antidiabetics. Type B reactions are not dependent on the pharmacological activity of a drug, and are unpredictable and not dose-dependent. An example of a type B reaction is an immunoallergic reaction. Drug *interactions* may result from changes in either the pharmacokinetics or the pharmacodynamics of the drugs involved (11). Pharmacokinetic interactions may take place at any stage of absorption, distribution, metabolism or excretion.

Sometimes, components which are added to active drug substances may cause adverse reactions, such as in the disaster in 1937 with the elixir of sulphanilamide, which contained diethylene glycol. Other examples are lactose induced diarrhoea (12) and bioavailability problems with digoxin due to a change in particle size (13).

Three different stages in the life of a drug can be distinguished: the premarketing stage, the marketing stage, and the postmarketing stage. Marketing means the process in which a new drug is put onto the market after registration by the authorities, separating the premarketing ('test') stage and the postmarketing stage.

2.3 The premarketing & marketing stage

a. Drug development: The premarketing stage

Substances may become drugs in different ways: from primitive medicine or folklore (e.g. quinine for malaria), from investigation of natural products (e.g. digitalis), from synthesis of new chemicals resembling natural substances (e.g. aspirin) or existing drugs, or from studies of physiological and pathological processes in animals and humans (e.g. insulin). In present times, whatever the background or reason for belief in the action of a compound, before a new potential drug can be used for the treatment of patients, it should be tested, in-vitro and in-vivo, and in animals and in humans.

Before the 20th century, only anecdotal examples of trials on the effects of drugs are available. One of the first recorded, if not the first, therapeutic trial was performed in the early 17th century: In 1600, four ships were sent to India by the East India Company, of which ships one was provided with lemon juice as part of the rations; this crew was free from scurvy. Nowadays most new drugs are discovered and developed by the pharmaceutical industry, and before marketing of a drug three phases of studying drugs in humans can be distinguished:

Phase I - The drug is tested on a small group of human volunteers (N=20-80) in order to obtain data on pharmacokinetic and pharmacodynamic characteristics of the drug. In approximately 30% of compounds, unacceptable risks are present and further testing is terminated.

Phase II - In this phase the drug is tested on small groups of patients ($N \leq 200$). Among others, the optimal dose is assessed, and the first estimates of potential therapeutic efficacy can be obtained.

Phase III - In this phase large experimental studies, trials, are performed. Most trials are nowadays randomised, placebo controlled, and (double) blinded.

Before phase I, many chemical substances are synthesized. It has been estimated that 2300, 4300 and 6200 compounds are synthesized for each new drug that is approved for Japanese, European, and United States companies, respectively (14). The studies performed in phase III are the most important for registration and for clinical practice. The "double blind, randomized parallel group trial", can be seen as the paradigm to demonstrate the efficacy of a new drug.

The majority of controlled clinical trials of drugs are carried out in the pre-marketing phase of new drug development, although there are exceptions (15). Control groups may include placebo-treated patients, patients treated using registered standard drugs or both. The main advantages of these studies are those of randomization, placebo control and blinding in the measurement of the outcomes, to achieve comparability of prognosis, extraneous effects and observation (16). In chapter 2.5, some limitations and disadvantages of clinical trials will be discussed.

b. Registration: The marketing stage

The marketing stage of a drug is for a great part a matter of regulatory authorities. In January 1995, the European Medicines Evaluation Agency (EMEA) was established, and since then a new system has started of marketing medicines in countries of the European Community. The EMEA, which is based in London, acts as a coordinating centre, housing and servicing the Committee for Proprietary Medicinal Products (CPMP), to advise the European licensing authority (European Commission). From 1998 there will be two routes to a European licence. One through the *Centralized* Procedure and the other through the *Decentralized Procedure*. In the Decentralized procedure, again there are two routes. A manufacturer may apply for registration in one country or make applications simultaneously in all Member States. Once one Member State has granted the licence the assessment procedure will be halted in all other Member States, which must then either recognise the authorization or raise objections.

In the U.S. the secretary of Health and Human Services has the authority, to regulate approval of drugs offered in interstate commerce, delegated to the Food and Drug Administration (FDA). The regulatory process begins when a company submits a so called 'Investigational New Drug Application' (IND), which describes the chemical composition of the drug, the results of preclinical investigations, including animal studies, and a protocol for clinical investigations. This application is reviewed by the FDA, and if there is no objection, phase I - III studies can start. Of these drugs under investigation, the FDA asks for reports annually and immediately of reactions that are serious ($\leq$ 10 days) or life threatening ($\leq$ 3 days). If the human investigations are successful, the company submits a so called 'New Drug Application' (NDA) to the FDA. After review and approval of the NDA by the FDA, marketing of the drug is allowed.

In 1993, the Dutch Medicines Evaluation Board (DMEB) handled 397 products, compared to 413 in 1992 (17). The 397 products concerned 195 national marketing authorizations (193 in 1992), 134 through the EU system (1992, 111) and 68 variations to national product licences (1992, 109). A total of 957 registration applications were received by the DMEB in 1993, of which 460 were for parallel imports and identical products (in 1992 814 and 269 respectively). 604 products were approved, of which 384 were parallel imports (578 and 275 respectively in 1992). 16 of the approvals were for new chemical entities.

The number of pharmaceuticals registered in the Netherlands at the beginning of January 1994 was 8,498 of which 2,332 were parallel imports. This compares with 8,175 and 2,080 in January 1993.

2.4 History of 'postmarketing' monitoring of adverse drug reactions

Even in the ancient world it was known that medicine not only cures patients, but can also be bad for patients. The need for prescribers to be cautious was reflected already in the statement in the Babylonian 'Code of Hammurabi' (2200 B.C.) that "a physician who caused a patient's death should lose his hand" (18).

One of the oldest descriptions of an adverse reaction to a specific drug concerns William Witherings description of the side effects of digitalis in 1785 (19). In the 19th century, there was in the UK concern about the safety of chloroform anaesthesia (20), although the second Hyderabad Chloroform Commission still claimed that 'chloroform is as safe as whisky and water' (21). However, as with pharmacotherapy in general, most advancements in knowledge about postmarketing adverse reactions to drugs, have occurred after 1900. In 1906, the Pure Food and Drugs Act was passed in the USA which was primarily focused on impure and contaminated food and drugs. During the rest of the 20th century drug safety has attracted particular attention in cases of disasters associated with certain drugs.

At the end of the first World War there was an official enquiry of the Medical Research Council in the UK concerning an outbreak of massive hepatic necrosis in patients treated for syphilis with neoarsphenamine benzoate at the Cherry Hinton Military Hospital near Cambridge in 1917 and 1918. The Committee reported that the most probable cause of the outbreak was the toxicity of the organo-arsenical compounds (22), although other authors claimed that an infection was the cause (23).

In retrospect it is likely that it concerned viral hepatitis. In 1923 a physician in London described jaundice in a patient who had been treated for gout with cinchophen (24).

In January 1937, after careful animal and clinical studies, Long and Bliss endorsed the use of sulphanilamide for streptococcal infections (25). Among other companies (sulphanilamide was not subject to patent restrictions), the S.E. Massengill Company of Bristol, Tennessee began to produce sulphanilamide. This company decided to produce also a liquid preparation of sulphanilamide, consisting of 10% sulphanilamide, 72% diethylene glycol, 16% water, and small amounts of elixir flavour, raspberry extract, saccharin solution, amaranth, and caramel (26). Despite the lack of ethanol, the solvent was called "Elixir Sulphanilamide". By early September 1937, 240 gallons of Elixir Sulphanilamide had been produced by the Massengill Company. However, before the end of October 1937, both the American Medical Association, the Food and Drug Administration (FDA) and the Massengill Company were aware of several patients who had unexpectedly died from renal failure after ingesting Elixir Sulphanilamide. Because nephrotoxicity was not a known adverse reaction of sulphanilamide, the diluent diethylene glycol was very soon suspected to have caused this adverse reaction. The legal grounds for action on the part of the FDA were limited because of the absence of appropriate regulatory law. Fortunately, because Elixir Sulphanilamide was marketed as an 'elixir' but lacked ethanol, the FDA could seize the drug for 'misbranding regulation', and retrieved 228 of the 240 gallons before distribution to patients. It is estimated that if all 240 gallons had been consumed, the number of deaths could amount to 4000 (27). Still, in its short marketing period the Elixir had caused at least 76 deaths due to its 72% content of diethylene glycol (28). Diethylene glycol is still manufactured as an industrial solvent, for example in anti-freeze solutions. It received some attention a few years ago because several white wines in Europe were found to be contaminated by diethylene glycol that had been added by wine producers to improve the taste of the wine (29). Furthermore, paracetamol elixirs with diethylene glycol (which was possibly substituted for the more expensive propylene glycol) were associated with epidemics of fatal renal failure in children in Nigeria (30) and Bangladesh between 1990 and 1992 (31).

Partly because of the 'Elixir epidemic' in 1937 and the attention it attracted, the Federal Food, Drug and Cosmetic Act was passed by the U.S. Congress and signed

into law by President Franklin Delano Roosevelt in 1938. This legislation required that toxicity must be tested before the release of a new drug or preparation. Now, for the first time, pharmaceutical manufacturers had to show product safety before distribution. Furthermore, formula disclosures of all active ingredients had to be given. However, no proof of efficacy was required.

In 1951, the Humphry-Dunham Drug Prescription Act in the US separated drugs into those requiring a physician's prescription and those that could be sold over the counter (32). One of the first textbooks of adverse reactions was published in 1952 (33).

In 1950 the first fatal case of aplastic anaemia due to chloramphenicol was described (34). As a result a systematic attempt to record adverse reactions to drugs started in the US in 1955, when a registry for blood dyscrasias under the auspices of the American Medical Association was set up. The idea came from two haematologists, Wintrobe and Sturgeon, who had both observed aplastic anaemia in patients treated with chloramphenicol (35). However, this system stopped, due to lack of cooperation from physicians.

Thalidomide was introduced in 1956 in West Germany and in 1958 in the UK as a hypnotic with few residual side effects. However, in 1961, use of thalidomide was associated with a specific form of congenital abnormality, phocomelia (36, 37). Case reports of phocomelia in exposed patients were followed by case-control studies (38), analyses of secular trends (39) and a retrospective cohort study (40). An estimated 10,000 children worldwide were born with this birth defect. Fortunately, the drug had not yet been marketed in the U.S. primarily because of the foot-dragging of a FDA reviewer, Dr. Francis Kelsey.

In 1962, six months after the thalidomide disaster became known, the Fifteenth World Health Assembly recognized the seriousness of drug safety problems and recommended first measures for dealing with them, finally resulting in Resolution WHA20.51 of May 1967 in which the basis was laid for an international system for monitoring of adverse reactions to drugs. The WHO started with a pilot project on the feasibility of an international system for monitoring of adverse reactions to drugs, with data provided by 10 countries (Australia, Canada, Czechoslovakia, Federal Republic of Germany, Ireland, The Netherlands, New Zealand, Sweden, the United Kingdom, and the USA, later joined by Denmark and Norway). The 23rd World Health Assembly initiated the operational phase of the international drug monitoring project.

In the US, in 1963 the Kefauver-Harris Amendments came into law, strengthening the requirements for testing of drug safety and efficacy prior to marketing of a drug.

Since the thalidomide disaster there have been problems with several drugs, and some drugs have even been withdrawn from the market (41). Examples of important adverse reactions to drugs are Reye's syndrome by aspirin in children (42), diethylstilbestrol (DES) and adenocarcinoma of the vagina (43), practolol and sclerosing peritonitis (44), and adverse reactions to triazolam (45). More recently examples consist of the analgesic glafenine (46) and the antibiotic Centoxin which were withdrawn from the market, and the restriction of the indication for ibopamine (47).

2.5 Limitations of premarketing studies

As was mentioned in paragraph 2.2, the randomized trial provides a powerful means to demonstrate the efficacy and the most frequent adverse reactions of a drug. However, trials, which are mainly performed before marketing, have several limitations, some of which are summarized in table 1.

TABLE 1
Potential limitations of clinical trials

Inherent limitations	
1.	Selection of patients (generalizability)
2.	Limitations to sample size
3.	Limitations to follow-up period
4.	Expensive
Other limitations	
4.	Randomisation not always successful
5.	Often only secondary or intermediate end points
6.	Not all specific tests can be done
7.	Often comparison with placebo, rather than "next best"
8.	Blinding sometimes difficult or not possible

These limitations can be classified into those that are inherent to the setting of the premarketing trials, and others. A few limitations will be briefly discussed.

Limitations inherent to the setting

Generalizability Patients who enrol in premarketing clinical trials differ from patients who receive the drug after marketing. Important groups of patients who are less often studied in the clinical trials include the elderly, children, females and patients with concomitant diseases or drug use. Examples of differences between the sick population, the therapist's target population of patients, and the study population are given by Collet, Boissel, and the VALIDATA Group (48). In the GISSI study, on the effect of thrombolytic treatment in acute myocardial infarction, of the 31,826 patients admitted with an acute myocardial infarction, 11,806 patients (37%) were included in the study (49). In the international randomized trial on the effect of surgery for carotid stenosis, more than two times the study population was excluded from the study, and had immediate surgical treatment (50). The latter example shows that in clinical trials the inclusion of patients is not only based on the criteria in the protocol, but also secondary to consideration of optimal patient treatment. Hence, generalizability is not always straightforward.

Limited sample sizes A priori sample size calculations of clinical trials are almost invariably based on the potential to show a beneficial effect of the drug(s) of investigation. Before marketing, in trials, between 500 and 3,000 subjects are usually exposed to a drug. In general this means that there is a chance of 95% of observing at least one adverse reaction with a frequency of 1 per 160 and 1 per 1,000 exposed subjects respectively. Such frequency is still high for many adverse reactions.

Other limitations

Use of placebos In the nineteenth century a placebo effect was defined as 'quality ascribed to any drug prescribed to please the patient rather than to be useful'. More recently, Gøtzsche defined a placebo as follows (51): 'A placebo is an intervention which is believed to lack a specific effect-i.e., an effect for which an empirically supported theory exists for its mechanism of action-on the condition in question, but which has been demonstrated to be better than no intervention.' Although a placebo is a substance without known pharmacological effects, both patients and healthy volunteers attribute effects to it (52). In a review of 109 double-blind, placebo controlled studies involving 1228 healthy volunteers, it was shown that adverse events were reported by 19% of the volunteers after use of a placebo (53).

The majority of randomized clinical trials use placebo groups as comparison (54).

Besides the question whether it is ethical to give patients placebo treatment and withhold the 'best proven' or 'next best' treatment, as Bradford Hill already pointed out (55), these controlled trials are in fact of limited value for clinical practice when the treatment tested has available alternatives. Most important is not whether the new treatment is better than nothing (or than a placebo), but whether the efficacy and safety of the new treatment is similar or better than an already existing treatment.

Fortunately, there are more and more authors who promote the comparison of new drugs against active treatment (if available), rather than against placebos (56). Some have even suggested additional post marketing randomised trials (57).

Secondary and intermediate end-points Many trials have only secondary and intermediate end points rather than the outcome that is the one of ultimate clinical interest. Simvastatin, for example, has been marketed since 1989 in The Netherlands for reducing serum cholesterol levels. Since a high serum cholesterol concentration is associated with an increased risk of atherosclerosis and cardiovascular disease, it was suggested that simvastatin would result in decreased morbidity and mortality. However, it was not before 1994 that it was demonstrated, in a large placebo-controlled trial in patients with coronary artery disease, that simvastatin indeed reduced mortality (58).

Randomization not always optimal The concept of randomization in the conduct of clinical research was introduced by Sir Austin Bradford Hill. His streptomycin trial in tuberculosis, published in 1948, may be considered as one of the first randomised clinical trials (59). In the same year, the first randomised clinical trial was published in The Netherlands (60). Although the aim of randomization is to create prognostically comparable groups at baseline (61), it has been shown by Altman and Doré in a review of 80 published reports of randomised clinical trials, that this is not always achieved (62). They found a statistically significant difference in one or more baseline variables in 37% of the trials. Schulz et al. (63) reviewed 206 reports of trials published during 1990 and 1991 in 4 obstetrics and gynaecology journals. Only 66 (32%) of the trials reported on how the randomization was technically achieved.

Not all tests can be done During the clinical trials only a limited number of (laboratory) tests can be done. In particular type B adverse reactions to drugs, for example deafness by an antibiotic, will not be observed.

Blinding not always possible Blinding means no knowledge about the treatment which is given, and can be single (only the patient does not know) or double (both the patient

and the physician do not know). The objective of blinding is to achieve comparability of extraneous effects and allow unbiased outcome assessment. However, in several trials it is not possible or very difficult to blind. An example is the randomized trial on thrombolysis versus PTCA for treatment of acute myocardial infarction (64, 65). Moreover, while blinded in theory, for many studies the effectivenes of blinding may be questioned.

Because of the limitations of clinical trials, the results of these trials may differ from the effects of a drug under every-day circumstances. For that reason it is always important to follow a drug after marketing.

2.6 Methods of postmarketing surveillance

There are several aims of postmarketing surveillance, which are summarized in table 2.

TABLE 2
Selected objectives of postmarketing surveillance

- Risk-benefit assessment
- Assessment of effects of drugs in specific (sub-)groups
- Detection of unknown (rare) adverse reactions
- Estimation of the incidence of adverse reactions
- Detection of risk factors for development of adverse reactions
- Translation of 'secondary end points' to primary ones
- Comparison of different drugs with the same indication
- Assessment of patterns of drug utilisation
- Study of effects of overdoses
- Economic evaluation of pharmaceuticals

Until now, most of the attention in postmarketing surveillance has focused on unintended drug effects, especially the discovery of (rare) unknown adverse reactions, or the assessment of the incidence of these adverse reactions. In postmarketing surveillance, many epidemiological techniques have been developed, resulting in a discipline which is now called pharmacoepidemiology. Although several methods in pharmacoepidemiology can be distinguished, all are, in fact, identical to the methods

used in epidemiology in general. The most important research approaches are summarized in table 3.

TABLE 3
Most important research methods in pharmacoepidemiology

- Case reports & case series
- Clinical trial
- Cohort study (non-experimental)
- Cross-sectional study
- Case-control study
- Analyses of secular trend

More information on these designs can be obtained from any textbook of epidemiology.

In pharmacoepidemiology, several systems are used to obtain empirical data (table 4) of which some are briefly discussed below.

TABLE 4
Selected systems used in pharmacoepidemiology

- Spontaneous reporting schemes
- Intensive Medicines Monitoring Programme
- Prescription-event monitoring
- Record linkage systems
- Field studies

a. *Spontaneous reporting schemes*

Spontaneous reporting schemes are considered an efficient means to rapidly identify new and rare adverse reactions (66).

Single case reports are frequently criticized as not being substantial enough to reveal a new drug-safety problem. However, the potential impact of a published single case report has been shown by Venning, who demonstrated that most of the major adverse reactions to drugs were first spotted by means of case reports (67). Also,

publication in a medical journal is likely to attract more attention among doctors than the submission of a report to a manufacturer or drug regulator.

Spontaneous reporting systems have several advantages. They are relatively inexpensive, cover all drugs used by the entire population, and can rapidly react to a signal. The major disadvantage is (selective) underreporting. The reporting rate shows large differences between different countries (68). Another problem in reports on adverse reactions, concerns the assessment of the causal relationship between the use of a drug and a possibly associated adverse event. It has been demonstrated that even with standardized procedures agreement between different observers is difficult (69). Furthermore, among the national spontaneous reporting schemes different methods are used in causality assessment (70). In general, especially adverse reactions with a clear temporal relationship with use of the drug can be observed with this approach.

As a reaction to the thalidomide disaster, the Netherlands Centre for Monitoring of Adverse Reactions to Drugs (NARD) was founded in 1963 as a collaborative initiative of the Dutch Medical Association, the Inspectorate for Pharmaceuticals and the Medical Inspectorate (71). The most important objective of the centre is to discover unknown adverse reactions at an early stage in order to prevent an epidemic of drug-induced injury.

b. *Intensive Monitoring*

In 1966, Hershel Jick and Dennis Slone started a system in which large numbers of medical inpatients were monitored continuously in order to determine the frequency of adverse reactions in these patients. This system was called the Boston Collaborative Drug Surveillance Program (72).

In 1977 the Department of Health in New Zealand established a novel system: 'The Intensified Adverse Drug Reaction Reporting Scheme', now entitled 'Intensive Medicines Monitoring Programme' (IMP). Several specific drugs are in this system selected for 'intensive monitoring' mainly because they are newly registered drugs or because of important serious spontaneous reports. The IMP has two parts. Firstly an intensified spontaneous 'event' reporting component, and secondly a cohort formation of users of the drug of interest.

c. *Prescription-event monitoring*

Prescription-event monitoring (PEM) was developed in 1980 by the Drug Safety Research Unit (DSRU) in the UK as a novel national approach for the detection of adverse events occurring during drug treatment (73). In PEM the patient, drug and doctor are identified from the prescriptions gathered by the Prescription Pricing Authority (PPA). Thereafter, simple questionnaires (green forms) are posted to the prescribing doctors 6 to 12 months after the prescription has been written, about all 'events' that happened since the prescription and some other information, such as age and diagnosis. And although the majority of reported events are in fact not adverse drug reactions (but rather related to the disease being treated or co-incidental), it is a useful approach, especially for recently marketed 'new chemical entities'. However, the frequency of adverse reactions may be underestimated if only records of general practitioners are used. An example of this phenomenon in PEM was the estimated frequency of cough with enalapril (74, 75) as suggested by Waller (76). A number of studies from PEM has been published (77, 78).

d. Record linkage systems

In a record linkage system, data concerning both drug use and morbidity are linked on an individual patient level. Many studies have already been performed with such record linkage systems. An example of a record linkage system is the Dutch PHARMO system (79). Several studies have been published with data from the PHARMO system (80), and more results are awaited.

However, although in 1986 it was stated that 'the future of pharmacoepidemiology lies in record linkage' (81), others have demonstrated several limitations of automated record linkage systems (82).

e. Field studies

According to Rothman, field studies differ from clinical trials 'in that they deal with subjects who have not yet gotten disease and therefore are not patients' (83). As a consequence, all (clinical) data must be collected 'de novo' without clinical source documents. In postmarketing surveillance, field studies usually address a study population using a specific drug of interest (for instance acitretin or sumatriptan) or a study population with a specific (rare) disease (for instance primary pulmonary hypertension), permitting a cohort or a case-control study respectively.

Field studies have several disadvantages. In particular they are expensive and take a long time for completion. However, they may provide important information, which is not readily available from spontaneous reporting schemes or record linkage systems.

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PART II

REPORTS TO A NATIONAL VOLUNTARY REPORTING SCHEME

CHAPTER 3

THE NETHERLANDS CENTRE FOR MONITORING OF ADVERSE REACTIONS TO DRUGS

Ned Tijdschr Geneeskd 1993;137:1784-7.

Ned Tijdschr Geneeskd 1994;138:2110-13.

Introduction

The potential power of a published case report has been shown by Venning, who demonstrated that most of the major adverse reactions to drugs were first spotted in this way (1). While a publication in a medical journal is likely to attract more attention among doctors than the submission of a report to a manufacturer or drug regulator, there are also limitations to published reports as a single source of information. Publications in the literature, however, often omit important information (2), depend on editorial decisions, are a very small proportion of the observed adverse reactions seen in clinical practice, and are not systematic (3).

Spontaneous reporting schemes are considered a valuable tool to rapidly identify new and rare adverse reactions (3). In this chapter, some characteristics of the Netherlands Centre for Monitoring of Adverse Reactions to Drugs are discussed.

Methods

As a reaction to the thalidomide disaster, the Netherlands Centre for Monitoring of Adverse Reactions to Drugs (NARD) was founded in 1963 as a collaborative initiative of the Dutch Medical Association, the Inspectorate for Pharmaceuticals and the Medical Inspectorate (4, 5). Since 1963, the NARD has been a subunit of the Inspectorate for Pharmaceuticals of the Ministry of Health and Environmental Hygiene, currently the Ministry of Public Health, Welfare and Sports. The objective of the centre is to discover unknown adverse reactions at an early stage in order to prevent an epidemic of drug-induced injury. In particular, the reporting is encouraged of (6):

- unknown adverse reactions
- adverse reactions of new drugs (especially new chemical entities)
- serious adverse reactions
- confirmed adverse reactions (e.g. by rechallenge)

All reports are evaluated by a medical officer and discussed during monthly meetings of the Adverse Reaction Advisory Committee. This committee supports the NARD in particular for auditing the causal relationship between drug exposure and the potential adverse reaction. Assessment of the causal relationship is based on the temporal relationship between drug use and onset of the adverse reaction, pharmacological potential of the suspected drug(s), exclusion of other possible causes of the adverse

reaction, and the results of re-exposure (=rechallenge) (7). The received reports are classified into one of the following categories of likelihood of the causal relationship between use of the suspected drug and the adverse reaction:

- *Certain* This concerns a well-documented report of an objective adverse reaction, with a clear temporal relationship, and with a positive rechallenge. All other causes have been excluded.
- *Probable* Also well-documented, but without a rechallenge. All other causes have been excluded. Also subjective reactions with a rechallenge
- *Possible* This classification varies between 'nearly probable' and 'not impossible'. Also used if two or more drugs are suspected. Often, other causes are not sufficiently excluded.
- *Unlikely* A report in which another cause than the suspected drug is a more likely cause of the reaction.
- *Unclassified* A report with incomplete (e.g. as to age or gender) or conflicting data. Also congenital malformations, or overdoses.

The NARD participates in the monitoring program of the World Health Organization's Collaborating Centre for International Adverse Reaction Monitoring in Uppsala, Sweden, and routinely exchanges information with this centre which gathers spontaneously reported data from many countries all over the world. Furthermore, information on adverse reactions to drugs by the NARD is given directly by telephone, by publication in the medical literature, by advising the Dutch Medicines Evaluation Board to include an adverse reaction into the data sheet, and by 'Dear Doctor' letters.

The data

In September 1964 the first reports were received, finally resulting in a total of 377 reports in 1964 (8). In 1965, 362 reports were received, whereas in 1966 172 reports were received by the Centre. The annual number of reports between 1964 and 1995 is depicted in figure 1.

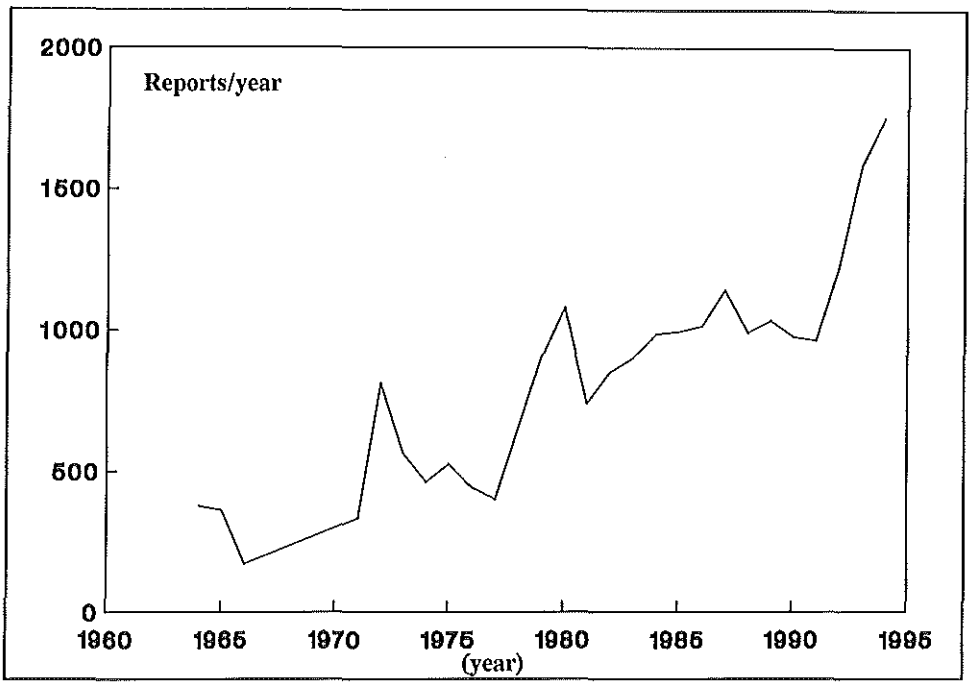

Figure 1 - *Reports received by the Netherlands Centre*

As is demonstrated, especially since 1992, there has been a strong increase in the annual number of reports. Several examples of adverse reactions to drugs which were published in the international literature are shown in the table.

TABLE

Examples of adverse reactions to drugs published in the international medical literature by the Netherlands Centre for Monitoring of Adverse Reactions to Drugs in recent years

Drug	Adverse reaction
Omeprazole	Agranulocytosis
Paroxetine	Bleeding risk
Nicotine patches	Myocardial infarction
Trazodone	Agranulocytosis
Sumatriptan	Myocardial infarction
Terbinafine	Taste loss
Nicotine patches	Atrial fibrillation
Itraconazole	Hepatic injury
Diclofenac	Myonecrosis
Benzbromarone	Hepatic injury

In 1993, the Netherlands centre received 1585 reports (9), compared to 1248 in 1992 (10). The causality of the Dutch reports was: certain 2.5%, probable 30.3%, possible 43.8%, unlikely 4.2%, and unclassified 19.2%. Of the reports, 55% were received from general practitioners. 232 reports (14%) were received from the pharmaceutical companies. Of the latter reports, the causal relationship of 107 reports (46%) was classified as "unlikely" or "unclassified" which was a significantly larger fraction than the reports from medical practitioners ($p < 0.001$).

Examples of letters sent by the Inspectorate in 1995 concerned the indication restriction of ibopamine and the risk of thromboembolism in users of desogestrel or gestodene containing oral contraceptives.

Discussion

The Netherlands Centre for Monitoring of Adverse Reactions to Drugs suffers from the limitations shared by all spontaneous reporting systems, i.e. underreporting and false-positive reporting. In comparison with other countries, such as Sweden and the United Kingdom, there appears to be considerable underreporting in the Netherlands (11). It has been shown for general practice in the UK that important reasons for not reporting an adverse reaction are the fact that the adverse effect is well-known or trivial, insecurity about the causal relationship, and a lack of feedback from the monitoring centres (12, 13). The NARD has in the past years used several methods to stimulate reporting. It is attempted to increase the feed back both to reporters (by telephone or letter) and to all health care professionals by publishing reports in the medical literature. Maybe as a result of this, the annual number of reports has increased to a total of 1750 in 1994.

The increase in the annual number of reports is remarkable, since in The Netherlands a regional reporting system has also existed since 1984 (14). In 1987, it was demonstrated that the NARD received relatively more serious and more well-documented reports than this regional system. The increase of the number of reports to the NARD endorses, however, the possibility that health care professionals prefer to report to a national centre within the Ministry of Health. Hence, it seems to be important that a reporting centre will remain in the vicinity of the Ministry.

Causality assessment in the reports was performed on the basis of previously published criteria (7). It has, however, been suggested that there is often misclassification, and that in general in most reports the causal relationship between

the drug and the event is no more than 'possible' (16).

The new regulations in Europe concerning reporting adverse reactions to drugs (17) will result in a growing number of reports from pharmaceutical companies. The reports to the NARD show, however, that these reports are significantly more frequently 'unclassified' or 'unlikely'. If this means that these reports are more often less well documentated or more often concern unrelated 'events' this is not a favourable development. Maybe, education of drug safety officers of pharmaceutical companies may improve these reports.

In conclusion, since 1963 the Netherlands Centre for Monitoring of Adverse Reactions to Drugs (NARD) has been responsible for a nationwide spontaneous reporting scheme. In recent years, an increase in the annual number of reports to the centre was observed, resulting in a total of 1750 reports in 1994. In the future, it is not only important to increase the annual number of reports, but also to improve the quality of the reports, in particular those from pharmaceutical companies.

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CHAPTER 4

DRUG-INDUCED CHEST PAIN AND MYOCARDIAL INFARCTION: REVIEW OF REPORTS TO A NATIONAL CENTRE

submitted

Introduction

Research on adverse reactions to drugs is an issue of growing professional and public interest. Because serious adverse reactions to drugs are often rare, they are difficult to detect and to investigate. In spite of the low incidence, it is important to recognize drugs as the cause of serious illness. Firstly, if drugs are used for minor ailments, even a low incidence of a serious adverse reaction may unfavourably affect the benefit/risk ratio. Secondly, timely recognition of drugs as the cause of disease, and subsequent discontinuation may be life-saving. Finally, knowledge on adverse drug reactions may help to identify groups of patients at particular risk.

The different adverse effects of drugs on the heart, are summarized in table 1.

TABLE 1

Different adverse effects of drugs on the heart

Arrhythmias and conduction disorders
Heart failure
- Direct: Negative inotropism or chronotropism
- Indirect: Salt and water retention
Myocardial ischemia/infarction
- Direct: Reduced coronary blood flow, thrombosis
- Indirect: Coronary 'steal', interaction with anti-anginal drugs
Pericardial disease
- Hemopericarditis
- Others

The commonest way in which drugs adversely affect the function of the heart is by the production or aggravation of cardiac arrhythmias or conduction disorders. The next most common adverse effect of drugs on the heart is the initiation or aggravation of heart failure. Less frequently, drugs may cause myocardial ischemia or infarction, or may make the patient more susceptible to these disorders.

Although voluntary reporting systems have several disadvantages, especially underreporting, they have fundamental value in detecting and characterising rare adverse drug reactions (1, 2). In this paper, we present an analysis of the reports on drug-induced chest pain and myocardial infarction, received by the Netherlands Centre for Monitoring of Adverse Reactions to Drugs between January 1st 1975 through December 31st, 1994.

Methods

The Netherlands Centre for Monitoring of Adverse Reactions to Drugs (NARD) holds a

nationwide voluntary reporting scheme for adverse reactions to drugs. All reports are evaluated by a medical officer and discussed at monthly meetings of the Advisory Board. All reports received by the NARD between January 1st 1975 through December 31st 1994 concerning drug-induced chest pain, myocardial ischemia or infarction were included in this study. Only adverse drug reactions due to drugs in therapeutic doses were considered. All reports came from general practitioners, specialist doctors or hospitals. Minimally requested were data about the age and sex of the patients, dose and duration of the suspected drug, and clinical signs and symptoms. Each report was evaluated carefully, whereafter the likelihood of a causal relationship was assessed between use of the suspected drug(s) and the symptoms. Evaluation of potential causality of the relationship was based on the temporal relationship of the adverse reaction, pharmacological potential of the suspected drug(s), exclusion of other possible causes of myocardial ischemia, such as coronary stenoses, and the results of re-exposure (=rechallenge) (3). A causal relationship was considered 'unclassified' or 'unlikely', respectively, when too few data were available or when more likely causes were found. In the analysis, reports were excluded if the causal relationship was unlikely or unclassified.

Acute myocardial infarction was considered to be present if at least two of the following criteria were present: 1) A recent positive clinical history of chest pain of at least 30 minutes; 2) Characteristic changes in the electrocardiogram; 3) Peak elevation of serum enzymes (CPK, SGOT) of at least 2 times the upper limit of normal.

Differences between group means were tested by two-tailed Student's t test. A chi-square statistic was calculated to test differences between proportions. Statistical significance was defined as a p-value of less than 0.05.

Results

The Netherlands Centre for Monitoring of Adverse Reactions to Drugs received during the study period a total of 19,141 reports on adverse reactions to drugs. Of these reports, 220 (1.1%) concerned reports of drug-induced chest pain or myocardial infarction. 22 reports (10%) were poorly documented and of 15 reports (6.8%) the causal relationship was unlikely. The poorly documentated reports, and the reports in which the causal relationship was unlikely were excluded from further analysis. Three reports, on myocardial infarction to sumatriptan, nicotine and sulprostone respectively, were previously reported in the literature as a case-report (4).

The 183 reports which were suitable for analysis, concerned 103 females (56%) and 80 males (44%), with an average age of 51 years. In table 2 an overview is given of the suspected drugs.

TABLE 2

*Overview of drugs which were related to chest pain or myocardial infarction in 183 reports**

Drug-group (number of reports)	Drug (number of reports)
Cardiovascular (37)	
Ca-antagonists (15)	Nifedipine (9), diltiazem (4), verapamil (2)
ACE-inihibitors (6)	Captopril (1), lisinopril (2), perindopril (2), enalapril (1)
ß-blockers (5)	Oxprenolol (1), pindolol (1), atenolol (1), metoprolol (2)
α1-blockers (2)	Urapidil (1), prazosin (1)
Other (9)	Diuretics (7), ibopamine (1), disopyramide (1)
Central nervous system (53)	
Antidepressants (17)	Imipramine (1), amitriptyline (2), mianserin (1), moclobemide (4), fluvoxamine (2), trazodone (2), fluoxetine (3), maprotiline (1), doxepine (1)
Antipsychotics (1)	Clozapine (1)
Anti-migrainous (35)	Ergotamine (1), sumatriptan (33), methysergide (1)
Respiratory system (15)	
ß-mimetics (7)	Salbutamol (3), salmeterol (4), formoterol (2)
Antihistamines (5)	Terfenadine (1), cetirizine (2), cinnarizine (2)
Other (3)	Theophylline (1), beclomethason (1), noscapine (1)
Hormones (12)	Oral contraceptives (4), oestrogens (3), sulproston (1), epoetin (1), desmopressin (3)
Anti-infectives (15)	
Antibiotics (10)	Nitrofurantoin (4), co-trimoxazol (1), amphotericin (1), amoxicillin (1), metronidazole (1), norfloxacin (1)
Others (6)	mefloquine (3), niridazole (2), ketoconazole (1)
Analgesics (10)	NSAIDs (6), glafenine (2), penicillamine (1), aspirin (1)
Gastro-intestinal drugs (5)	Cisapride (2), cimetidine (2), domperidone (1)
Miscellaneous (44)	Alfuzosin (3), nicotine (9), amphetamines (2), fenfluramine (2), ß-blocker containing eye drops (4), various (24)

* In 9 reports more than one drug was suspected

There were 130 reports (71%) of drug induced chest pain and 53 reports (29%) of drug induced myocardial infarction. Of the 130 patients with chest pain attributed to use of drugs, 40 patients (31%) had a positive rechallenge after renewed exposure to the drug. Compared to drug-induced chest pain, drug-induced myocardial infarction was more frequently reported in males (63% vs. 35%; $p < 0.001$). 18 patients (9.8%) died after myocardial infarction. Age was not related to myocardial infarction or death. Only in a few patients with drug-induced chest pain was an ECG performed, but by the time this was done, in almost every patient the chest pain had already disappeared. In 6 patients abnormal ECGs were observed.

In 174 out of 183 reports, one drug was suspected to have caused the adverse

reaction, whereas in 5 reports two drugs were suspected and in 4 reports more than two drugs were suspected. Chest pain or myocardial infarction were attributed to a total of 98 different drugs. The drugs most frequently reported were sumatriptan (33 reports), nicotine (9 reports), nifedipine (9 reports), diltiazem (4 reports), moclobemide (4 reports) and salmeterol (4 reports).

There were several reports of chest pain or myocardial infarction attributed to the use of cardiovascular drugs. 15 reports concerned calcium-channel blocking agents: 9 reports concerning nifedipine (7 chest pain, 2 acute myocardial infarction), 4 reports concerning diltiazem (all chest pain) and 2 reports concerning chest pain attributed to use of verapamil. There were 3 reports of chest pain induced by systemic use of ß-blockers (oxprenolol, pindolol and atenolol). ACE-inhibitors were suspected in 5 reports: captopril (1 report of chest pain), lisinopril (1 report of chest pain, 1 report of myocardial infarction) and perindopril (1 report of chest pain, 1 report of myocardial infarction).

There were 17 reports of chest pain or myocardial infarction attributed to use of antidepressants. Three of them concerned fatal myocardial infarction after use of tricyclic antidepressants (1 imipramine, 2 amitriptyline). These concerned 2 females and one male. Four reports concerned myocardial infarction attributed to use of the MAO-A inhibitor moclobemide, of which two concerned a fatal reaction.

Several reports concerned chest pain or myocardial infarction attributed to drugs for respiratory problems, of which 7 reports concerning ß-mimetics are of special interest. These comprised 6 reports of myocardial infarction and 1 report of chest pain attributed to salbutamol (4x), salmeterol (3x) or formoterol (2x) (in two reports both salmeterol and salbutamol were suspected). These reports concerned 7 males with a mean age of 49 years.

Four reports concerned adverse reactions attributed to use of oral contraceptives (two myocardial infarction, two chest pain), whereas in 3 reports chest pain or myocardial infarction was attributed to other oestrogens. One report concerned a myocardial infarction due to intravenous administration of sulprostone. Three reports concerned chest pain (one report) or myocardial infarction (two reports) attributed to desmopressin.

There were two reports of acute myocardial infarction and one report of chest pain attributed to use of alfuzosin. One report concerned a 53-years-old male, who experienced severe angina pectoris within one hour after intake of the first tablet of alfuzosin 2.5 mg. He was admitted to a hospital, and a diagnosis of acute myocardial infarction was made. This patient had never had chest pain before use of alfuzosin, and a causal relationship seems probable.

Discussion

The most common cause of myocardial ischemia is coronary artery sclerosis and stenosis, whereas an acute myocardial infarction is mostly caused by occlusive thrombi in atherosclerotic coronary arteries. Transmural myocardial infarction with angiographically normal coronary arteries is rare (5) and has been associated with a defect of fibrinolysis (6), early age (7), cigarette smoking (8) and drug use. Especially in patients with chest pain or myocardial infarction and normal coronary arteries it is important to consider drugs as a potential cause of the complaints.

Although the incidence of acute myocardial infarction due to drug-induced ischemia is probably low, there are several reasons why it is important to know which drugs can induce myocardial ischemia, and which mechanism is involved. Firstly, drugs can be identified which should be used cautiously, especially in patients with coronary artery disease. Secondly, it is important to consider a cardiac origin if chest pain occurs in a patient using some specific drugs, in particular if it is a patient without any reason to suspect a cardiac origin of the complaints, for example, a young female. Under certain circumstances, discontinuation of a specific drug may prevent myocardial infarction and may be life-saving. Thirdly, in patients diagnosed as having myocardial infarction or angina pectoris with normal coronary angiography, the possibility of an association with the intake of some drugs should be considered. Fourthly, the diagnostic and therapeutic approach of patients with drug-induced myocardial ischemia or infarction may differ from patients with regular myocardial ischemia or infarction. Finally, the pharmacological mechanisms may also provide insight into the pathophysiology of 'not-drug-induced' myocardial ischemia.

Cardiovascular drugs

There were several reports of chest pain or myocardial infarction after use of cardiovascular drugs. Especially interesting were 15 reports of chest pain or myocardial infarction attributed to calcium-antagonists. Recently, in a case-control study of hypertensive patients a relatively higher risk of myocardial infarction was found in patients taking calcium antagonists (9). In a meta-analysis by Furberg et al, a dose-dependent association of use of nifedipine with mortality was observed (10). Since hypertension is associated with both myocardial infarction and mortality, these associations are explained by some as a result of confounding by indication (11). Confounding by indication can even result in a dose-dependent association. There are, however, several case-reports in which a relationship between administration of nifedipine and aggravation of myocardial ischaemia was observed (12, 13).

There were 3 reports of chest pain induced by systemic use of ß-blockers (oxprenolol, pindolol and atenolol), and 4 reports of chest pain induced by ß-blocker containing eye drops (timolol 2x, betaxolol, metipranolol). Acute myocardial infarction

has been associated with propranolol (14) and metoprolol (15). Also ß-blocker-containing eye drops have been associated with chest pain (16) and myocardial infarction (17). The pathophysiologic mechanism of ß-blocker induced myocardial ischemia is probably coronary vasospasm mediated by alpha-adrenergic receptors (15).

A few reports concerned chest pain or myocardial infarction attributed to use of ACE inhibitors. In the literature, several case reports of angina pectoris related to captopril have been published (18, 19).

Central nervous system

There were three reports of fatal myocardial infarction, attributed to tricyclic antidepressants. This is especially of interest, because recently in a case control study an unexpected 6-fold increase in risk was demonstrated of fatal myocardial infarction in young women associated with current use of tricyclic antidepressants (20). In general, the cardiovascular effects of tricyclic antidepressants are considered to consist mainly of conduct disturbances, arrhythmias and orthostatic hypotension (21, 22). Myocardial infarction was attributed to moclobemide in four reports. Recently, hypertension was described as an adverse reaction of this MAO-A inhibitor (23).

Anti-migrainous drugs

In the literature, there have been several reports of cardiac ischemia due to the antimigrainous drugs ergotamine (24, 25), methysergide (26), sumatriptan (27) and isometheptene (28). The proposed mechanism is coronary spasm. There was a large number of reports to our centre of chest pain (29 reports) and several reports (four) of myocardial infarction attributed to use of the new anti-migrainous drug sumatriptan. One report of myocardial infarction (29) and 13 reports of chest pain (30) were published in the literature as case reports. In clinical trials, the frequency of chest pain after use of sumatriptan was approximately 5% (31, 32), whereas in a postmarketing study the frequency was estimated to be 8% (33). Furthermore, several cardiac adverse reactions have been associated with use of sumatriptan in the literature (27, 34, 35). It is, however, not yet known whether the frequency of cardiac adverse reactions to sumatriptan is more frequent than to ergotamine.

Respiratory system

There were six reports of myocardial infarction and one report of chest pain attributed to use of ß-mimetics and one report of myocardial infarction attributed to theophylline. In the literature, acute myocardial infarction following both intravenous and inhaled treatment with salbutamol has been described (36, 37). An increase of mortality in regular users of $ß_2$-agonists has been demonstrated, but drug-induced myocardial ischaemia is not considered to be one of the mechanisms (38). A case report of a patient who experienced a myocardial infarction attributed to use of theophylline was previously published (39). Furthermore, it has been demonstrated that theophylline can cause

tachycardia and myocardial ischemia, even at recommended doses (40). However, since cardiac and respiratory disease commonly co-exist (and have several risk factors in common such as smoking) the causal implications remain difficult to assess.

Hormones

There were two reports of myocardial infarction during use of oral contraceptives. In fact, this potential association can not be clarified by case reports, since there is a lack of clear temporal relationship. In a case-control study Thorogood et al demonstrated that current users of oral contraceptives had an increased, although not statistically significant, risk of fatal myocardial infarction (41).

In two reports of myocardial infarction and in one report of chest pain, the reactions were attributed to use of desmopressin. This association has previously been described in the literature (42).

Analgesics

Coronary spasm has been described after use of naproxen (43) and glafenine (44). The proposed mechanism is an allergic reaction (43).

Miscellaneous

Of the reports to the national centre of chest pain (n=4) or myocardial infarction (n=5) attributed to use of nicotine, one was previously published as a case report (45). There have been reports of serious cardiovascular adverse reactions in literature, including acute myocardial infarction and cardiac arrest, associated with continued smoking during use of the patches (46-48).

There were two reports of acute myocardial infarction and one report of chest pain attributed to use of alfuzosin. Alfuzosin is a relatively new drug, used for the symptomatic treatment of benign prostatic hyperplasia, which acts as an antagonist of α1-adrenoceptors (49). According to the close temporal relationship with intake of alfuzosin, the relationship between use of this drug and the adverse reactions seems to be probable. Alfuzosin is, however, often prescribed in patients with a high risk for coronary diseases (elderly males). There were also reports on two other α1-blockers, urapidil and prazosin, which were used for hypertension, concerning chest pain attributed to use of these drugs.

Two reports concerned chest pain attributed to use of fenfluramine. Myocardial infarction associated with dexfenfluramine has been described previously (50).

Underreporting and selective reporting

The most important disadvantages of a spontaneous reporting system are underreporting and selective reporting. According to the latter, it is in particular interesting that chest pain or myocardial infarction was in not even one report attributed to cytostatic drugs, blood coagulation factors or cocaine.

Malignancy may affect the heart by direct invasion as in lymphoma, or by blood

borne metastases as in malignant melanoma (51). Moreover, several antiproliferative drugs and/or irradiation to the mediastinum can cause cardiac damage (52-54). These drugs include 5-fluorouracil (55), taxol (56), bleomycin and etoposide (57) and cisplatin (58).

Several cases of myocardial infarction attributed to the administration of blood coagulation factors have been documented in the literature (59-61). In most cases, patients with haemophilia were involved.

Cases of cocaine-induced myocardial infarction were previously reviewed in the literature (62).

Conclusions

The present study demonstrated the reports of drug-induced chest pain or myocardial infarction as reported to the Netherlands Centre for Monitoring of Adverse Reactions to Drugs during the period 1975 through 1994. The reviewed reports give an impression of the different drugs and the different mechanisms in the difficult field of drug-induced myocardial ischemia or infarction.

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CHAPTER 5

ADVERSE REACTIONS TO SUMATRIPTAN: REPORTS TO THE NETHERLANDS CENTRE FOR MONITORING OF ADVERSE REACTIONS TO DRUGS

CHAPTER 5.1

CHEST PAIN ATTRIBUTED TO SUMATRIPTAN

Ned Tijdschr Geneeskd 1992;136:1774-6.

Introduction

Sumatriptan is a selective serotonin-1 agonist which was registered in May 1991 in the Netherlands. As a result of this registration, the Netherlands was the first country in the world where this drug, used in the treatment of acute attacks of migraine and cluster headache was marketed. In premarketing research it was already observed that use of sumatriptan may lead to feelings of 'heaviness' in several parts of the body, which can be accompanied by chest tightness.

The Netherlands Centre for Monitoring of Adverse Reactions to Drugs received 13 reports, demonstrating that these complaints can resemble the clinical picture of an acute attack of angina pectoris, with chest pain radiating to the throat and left arm. The British Committee on Safety of Medicines recently received 34 similar reports after subcutaneous administration of sumatriptan (1).

Case histories

Since the registration of sumatriptan (Imigran) in May 1991, until June 1992, the Netherlands Centre for Monitoring of Adverse Reactions to Drugs received 13 reports of substernal chest tightness or pain attributed to its use (table). These concerned eleven females and two males with an average age of 41 years (range 19 to 61 years), who all developed angina-like symptoms. The onset of symptoms was in almost all patients within one hour after administration of sumatriptan. In particular after subcutaneous adminstration a close and immediate temporal relationship was evident.

Symptoms varied from substernal tightness to severe cramping angina-like pain radiating to the left arm and hand. In one patient a transient increase in blood pressure to 200/120 mm Hg was noted, which later fell to 160/90 mm Hg. Three patients had complaints of dyspnoea, without signs of bronchospasm or laryngospasm. Five reporting medical practitioners classified the symptoms as anginal, and three of them notified these as 'classical' or 'real' angina pectoris. In all patients, symptoms resolved without further treatment. Most patients also used concomitant drugs (table), but only one patient used a cardiovascular drug (isosorbide dinitrate). Propranolol and clonidine as used by patient H and L respectively, were both used as a prophylaxis in the treatment of migraine.

Electrocardiograms (ECG) were normal in cases C, E and H, but were obtained after the chest symptoms had resolved. In the other patients no ECG was performed. An echocardiogram and results of an exercise test performed after the first episode of

TABLE

Details of 13 cases of chest pain after sumatrtipan as reported to the Netherlands Centre for Monitoring of Adverse Reactions to Drugs between May 1991 and June 1992

Case	Age/sex	Dose and route	Latent period (minutes)*	Symptoms	Recurrence after rechallenge#	Other drugs
A	36, F	100 mg orally	30 - 45	Substernal pressure, drowsiness, "shaky"	ND	Terfenadine 60 mg
B	38, F	100 mg orally	30	Substernal pressure and pressure in the shoulders/neck	> 10 times	Carbamazepine 600 mg, lactulose, hydroquinone hydrobromide dihydrate
C	61, F	100 mg orally	Same day	Anginal pain radiating to the left arm	2 times	Isosorbide dinitrate 5 mg
D	46, F	100 mg orally	15	Substernal pain, sweating	3 times	Oral contraceptive
E	53, M	100 mg orally	About 30	Anginal pain	ND	None
F	44, M	100 mg orally	30	Substernal chest pain, palpitations, pain in throat	ND	None
G	27, F	100 mg orally	30	Substernal chest pain, malaise, Paraesthesia, heaviness of arms	ND	None
H	33, F	6 mg subcutaneously	1 - 5	Angina pectoris radiating to left arm and hand, dyspnoea	2 times	Propranolol 60 mg
J	45, F	100 mg orally	Same day	Substernal pressure, muscle stiffness	ND	None
K	19, F	6 mg subcutaneously	30 - 60	Chest pain, dyspnoea, nausea	ND	Oral contraceptive
L	50, F	6 mg subcutaneously	1 - 5	Anginal pain radiating to the jaw, hypertension	ND	Clonidine 100 μg, aspirin 600 mg
M	36, F	100 mg orally	30	Substernal chest tightness	ND	None
N	39, F	6 mg subcutaneously	1 - 5	Angina pectoris, radiating to the throat	2 times	None

* Between first intake and onset of symptoms as notified by reporting doctor. # ND = Rechallenge not done.

chest pain in case H were normal. Except for case L, who had experienced a similar reaction to ergotamine in the past, none of the patients had had similar episodes before using sumatriptan and none developed these symptoms again after stopping it. None of the patients had a history of cardiovascular disorders or diabetes mellitus.

Discussion

According to the close temporal relation between administration of sumatriptan and onset of chest pain, a causal relationship between use of the drug and the complaints seems to be probable in these patients. Furthermore, in five patients there was recurrence of symptoms after renewed exposure to sumatriptan. Other causes of chest pain were excluded in most patients, and most of them were young.

Although the majority of patients was female, it would not be justified to conclude that females have a higher risk of sumatriptan-induced chest pain compared to males. Firstly, consumption patterns should be taken into account, in particular because females have more often complaints of migraine. Secondly, spontaneous reporting schemes have several disadvantages, not only of underreporting, but also of selective reporting.

Unfortunately, in only few patients an ECG was performed. Because the ECGs were not obtained during the sumatriptan-induced complaints, but after the chest symptoms had resolved, it remains unclear whether ECG abnormalities were present during these complaints. In a recently described case history (2), chest pain within four minutes after subcutaneous administration of sumatriptan was accompanied by ST elevation on ECG, which suggests myocardial ischaemia.

Angina pectoris and myocardial ischaemia have been described as a result of use of the antimigrainous drug ergotamine (3). These concern potentially serious adverse reactions, which can result in acute myocardial infarction (4).

Early studies suggested that serotonin-1 receptors are largely confined to the cranial circulation rather than to the coronary circulation. As serotonin-2 receptors are more common in coronary arteries than serotonin-1 receptors the effect of sumatriptan (a serotonin-1 agonist) on coronary vasculature is considered to be relatively mild. Serotonin itself may cause constriction of isolated epicardial coronary arteries (7), but the vasoconstrictive effect of sumatriptan has been estimated to be only 30% of serotonin (5). In general, this should not lead to myocardial ischaemia, but if the

coronary arteries have atherosclerotic abnormalities, the constriction can be more severe or result in a significantly reduced blood flow. The enhanced vasoconstrictive response of atherosclerotic isolated epicardial coronary arteries to histamine is also seen after administration of serotonin (7, 8).

A study by the manufacturer of sumatriptan in 10 patients with suspected coronary artery disease showed an average constriction of coronary arteries of 13.9% 10 minutes after subcutaneous administration of 6 mg sumatriptan (Glaxo, unpublished data). However, in this study in one patient a 60% reduction of the diameter of the left anterior descending artery was observed. Although in this study mean aortic and pulmonary artery pressures were raised, cardiac output did not change. No electrocardiographic abnormalities were noted, and only one patient experienced chest tightness.

Two explanations for the chest symptoms after use of sumatriptan are plausible. Firstly, it may be a result of direct stimulation of serotonin-1 receptors in several organs, since in clinical trials relatively many patients experience paraesthesia and feelings of heaviness in several parts of their body. Another possibility is that chest pain is caused by myocardial ischaemia. Patients with atherosclerosis of the coronary arteries may be a risk group for myocardial ischaemia induced by sumatriptan. This seems unlikely in the patients we described, because most of them were young and had no history of cardiovascular diseases. However, myocardial ischaemia might occur as a part of variant angina with spasm of coronary arteries.

In conclusion, sumatriptan can cause symptoms resembling acute attacks of angina pectoris. In the literature, a case has been reported with sumatriptan-induced chest pain accompanied by ST elevation on ECG, but this was a patient with a history of angina pectoris prior to use of sumatriptan (2). However, although sumatriptan seems to be an effective drug in the treatment of migraine, we advise cautious use of sumatriptan, especially in any patient who has chest pain or tightness after use of this drug, as in some patients sumatriptan may cause myocardial ischaemia or even myocardial infarction. It is not yet clear which patients are at increased risk of myocardial ischaemia to sumatriptan, but patients with coronary atherosclerosis and patients with a history of variant angina pectoris should not use this drug, as is stated in the data sheet of sumatriptan

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CHAPTER 5.2

TRANSMURAL MYOCARDIAL INFARCTION WITH SUMATRIPTAN

Lancet 1993;341:861-62.

Introduction

Sumatriptan is a serotonin-1 agonist used to treat acute attacks of migraine and cluster headache (1). In trials, sensations of pressure and tightness in the chest occurred in 3% of patients treated with 100-300 mg orally and in 5% of patients after subcutaneous administration of 4-8 mg, but no electrocardiographic (ECG) evidence of cardiac ischaemia was demonstrated (2). In postmarketing experience with sumatriptan, angina-like pain was noted, but a cardiac cause has not been established (3, 4). One patient developed chest pain with ST elevation after sumatriptan 6 mg subcutaneously (5). In this patient, pain subsided and the ECG returned to normal in 22 minutes without subsequent increase in cardiac muscle enzymes. Two cases of serious ventricular arrhythmias have been reported after use of this drug (6). We report a patient who developed acute myocardial infarction after use of sumatriptan.

Case report

A 47-year-old woman was admitted to hospital at 1800 h complaining of several hours of severe substernal pain radiating to the left shoulder and nausea without vomiting . She had had these symptoms since 0700 h that day, 15 minutes after she had administered sumatriptan 6 mg subcutaneously for an acute attack of cluster headache. She had had episodes of left-sided cluster headache for several years, which were not relieved by ergotamine. She had never experienced chest pain after use of ergotamine or any other drug. Her history revealed no signs of diabetes mellitus, Raynaud's phenomenon, hypertension, angina, or pre-existing vascular disease; she smoked ten cigarettes a day. She had used ranitidine 150 mg daily for an endoscopically proven duodenal ulcer for the past 3 months, but she used no other drugs, including oral contraceptives. There was no family history of coronary heart disease.

1 week before admission she had started sumatriptan, which relieved the headache. But 15 minutes after administration of sumatriptan, she had chest pain for about 20 minutes. The next day she had the same chest symptoms after the subcutaneous injection. 1 week later, on the day of admission, she again had chest pain 15 minutes after drug administration, but this time chest pain did not disappear. So, in total, she had self-administered three doses of sumatriptan 6 mg subcutaneously.

On admission, the patient was normotensive (110/60 mm Hg), had normal peripheral pulses, and had no signs of congestive heart disease. ECG showed a regular

sinus rhythm of 60/min with a normal PQ interval. However, in leads III and aVF, inverted T-waves were seen, accompanied by pathologic Q waves (figure).

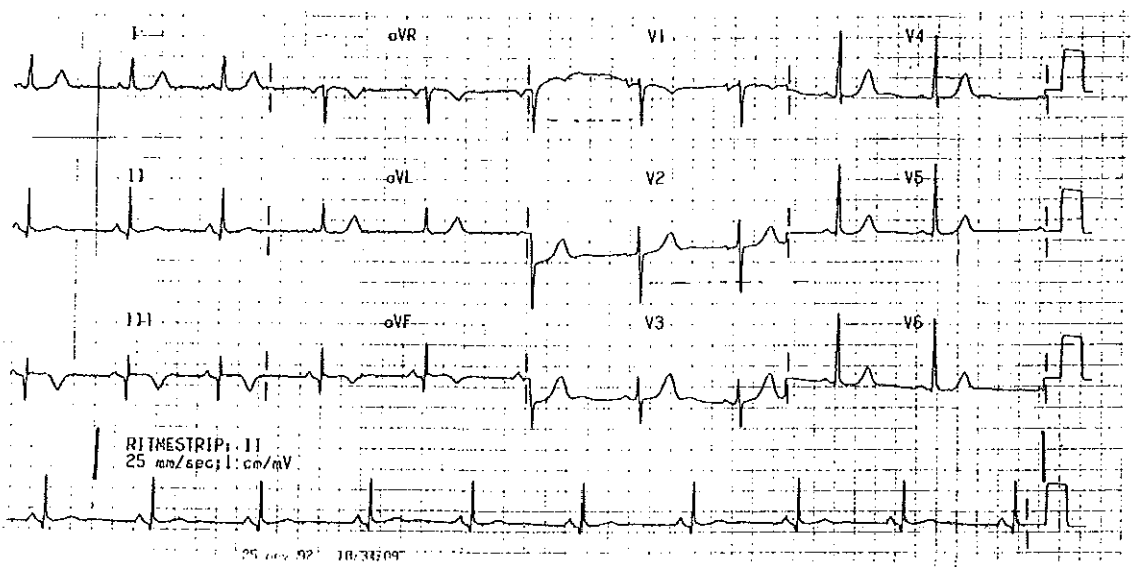

Figure - *ECG of a 47-year-old woman, admitted with several hours during chest pain, which started 15 minutes after she had administered sumatriptan 6 mg subcutaneously for an acute attack of cluster headache.*

Creatine kinase was 442 IU/L (normal <100 IU/L) with an MB fraction of 20%. A recent transmural inferior myocardial infarction was diagnosed, and therapy with nitrates and heparin was started. The following day, creatine kinase had increased up to 873 U/L. During the next few days, the patient recovered without complications.

A symptom-limited bicycle test 1 day before discharge demonstrated a maximum work-load of 95 W (normal 120 W). There was a normal increase in heart rate and blood pressure. The patient did not have anginal pain at any moment during or after the bicycle test. At maximum workload there was a 1.5 mm ST segment depression in lead I, V5, and V6 with slight upsloping of the ST segment. The test was regarded as indicative of possible ischaemia.

Discussion

According to both the close time relation between administration of sumatriptan and onset of chest pain and the recurrence of symptoms after every exposure, the chest pain in our patient was due to use of sumatriptan 6 mg subcutaneously. There is no doubt that the patient developed an acute transmural inferior myocardial infarction, after the third time that she administered sumatriptan. In view of the outcome after the third injection, we assume that the chest pain after the first and second injection was caused by reversible myocardial ischaemia.

Postmarketing experience with sumatriptan has failed to show any evidence of myocardial ischaemia in the absence of symptomatic cardiac disease (7). Willet et al (5) described an episode of coronary vasospasm without myocardial infarction after subcutaneous administration of sumatriptan. However, this patient had a history of retrosternal chest pain, not only in relation to methysergide and sumatriptan but also on awakening. Our patient had never had chest pain before she used sumatriptan.

Coronary vasospasm and myocardial infarction after ergotamine, another antimigrainous drug, has been well documented (8, 9), but the effect of sumatriptan on coronary vasculature is thought to be mild (10). Our patient had, however, not developed chest pain after use of ergotamine.

The case we report shows that chest pain after subcutaneous use of sumatriptan in patients without any history of underlying ischaemic heart disease or Prinzmetal's angina can result in an acute myocardial infarction. We advise cautious use of sumatriptan, especially in any patient who has chest pain or tightness after use of this drug.

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***Ottervanger JP, Stricker BHCh. Sumatriptan and chest pain. Letter to the editor. Lancet 1993;342:176.**

To the Editor: In their June 19 commentary about sumatriptan and chest pain (1), Dr. Hillis and Dr. MacIntyre suggested that our case of transmural myocardial infarction which we reported earlier in an issue of this journal (2), can be explained by a previous myocardial infarction, before administration of sumatriptan. However, we think that this is highly improbable. In general, the diagnosis of acute myocardial infarction is based upon at least two of the following criteria: 1) A recent positive clinical history of chest pain; 2) characteristic changes in the electrocardiogram (ECG); or 3) peak elevation of serum enzymes (creatine kinase, aspartate aminotransferase, lactic dehydrogenase). We described in our case report a recent history of chest pain (beginning 11 hours before admission) with a rise in serum enzymes (peak values for creatine kinase at the day after admission) and changes in the ECG suggestive of myocardial infarction. In view of the pattern of enzyme release (3) and the recent history of chest pain, in our view there is no doubt that this concerns a recent myocardial infarction. Pattern and evolution of ECG after acute myocardial infarction vary among patients. The patient we described was admitted 11 hours after onset of chest pain. It is likely that at that time an elevation of the ST segment did return to the baseline.

Furthermore we think that Hillis and MacIntyre's conclusion that the coronary vasoconstrictive effects of sumatriptan are less than that of serotonin or the ergot alkaloids is premature. Firstly, their angiographic studies of sumatriptan were small (4, 5), and postmarketing experience with sumatriptan is much less than with ergot alkaloids. Secondly, whereas Hillis and MacIntyre and co-workers showed a moderate reduction of coronary artery diameter induced by sumatriptan in patients without substantial coronary atherosclerosis (4, 5), it has been demonstrated that serotonin has a *vasodilatory* effect on normal human coronary arteries (6). Thirdly, it is incorrect to compare the coronary vasoconstrictive effects of subcutaneous or intravenous sumatriptan in patients without coronary artery stenosis of $\geq 50\%$ (4, 5), with the effects of *intracoronary* serotonin in patients with angina of whom most had substantial coronary stenoses (7). Finally, any conclusion about the comparative effects on the coronary artery diameter of sumatriptan and ergot alkaloids requires a

pharmacodynamic study with both drugs in one study population. Hence, further studies are warranted before an explicit statement regarding the comparative coronary effects of sumatriptan and ergot alkaloids is justified.

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CHAPTER 6

CARDIOVASCULAR ADVERSE REACTIONS TO SUMATRIPTAN: CAUSE FOR CONCERN?

CNS Drugs 1995;3:90-98.

Introduction

Although most drugs are relatively safe (1), it is still important to consider and to estimate their potential risk. A drug-related problem as the primary cause of hospitalisation is generally estimated at approximately 5 - 10 % of all hospital admissions (2). Sometimes, new insights into the risk of adverse reactions lead to withdrawal of a drug more than 20 years after marketing (3, 4). Hence, on-going risk assessment cannot be omitted, not even if it concerns widely accepted drugs. For obvious reasons, the need for postmarketing surveillance of new chemical entities is even stronger.

The serotonin-1 (5HT-1) agonist sumatriptan is a relatively new antimigrainous drug, which has been registered in several European countries and in the United States since 1991 (5-8). It has been demonstrated that use of sumatriptan is highly effective, rapid-acting and well-tolerated in the treatment of acute attacks of migraine (9). Recently, it was stated that sumatriptan has now established itself as the gold standard against which other treatments of acute migraine attacks should be compared (10). After marketing of sumatriptan, reports were published on angina pectoris, cardiac arrhythmias and myocardial infarction, attributed to the use of sumatriptan. A warning statement about drug-related fatalities was added to the labelling of sumatriptan in August 1994 in the USA (11). In this chapter on chest pain and cardiovascular adverse reactions to sumatriptan, we also discuss the pharmacology and efficacy of, and the adverse reactions in general to sumatriptan, the association of migraine and serotonin with cardiovascular disease, and the differential diagnosis of chest pain.

Migraine, cardiovascular disease and serotonin

Migraine is a common neurological disorder (12), that can severely affect quality of life and daily function. The disorder is more common in women and less frequent at older age (13). Several disorders seem to be related to migraine. For example, a higher prevalence of depression in patients with migraine has been demonstrated (14), and in a recently published case-control study an independent association between migraine and the risk of ischaemic stroke in young females was demonstrated (15). Furthermore, a temporal relationship between symptoms of migraine and the menstrual cycle, use of oral contraceptives, pregnancy and menopause has been described (16, 17).

An association between cardiac events and migraine per se was first suggested by

Thomas and Post in 1925 (18). Since then, a number of case reports and case series has been published about the possible relationship between migraine and cardiac events (19-27). Furthermore, reports of patients in whom headache was a presentation of angina pectoris have been described (28-33).

It has been shown that in patients with migraine, Raynaud's phenomenon is more frequent than in a nonmigrainous population (34). Furthermore, an increased prevalence of migraine and Raynaud's phenomenon has been reported in patients with variant angina, and it has been suggested that migraine, Raynaud's phenomenon and variant angina are components of a generalized vasospastic disorder (35, 36). Also in a more recent study, an increased prevalence of migraine was found in patients with primary Raynaud's disease (37). In this study, chest pain was common in patients with primary Raynaud's phenomenon, in particular in those who had co-existing migraine. However, a small study failed to show signs of coronary vasospasm more frequently in patients with common attacks of migraine, when compared to patients with tension headache or to healthy individuals (38). Also another small study did not demonstrate a higher frequency of migraine or Raynaud's phenomenon in patients with variant angina (39).

Serotonin has long been implicated in the pathophysiology of migraine (40). Furthermore, serotonin plays an important role in haemostasis and regulation of cerebral (41), coronary (42) and gastrointestinal (43) blood flows, and has been associated with a variety of diseases and disorders, such as cerebral (44) and coronary (45) vasospasm, Raynaud's phenomenon (46), thromboangiitis obliterans (Buerger's disease) (47), Carcinoid syndrome (48), pre-eclamptic hypertension (49), pulmonary arterial hypertension (50) and essential hypertension (51, 52).

Within the past few years, several advances in the knowledge about vascular serotonin receptors have occurred (53). Firstly, it was observed that the diversity of serotonin receptors within one species is far greater than was previously thought. Secondly, substantial pharmacological variability may occur between species, indicating that studies in animals may be misleading, and cannot be extrapolated to humans. Thirdly, one specific serotonin receptor subtype within a particular species, may have different pharmacological effects, dependent on the specific characteristics of the subject. Endothelial dysfunction, for example, may lead to paradoxical effects on blood vessels. Fourthly, there are regional differences in the distribution of serotonin receptor subtypes, by example, relatively more 5-HT2 receptors in human

temporal arteries when compared to cerebral arteries (54).

The local effects of serotonin on the blood vessels of the tissues in which it is formed and released, illustrate the duality of its vascular effects, causing either constriction or dilatation. In animals with coronary arteries without endothelial damage, serotonin causes a dose related biphasic response characterized by an initial increase in coronary-artery diameter followed by delayed vasoconstriction (55). It has been demonstrated that in beagle dogs, constriction of endothelium-denuded coronary arteries due to serotonin, is mediated by 5-HT_1 -like receptors (56).

In vitro studies demonstrated that serotonin constricts isolated human coronary-artery rings (57). It has been shown that both 5-HT_1-like and 5-HT_2 receptors mediate constriction of human epicardial coronary arteries (58), and that the effects mediated by 5-HT_1-like receptors but not 5-HT_2 receptors are preserved in patients with ischaemic heart disease (59). Recently, it was reported that the relative contribution of 5-HT_1 like receptors in mediating constricting human epicardial coronary arteries predominate over 5-HT_2-like receptors (60). In angiographic studies, serotonin has a vasodilating effect on normal coronary arteries (61). However, patients with coronary artery disease and patients with variant angina pectoris, do not have the normal vasodilator response to intracoronary serotonin, but rather exhibit progressive constriction (62). This phenomenon is comparable with the effects of acetylcholine on normal and diseased human coronary arteries (63). Possibly, the vascular responses to serotonin and acetylcholine are influenced by endothelial (dys-)function (64). Serotonin can stimulate release of the vasodilator nitric oxide (65) from endothelial cells (66), and it has been suggested that serotonin-induced vasodilation of peripheral arteries is mediated by nitric oxide (67). The vasodilation of coronary arteries after exposure to serotonin or acetylcholine may be mediated by the "nitric oxide (NO)-pathway", whereas the vasoconstriction may be an effect of direct stimulation of the smooth muscle cells in the arterial wall by serotonin or acetylcholine (figure 1).

A coronary endothelial vasodilator dysfunction has been associated with factors like aging (68) hypertension and hypercholesterolemia (69) and smoking (70). However, further research is necessary to determine the associations between transmitters such as serotonin and acetylcholine, endothelial dysfunction and nitric oxide in causing cardiovascular disease (71).

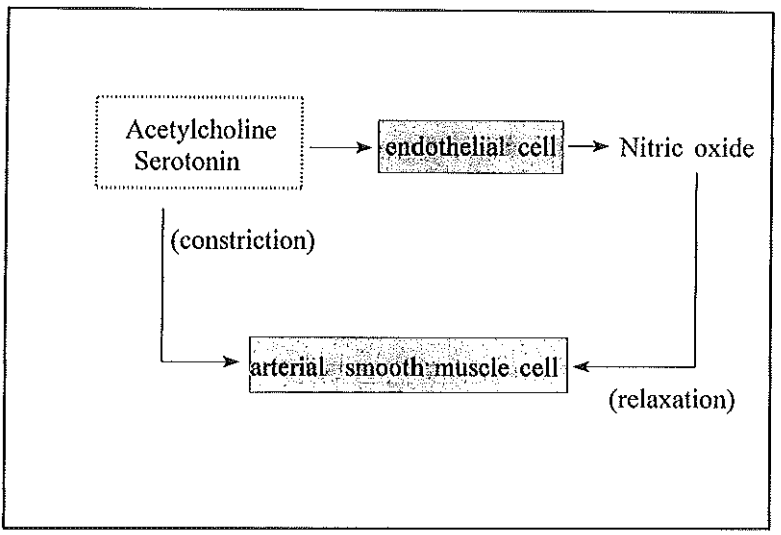

Figure 1 - *Possible effects of transmitters such as serotonin and acetylcholine on arterial smooth muscle cell. Acetylcholine or serotonin are bound to receptors on an endothelial cell, resulting in release of nitric oxide to the smooth muscle cell in the arterial wall, which causes relaxation ('indirect' or 'normal' pathway). Acetylcholine and serotonin act directly on smooth muscle cells of the arterial wall (particularly in case of endothelial dysfunction), and cause vasoconstriction ('direct' or 'diseased' pathway).*

Pharmacology and efficacy of sumatriptan

The pharmacodynamic and pharmacokinetic properties of sumatriptan have been reviewed previously (72, 73). In short, sumatriptan is a potent vascular 5-HT_1 agonist. Radioligand binding studies in animals demonstrated that sumatriptan has high affinity and relative specificity for 5-HT_{1D} receptors, with minor affinity for 5-HT_{1A} receptors. The chemical structure of sumatriptan resembles serotonin (figure 2). Studies of animal and human isolated cerebral blood vessels showed a vasoconstrictor effect of sumatriptan.

At the recommended dose of 6 mg subcutaneously or 100 mg given orally, mean peak plasma concentrations (C_{max}) of 72 μg/L and 54 μg/L sumatriptan were demonstrated after 10 minutes and 1.5 hours respectively. The bioavailability is over 90 percent after subcutaneous administration, but only 14 percent after oral administration. The drug is transformed in the liver to an inactive indoleacetic acid metabolite that is excreted predominantly in the urine. The elimination half-life of sumatriptan is approximately two hours. The presence of a migraine attack does not affect the pharmacokinetic profile.

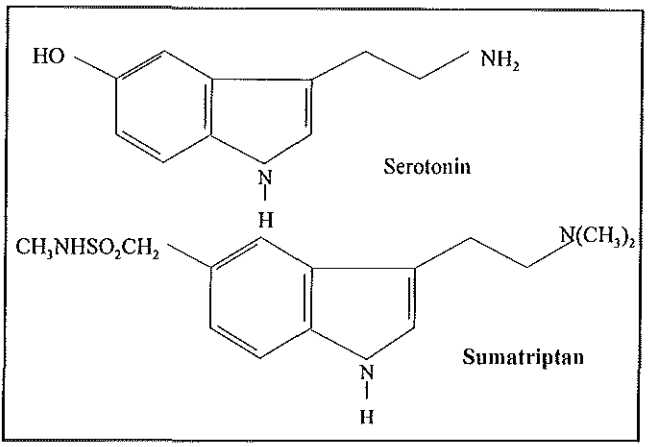

Figure 2 - *Structural formulae of serotonin (5-hydroxytryptamine; 5-HT) and sumatriptan.*

The major clinical trials in which the therapeutic effects of sumatriptan were studied, were conducted using a randomised, double blind, parallel group design, and included a placebo group (74). It was shown in these trials, that sumatriptan is effective in the treatment of acute attacks of migraine as well as cluster headache, and the use is widely advised (75).

Trials in which sumatriptan is compared with active treatment, are less obvious. In a randomized double-blind comparison of sumatriptan and ergotamine, it was demonstrated that use of sumatriptan resulted in a more frequent reduction of migraine (66% vs 48%), but was also associated with a higher recurrence of migraine within 48 hours (76). In a recently published trial, in which sumatriptan was compared with both placebo and aspirin combined with metoclopramide, it was demonstrated that both the combination aspirin and metoclopramide and sumatriptan were more effectiver than placebo, but that aspirin + metoclopramide was as effective as sumatriptan (77).

Adverse reactions attributed to sumatriptan

According to the clinical trials, several adverse effects of sumatriptan occur early after its administration, but are short lasting and mild (78). Typical systemic symptoms are tingling, warm or hot feelings, nausea/vomiting, feelings of heaviness or pressure and flushing. A proportion of the adverse effects can be ascribed to migraine itself. A characteristic feature is the recurrence of headache within 24 hours

after administrating sumatriptan (79). The recurrence of headache after subcutaneous administration of sumatriptan can not be prevented but may be delayed by oral sumatriptan four hours after subcutaneous administration (80). After marketing of the drug, several patients were described who developed an increase in the frequency of migraine attacks with consequent dependence and misuse, after use of sumatriptan (81, 82). Preliminary results of a postmarketing study showed also misuse of sumatriptan by approximately 1% of the consumers (83). Two cases of hemiparesis have been reported, 12 hours and 1 week after subcutaneous administration of sumatriptan, respectively (84). However, according to the time-event relationship, a causal relation between use of sumatriptan and occurrence of the neurologic manifestations in these patients seems to be unlikely (85). The history of a 22-year-old woman was described, who developed a stroke within minutes of a subcutaneous injection of sumatriptan (86). In retrospect, she had received sumatriptan for symptoms of a superior sagittal sinus thrombosis.

Concern has been expressed about the safety in asthmatic patients with migraine (87). An analysis of the sumatriptan safety database of 75 clinical trials, however, showed no increase or change in the adverse reactions reported to sumatriptan in asthmatic patients (88).

Other adverse reactions to sumatriptan recently reported in literature, include ischemic optic neuropathy (89), depression (90) and skin sensitivity (91). There has been discussion about the safety of concomitant use of sumatriptan and selective serotonin reuptake inhibitors (92-94).

Chest pain and cardiac adverse effects of sumatriptan

Shortly after marketing of sumatriptan, the case histories of some patients with typical attacks of angina pectoris were described (95). Moreover, patients with sumatriptan induced chest pain accompanied by electrocardiographic alterations were reported in the United Kingdom (96), Denmark (97) and Sweden (98). Furthermore, cardiac arrhythmias attributed to sumatriptan were reported (99). Subsequently, myocardial infarction was reported in a middle-aged female without a history of cardiovascular disease (100). The reports published in literature are summarized in table 1.

TABLE 1 Cardiac adverse reactions to sumatriptan as reported in literature#

Reference	Age (years)	Gender	Route of administration	Cardiac abnormality	Comments
Brown, et al.[78]	?	?	intravenous	angina pectoris	ST-elevation on ECG
Willet, et al.[96]	47	male	subcutaneous	angina pectoris	ST-elevation on ECG
Abrahamsen et al.[97]	61	male	subcutaneous	angina pectoris	ST depression on ECG
SADRAC* [98]	44	female	subcutaneous	angina pectoris	T-negativety on ECG
Curtin, et al.[99]	42	female	subcutaneous	ventricular fibrillation	within three minutes after first injection
,,	67	male	subcutaneous	ventricular tachycardia	history of mitral valve surgery
Ottervanger, et al.[100]	47	female	subcutaneous	acute myocardial infarction	previously healthy woman
Lippolis et al.[101]	38	female	subcutaneous	angina pectoris	ST-elevation on ECG
Boyd and Rohan[102]	57	female	?	ventricular fibrillation	patient died
Weidmann, et al.[103]	49	female	oral	acute myocardial infarction	coronary angiography normal
Walton, et al[104]	46	female	subcutaneous	angina pectoris	ST-elevation on ECG
Kelly KM[105]	35	female	subcutaneous	cardiac arrest	patient with occult coronary artery disease
O'Connor P, et al$	43	male	oral	acute myocardial infarction	minor irregularities in left coronary artery

Only cardiac effects with electrocardiographic abnormalities

* SADRAC = Sweden Adverse Drug Reaction Advisory Committee

$ O'Connor P, Gladstone P. Oral sumatriptan-associated transmural myocardial infarction. Neurology 1995;45:2274-6.

Although chest symptoms after use of sumatriptan were noted in several clinical studies (106, 107), it is surprising that in some studies, of which one with a study population of more than 600 patients, chest pain due to sumatriptan was not reported (9, 108, 109). Other authors estimated the frequency of the experience of sensations of pressure and tightness in the chest at 3% to 5% of patients treated with sumatriptan (78). The frequency of chest pain attributed to sumatriptan was lower in postmarketing studies based on reports from physicians (87, 110, 111). An increasing incidence of chest symptoms with a higher dose of sumatriptan has been observed (112). During the early evaluation of sumatriptan, when it was administered intravenously, a case of possible myocardial ischemia was recorded: the patient experienced chest symptoms accompanied by ST-segment elevation on electrocardiography (78).

There is some pharmacological evidence for myocardial ischaemia due to sumatriptan. Sumatriptan constricted isolated coronary arteries of beagle dogs (56). Human isolated basilar artery rings constricted in response to sumatriptan (113), as did normal and atherosclerotic human epicardial coronary artery rings from explanted hearts (58-60, 113-116). Furthermore, two small studies, in which patients undergoing diagnostic coronary arteriography were studied, demonstrated a significant reduction in coronary artery diameter after both intravenous and subcutaneous administration of sumatriptan (117, 118). It has been suggested that α-adrenoceptor-mediated vasoconstriction might be part of the mechanism of an increased response of coronary arteries to sumatriptan (119). Other authors suggested that coronary vasospasm after sumatriptan may be caused by (occult) endothelial dysfunction (120). According to the latter mechanism, the coronary effects of sumatriptan may be comparable to those of serotonin itself and acetylcholine (see figure 1). The coronary vasoconstriction after sumatriptan may be more severe in the presence of thromboxane A_2 (121). Another explanation for sumatriptan-induced chest pain was recently reported (122): A small group of volunteers had abnormal oesophageal contractions after a supratherapeutic dose of sumatriptan. However, a previously reported case-history described a patient with sumatriptan associated chest pain without alterations of the pressure in the oesophagus following a sumatriptan injection (98).

Differential diagnosis of chest pain

It is of no doubt, that several patients experience chest pain or typical attacks of

angina pectoris after use of sumatriptan (87, 95, 110, 111). However, an important question is, whether or not this is a symptom of myocardial ischaemia. Classic angina pectoris was initially described by William Heberden in 1772 (123), whereas a variant form was described by Prinzmetal in 1959 (124). Angina pectoris is defined as a discomfort in the chest or adjacent areas, which is caused by myocardial ischemia and is associated with a disturbance of myocardial function but without myocardial necrosis (125). Because the discomfort of angina is not uniform, and other entities can mimic it, the differential diagnosis is often difficult. In general, no cardiac abnormalities can be identified in 10 - 30% of the patients with angina-like retrosternal chest pain (126), and oesophageal abnormalities can be found in 30-60% of these patients (127, 128). Another condition which causes pain that can resemble angina pectoris is a costosternal syndrome (129). Until now, there are only few studies in which sumatriptan related chest pain has been investigated, and it is still not clear what the cause of this chest pain in most patients is, and whether it is associated with cardiovascular risk factors.

Conclusions

Chest pain after use of sumatriptan seems to be a relatively common adverse reaction to this drug. As the reaction may also occur in young adults, it remains to be seen whether all such events can be solely explained by myocardial ischemia (130). On the other hand, since myocardial infarction due to sumatriptan has been demonstrated (100, 103), every case of chest pain after administration of sumatriptan, requires a careful evaluation, with respect to factors such as duration of chest pain, severity of the reaction and the presence of recognized cardiovascular risk factors. Sumatriptan is contraindicated in patients with ischaemic heart disease, (variant) angina pectoris or previous myocardial infarction. Because transient increases in blood pressure have been observed (78), the drug is also contraindicated in patients with uncontrolled hypertension. When these contraindications are taken into consideration and cases of chest pain are carefully evaluated, use of sumatriptan should not be the cause of unduly concern. Even so, however, postmarketing studies have to demonstrate which patients are at risk for developing chest symptoms and, in particular, cardiac adverse reactions. Another topic of interest concerns the exact mechanism of sumatriptan-induced chest pain, especially in those instances in which myocardial ischemia has been excluded.

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PART III

EXPLORATION OF THE PROBLEM

CHAPTER 7

FREQUENCY AND CHARACTER OF ADVERSE REACTIONS TO SUMATRIPTAN

CHAPTER 7.1

ADVERSE REACTIONS TO SUMATRIPTAN AS REPORTED BY DRUG DISPENSING GENERAL PRACTITIONERS

Med Contact 1993;48:169-71.
BMJ 1993;307:1185.

Introduction

Many adverse drug reactions (ADR) are discovered within the first two years of marketing (1, 2), whereas most serious new ADR are detected by single case reports (3, 4). Single case reports and national voluntary reporting schemes give, however, no insight into the frequency or incidence of an ADR.

In May 1991, the serotonin-1 (5HT-1) agonist sumatriptan was registered in The Netherlands for the treatment of acute attacks of migraine and cluster headache. In clinical trials, sensations of pressure and tightness in the chest were experienced by 3% to 5% of patients treated with sumatriptan, but no electrocardiographic (ECG) evidence of cardiac ischemia was demonstrated (5). In reports on postmarketing experience with sumatriptan, angina-pectoris-like pain was noted (6). In the literature, after subcutaneously administered sumatriptan, both chest pain, accompanied by ST elevation in the ECG (7), and an acute myocardial infarction in a previously healthy young female (8) have been reported.

To get more insight into the incidence of cardiovascular adverse reactions due to sumatriptan in postmarketing experience, a study was performed in co-operation with general practitioners with a drug dispensing outlet.

Patients and methods

In July 1992, an enquiry was held among all 687 drug dispensing general practitioners in The Netherlands. These general practitioners are encompassing a catchment population of approximately 1,500,000 inhabitants (10% of the total population in The Netherlands). They were asked to provide the date of birth and gender of every person to whom sumatriptan has been dispensed since it was marketed in May 1991. They were also asked about the route of administration and whether they had observed any adverse reaction in their patients. To avoid bias, in the questionnaire no adverse reactions were mentioned by name. The non-responders received two reminders, 11 and 17 weeks after the first request. Information was entered into a database and results were analyzed using two-tailed chi-square tests and t-tests.

Results

The request yielded a response rate of 86% (589 general practitioners). Of these 589 general practitioners, 474 had dispensed sumatriptan on at least one occasion to a total

of 1727 patients (24% males, 76% females). The general practitioners responded after an average of 26 working days (range 3 - 110 days). The mean age of the responding general practitioners was 47 years. There were no differences in age or gender between responding and non-responding general practitioners. Of the 589 GP, 477 (81%) were of the opinion that drug dispensing GP are suitable for this kind of postmarketing studies, since they have direct access to information on both dispensing drugs and disease data.

Mean age of the 1727 patients was 43.8 years (SD 11.2). Of the 1662 patients (96%) of whom information about the route of administration was available, 683 patients (41%) had taken sumatriptan orally, 842 patients (51%) had administered sumatriptan subcutaneously and 137 patients (8%) had taken the drug by both routes. Of the 1727 patients, 185 patients (10.7 %, 95% CI 9.3% - 12.1%) had reported one or more adverse reactions, which resulted in a total of 247 adverse reactions. Of these patients, 76 % was female. The mean age of the 185 patients was 43.3 years (SD 11.2). The most frequent adverse reactions attributed to the use of sumatriptan were dizziness, nausea or vomiting, drowsiness or sedation, and chest pain, which were reported in 30, 26, 25 and 23 patients, respectively. Cardiovascular adverse reactions are summarized in table 1.

TABLE 1
Cardiovascular adverse reactions to sumatriptan in 1727 patients as reported by 474 general practitioners

Adverse reaction	No	(%)
Chest pain	23	(1.3)
Palpitations	6	(0.35)
Hypertension	2	(0.12)
Syncope	2	(0.12)
Bradycardia	1	(0.06)

Of one patient both chest pain and bradycardia was reported

Chest pain was reported in 19 females and 4 males, of whom 8 patients had taken sumatriptan orally, 11 patients had administered sumatriptan subcutaneously and 4 patients had taken the drug by both routes. Mean age of patients with chest pain was 44.0 years (SD 6.4). The incidence of chest pain attributed to sumatriptan was 1.3%

(95% CI 1.2% - 1.5%). Age, gender and route of administration in these patients did not differ from the other 1718 patients who received the drug ($p > 0.05$).

Discussion

Our postmarketing study yielded a high response rate of 86% of the drug dispensing general practitioners, which is comparable to a study in 1990, in which a cohort of patients exposed to acitretine was traced by all Dutch drug dispensing outlets (hospital pharmacies, community pharmacies and drug dispensing GP) (9).

There were three reasons for performing this study. Firstly, reports of angina pectoris and acute myocardial infarction forced us to estimate the incidence of chest pain under everyday conditions. Secondly, it is the intention to approach all patients who were treated with sumatriptan with a questionnaire to investigate whether non-reported adverse reactions occurred as the incidence of chest pain in our study was lower than in clinical studies (5). However, in order to be recognized as an adverse reaction, patients have to visit their general practitioner and complain about their experiences. If patients fail to do so, the incidence of adverse reactions will be underestimated, in particular for reactions which are not severe. Finally, it is the intention to enrol patients with self-reported chest pain in a more detailed study to assess determinants of this adverse reaction.

In the current study no serious adverse reactions, such as death, myocardial infarction or stroke, were reported. Drug dispensing general practitioners have direct access to data on drug dispensing and disease. Because of the excellent co-operation of drug-dispensing general practitioners, and their direct access to information on both dispensing drugs and disease data on an individual level, we conclude that this group of physicians provides a very useful resource for studying acute problems with adverse reactions to newly marketed drugs.

An angiographic study suggested that sumatriptan may cause coronary artery vasoconstriction (10). The chest pain, as observed in 23 patients (1.3 %) in our study, and similar reports by others (6) highlight the need for an extensive study of this adverse reaction, especially as previous reports demonstrated both ECG abnormalities during chest pain due to sumatriptan (7) and myocardial infarction after chest pain due to sumatriptan (8).

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CHAPTER 7.2

ADVERSE REACTIONS TO SUMATRIPTAN AS REPORTED BY PATIENTS

Eur J Clin Pharm 1994;47:305-9.

Introduction

The serotonin-1 (5HT-1) agonist sumatriptan is a new anti-migrainous drug, which was registered in several European countries and recently also in the United States (1). It has been demonstrated that use of sumatriptan is highly effective, rapid-acting and well-tolerated in the treatment of acute attacks of migraine (2). Migraine is a common neurological disorder (3), that can severely affect quality of life and daily function.

In May 1991 sumatriptan was registered in The Netherlands for the treatment of acute attacks of migraine and cluster headache. However, shortly after marketing of the drug, The Netherlands Centre for Monitoring of Adverse Reactions to Drugs received several reports of typical attacks of angina pectoris after use of sumatriptan (4). The occurrence of these drug-related symptoms was confirmed by other investigators (5). Several reports from clinical trials did not mention chest symptoms after use of sumatriptan (2, 6, 7). Other authors estimated the frequency of the experience of sensations of pressure and tightness in the chest at 3% to 5% of patients treated with sumatriptan (8). Since no electrocardiographic (ECG) evidence of cardiac ischemia could be demonstrated in the clinical trials, the mechanism of these complaints remained unclear. However, after marketing of the drug, two patients were reported who developed chest pain, accompanied by serious ST abnormalities in the ECG, after sumatriptan 6 mg subcutaneously (9, 10), a young female developed an acute myocardial infarction after administration of subcutaneous sumatriptan (11), and two cases were reported of serious ventricular arrhythmias after use of this drug (12). Furthermore, two small angiographic studies demonstrated significant reduction of the coronary artery diameter in humans after both intravenous and subcutaneous administration of sumatriptan (13, 14).

The postmarketing experience with sumatriptan forced us to perform a pharmacoepidemiological study, to get more insight into the incidence and the character of (cardiovascular) adverse reactions due to sumatriptan.

Patients

In July 1992, an enquiry was held among all 687 drug dispensing general practitioners in The Netherlands. They were asked to provide the date of birth and gender of every person to whom sumatriptan had been dispensed since it was marketed in May 1991. Subsequently, the general practitioners who had dispensed sumatriptan, were asked to send a questionnaire to be completed at home, to the patients who had used

sumatriptan. The questionnaires were sent via the general practitioners in prestamped envelopes with a standard letter from our Centre. In the questionnaire, the patients were asked whether they had indeed used sumatriptan, and if so, whether they had observed possible adverse reactions after use of sumatriptan. Furthermore they were asked about the temporal relationship between administration of sumatriptan and the observed adverse reactions, and whether the possible adverse reactions recurred after rechallenge. Finally, they were asked whether they used other medication, and if so, what the indication was. To avoid bias, in the questionnaire no adverse reactions were specified, and the general practitioners were not informed regarding our particular interest in chest pain. Chest pain was defined as pain or pressure feelings, located substernally or at the chest. The enquiry was sent to the patients in December 1992. The physicians of whom no patients had responded, received a reminder in March 1993. Patients were classified as being diabetic if they used anti-diabetic drug therapy. Patients were considered as hypertensive if they were currently taking antihypertensive medication for the indication hypertension. Obstructive lung disease was assumed to be present if patients were using lung medication (mainly inhaled ß-agonists and corticosteroids) for one or more of the indications asthma, chronic bronchitis or emphysema.

Data analysis

Differences between group means were tested by Student's t test. A chi-square test was used to assess differences between proportions, with use of Fisher's exact test if there was an expected cell value of less than 5. 95% Confidence intervals of proportions were calculated on the basis of an assumed binomial distribution (15). All calculated P values are two-tailed. Statistical significance was defined as a two-sided p-value of less than 0.05. Relative risks were calculated with 95% confidence intervals (95% CI).

Results

The request to the 687 drug dispensing general practitioners yielded a response rate of 86% (589 general practitioners). Of these 589 general practitioners, 474 had dispensed sumatriptan on at least one occasion to a total of 1727 patients (24% males, 76% females). During the study period, seven patients were lost to follow up, all by a change of residence. Of the 1720 remaining patients, 1202 (70%) returned the questionnaire.

TABLE 1
General characteristics of the study population

Characteristic	Patients (number)	(%)
Males	284	(24)
Females	918	(76)
Mean age (years)	43	(11*)
Obstructive lung disease	28	(2.4)
Hypertension	49	(4.1)
Diabetes Mellitus	4	(0.3)

* Standard Deviation

Basic characteristics of this study population are summarized in table 1. It concerned 284 males with a mean age of 44 years and 918 females with a mean age of 43 years. Fifteen patients (two males, thirteen females) had not yet used sumatriptan, and were excluded from further analyses.

The most commonly suspected adverse reactions reported by the 1187 patients who had used sumatriptan, are shown in table 2. Most frequent were paraesthesia (139 patients, 95% CI 9.9% - 13.5%) and dizziness (96 patients, 95% CI 6.5% - 9.7%). Chest pain after use of sumatriptan was reported by 94 patients (7.9 %, 95% CI 6.4% - 9.4%) with a mean age of 41 years (not significantly different from the total study population), ranging from 19 to 69 years. This subgroup comprised 13 males (4.6%) and 81 females (9.0%), resulting in a relative risk of females compared to males of 1.9 (95% CI 1.1 - 3.4). 81 of these patients (= 86%) experienced chest pain within one hour after administration of sumatriptan, and in 83 patients (88%) the adverse reaction occurred more than once. Of the 94 patients who had experienced chest pain after use of sumatriptan, 6 patients (6.4%) had hypertension, a proportion that was not significantly different from the total study group. Dyspnea after use of sumatriptan was reported by 26 patients (2.2%, 95% CI 1.4% - 3.0%), 21 women and 5 men with an average age of 39 years. Of the 26 patients, 24 patients (92%) experienced dyspnea within one hour after administration of sumatriptan, whereas in 22 patients (85%) the reaction recurred after rechallenge. Of the 28 patients with obstructive lung disease, 3 patients experienced dyspnea after use of sumatriptan, as compared to 23 in the other patients, resulting in a relative risk of 5.4 (95% CI 1.7 - 16.9).

TABLE 2

Frequency of the most common adverse reactions (frequency >2%) attributed to sumatriptan as reported by 1187 consumers

Adverse reaction	Patients	Frequency (%)	95% confidence interval
Abdominal pain	31	(2.6)	1.7 - 3.5
Chest pain	94	(7.9)	6.4 - 9.4
Dizziness	96	(8.1)	6.5 - 9.7
Drowsiness/sedation	83	(7.0)	5.5 - 8.5
Dyspnea	26	(2.2)	1.4 - 3.0
Fatigue	54	(4.6)	3.4 - 5.8
Feeling of heaviness	95	(8.0)	6.5 - 9.5
Flushing	60	(5.1)	3.8 - 6.4
Headache	37	(3.1)	2.1 - 4.1
Injection site reaction	35	(3.0)	2.1 - 4.0
Muscle pain	28	(2.4)	1.5 - 3.3
Nausea and/or vomiting	87	(7.3)	5.8 - 8.8
Palpitations	33	(2.8)	1.9 - 3.7
Paraesthesia	139	(11.7)	9.9 - 13.5
Pressure in throat	39	(3.3)	2.3 - 4.3

Some patients reported more than one adverse reaction

Discussion

Postmarketing studies on adverse reactions to drugs can provide information not available from premarketing studies, mainly because premarketing studies are necessarily limited in size and often exclude important subgroups of patients. One of the most worrying findings in our study was the high frequency of chest pain (7.9 %) after use of sumatriptan. According to both the close temporal relationship between intake of sumatriptan and chest pain, and the occurrence of the same symptoms after renewed exposure (positive rechallenge) in many patients, a causal relationship between use of sumatriptan and chest pain is probable in most of the patients. Another interesting adverse reaction is dyspnea, as reported by 26 patients (2.2%).

To investigate adverse drug reactions via drug dispensing general practitioners by sending a questionnaire via them to the consumers of a specific drug in their practices, is a unique and novel approach. By reason of stringent privacy rules in The Netherlands (16), we sent the questionnaires not directly to the patients, but asked the

general practitioners to do so. The 687 general practitioners with a drug dispensing outlet in The Netherlands encompass a catchment population of approximately 1,500,000 inhabitants (10% of the total population in The Netherlands). For a physician-based study, 86% cooperation is in fact remarkably high, compared to studies as by example in the United Kingdom (17), and offers the opportunity for future studies. The fact that the drug dispensing general practitioners register both morbidity and drug dispensing, makes them a very useful source of information for studying ad hoc problems with newly marketed drugs. Although the catchment population of the drug dispensing general practitioners may not be representative of the total population in every aspect, we think that it is regarding the determinants in our study.

We did not include any reference group in our study for two reasons. Firstly, we were mainly interested in adverse reactions with a close temporal relationship with use of sumatriptan, and a relatively low background incidence in the middle-aged. As it is unlikely that many reference patients would have developed chest pain in the same short periods in which the index patients were exposed, a reference group was not deemed necessary. Secondly, as sumatriptan is contraindicated in patients with angina pectoris and variant angina, such patients might have been overrepresented in a reference group of patients with migraine.

The assessment of the likelihood of a causal relationship between intake of sumatriptan and several reported reactions was difficult. Reactions such as nausea or headache could well have also been symptoms of the underlying disease, migraine or cluster headache.

We have no direct data on the mechanism of the chest pain observed in our study group, but we can not exclude a cardiac origin. It is possible that in some patients the chest symptoms were caused by myocardial ischemia, due to sumatriptan induced coronary artery spasm. It is well known that coronary artery spasm can be induced by several drugs, including the antimigrainous drugs ergotamine and methysergide (18 - 20). Some evidence for this hypothesis with regard to sumatriptan can be found in the literature. Human isolated basilar artery rings constricted in response to sumatriptan (21), as did normal and atherosclerotic human epicardial coronary artery rings from explanted hearts (22, 23). Furthermore, two small studies, in which patients undergoing diagnostic coronary arteriography were studied, demonstrated a significant reduction in coronary artery diameter after both intravenous and subcutaneous

administration of sumatriptan (13, 14). Even during the early evaluation of sumatriptan, when it was administered intravenously, a case of possible myocardial ischemia was recorded: the patient experienced chest symptoms accompanied by ST-segment elevation on electrocardiogram (8). After marketing, several case reports on cardiac disturbancies due to use of sumatriptan were published (9-12). However, despite these indications for a cardiac origin of the chest symptoms, we can not exclude an other mechanism. In general, no cardiac abnormalities can be identified in 10 - 30% of the patients with angina-like retrosternal chest pain (24), and oesophageal abnormalities can be found in 30-60% of these patients (25, 26).

The frequency of chest pain attributed to sumatriptan is remarkably high in our study. Although the response of 70% of the patients to the questionnaire was high, the 30% of patients who did not respond to the questionnaire might have influenced the results. However, even if the 516 non responding patients comprised not one single case of chest pain attributable to sumatriptan, the frequency would have exceeded 5%. It is surprising that in several studies, of which one with a study group of more than 600 patients, chest pain due to sumatriptan was not reported (2, 6, 7). Furthermore, the frequency of chest pain attributed to sumatriptan in our study is higher than in several clinical trials (27, 28), and in postmarketing studies based on reports from physicians (5, 29). In trials, a low incidence may be explained by rigorous patient selection with exclusion of patients with a history of angina pectoris and variant angina. Our postmarketing study in patients gave a much higher figure of chest pain than our study based on data from general practitioners (29). Apparently, cases of chest pain are easily missed unless the patient is specifically asked for adverse reactions. It cannot be excluded that in some patients in our study, chest pain was induced by concomitant use of ergot alkaloids.

It is not yet clear whether the effects of the serotonin-1 agonist sumatriptan on coronary-artery dimensions differ between patients with and without coronary atherosclerosis. Serotonin itself has a vasodilating effect on normal human coronary arteries, but when the endothelium is damaged, as in coronary artery disease, serotonin has a direct, unopposed vasoconstricting effect (30), and in patients with variant angina it may cause occlusive coronary artery spasm (31). It has been suggested that in patients with ischaemic heart disease, constriction of coronary arteries are mediated in particular by 5-HT_1-like receptors (32). Some clinical studies suggested a dose relationship with chest symptoms (33). Another reason why the

frequency of chest pain in our study was higher, may be the fact that the patients in our study had used sumatriptan on several occasions during the study period. However, our study gives no insight into the incidence per administration of sumatriptan.

Dyspnea as an adverse reaction of sumatriptan has been previously reported (5), but the relationship with asthma has been disputed (34). We considered chronic use of lung medication for one or more of the indications asthma, chronic bronchitis or emphysema as a reliable marker of current obstructive lung disease. An association of dyspnea attributed to sumatriptan with obstructive lung disease, was demonstrated in our study. The mechanism of this adverse reaction is unclear, but an increase of both the pulmonary arterial pressure and pulmonary wedge pressure due to sumatriptan has been demonstrated (13, 14). Furthermore, serotonin itself is a bronchoconstrictor, although this para-sympathetic effect is in particular mediated by stimulation of 5-HT_2 receptors (35). It is, however, not clear whether the dyspnea in our patients was due to pulmonary congestion, bronchospasm or another mechanism.

Based on the results of this study, and other postmarketing reports, we advise cautious use of sumatriptan, in particular in patients who experience chest pain after use of this drug. In our opinion, every patient with chest pain suggestive of angina pectoris, drug-induced or not, requires a careful evaluation, including a history, physical examination, electrocardiogram, and simple laboratory tests (36). Furthermore, we recommend further investigations of the mechanism of the chest symptoms attributed to sumatriptan. It may be useful to assess risk factors for the development of chest pain due to sumatriptan. Finally, we conclude that sending a questionnaire to patients via their (drug dispensing) general practitioner is a very useful source of information for studying ad hoc problems with newly marketed drugs.

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CHAPTER 7.3

DIFFERENCES IN PERCEIVED AND PRESENTED ADVERSE REACTIONS TO DRUGS IN GENERAL PRACTICE

submitted

Introduction

Drugs are increasingly used, and drug use has become an economical factor of growing importance in health expenditure. In comparison with other therapeutic interventions, medications commonly are effective, cost-effective, and safe (1). However, although a new drug is tested nowadays in a number of trials in the premarketing stage, its safety profile has not yet been fully elucidated at the time a drug is marketed.

Spontaneous reporting schemes are considered good tools for the rapid identification of new and rare adverse reactions (2). Although single case-reports are frequently criticized as being not substantial enough to reveal a new drug-safety problem, the usefulness of case reports has been demonstrated by Venning, showing that most of the major adverse drug reactions were first described in case reports (3). However, spontaneous reporting has the disadvantage of selective reporting, false-positive reporting and underreporting, and valid estimates of the frequency or incidence of an adverse reaction may not be obtained.

An approach to determine the frequency of adverse reactions to a specific drug is the Prescription Event Monitoring (PEM) scheme in the UK (4). A number of studies based on this system has been published (5-8). A potential limitation is that only medical events registered by the general practitioner (GP) can be studied with this approach.

In a postmarketing cohort study on adverse reactions to sumatriptan, performed with assistance of drug dispensing GPs in The Netherlands, we compared the frequency of adverse reactions as reported by the GP with the adverse reactions reported by patients to this drug.

Methods & data analysis

In May 1991, sumatriptan was registered in the Netherlands for the treatment of acute attacks of migraine and cluster headache. Approximately one year after registration, in July 1992, an enquiry was held among all 687 drug dispensing GPs in The Netherlands. They were asked to provide the date of birth and gender of every person to whom sumatriptan had been dispensed since it was marketed in May 1991. They were also asked about the route of administration and whether they had observed any adverse reaction in their patients. To avoid bias, no adverse reactions were specifically mentioned in the questionnaire. The non-responders received two reminders, 11 and

17 weeks after the first request. Subsequently, the GPs who had dispensed sumatriptan, were asked to send a questionnaire to be completed at home, to the patients who had used sumatriptan. The questionnaires were sent via the GPs in prestamped envelopes with a standard letter from our centre. In the questionnaire, the patients were asked whether they had indeed used sumatriptan, and if so, whether they had observed any adverse reaction after use of sumatriptan. Similarly, in this questionnaire, no adverse reactions were specifically mentioned. The enquiry was sent to the patients in December 1992. Physicians of whom no patients had responded, received a reminder 11 weeks after the first request. Several details of the study have been published previously (9, 10).

Differences between group means were tested by Student's t test. A chi-square test was used to assess differences between proportions, with use of Fisher's exact test if there was an expected cell value of less than 5. 95% Confidence intervals (95% CI) of proportions were calculated on the basis of an assumed binomial distribution (11). All calculated P values are two-tailed, with statistical significance defined by a two-sided p-value less than 0.05.

Results

General characteristics of the study are summarized in the table.

TABLE
General characteristics of the study

Characteristic	Number (%)
Questionnaires to the GPs	
Total GPs with drug-dispensing outlet in The Netherlands	687
Responding GPs	589 (86)
GPs who had dispensed sumatriptan	474 (80)
Questionnaires to the patients	
Total patients using sumatriptan	1727
Lost to follow-up during study	7
Responding patients	1202 (70)

The request to the drug dispensing GPs yielded a response rate of 86% (589 GP's). There was no difference in age or gender between responding and non-responding GPs. Of the 589 responding GPs, 474 had dispensed sumatriptan on at least one occasion to a total of 1727 patients (24% males, 76% females). The average number of patients per GP to whom sumatriptan had been dispensed was 3.9 (range 1 - 29, median 3). Of the 1727 patients, 185 patients (10.7 %, 95% CI 9.3% - 12.1%), of whom 76% was female, had reported one or more adverse reactions, which resulted in a total of 247 adverse reactions. The mean age of the 185 patients was 43.3 years (SD 11.2). The most frequent adverse reactions attributed to the use of sumatriptan as reported by the GP's were dizziness in 30 (1.7%), nausea or vomiting in 26 (1.5%), drowsiness or sedation in 25 (1.4%), and chest pain in 23 (1.3%) patients.

During the study period, seven patients were lost to follow up, all by a change of residence. Of the 1711 remaining patients, 1202 (70%) returned the questionnaire. The velocity of response of GPs and patients is depicted in figure 1.

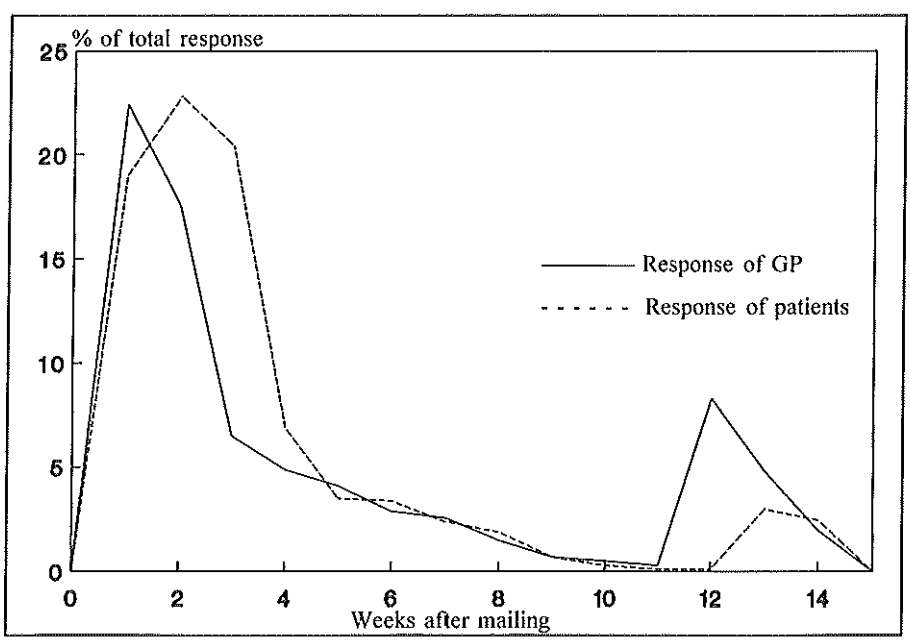

Figure 1 - *Velocity of response to the questionnaires. The patient questionnaires (- - - - - -) were sent via their GP. 11 weeks after the first questionnaires, a reminder was sent.*

Fifteen patients (two males, thirteen females) had not yet used sumatriptan, and were

excluded from further analyses. 905 patients (76%) reported a good efficacy of sumatriptan, whereas 67 patients (5.6%) reported no beneficial effect of sumatriptan on their complaints. Of the 654 patients (54%) who reported an adverse reaction, 369 (56%) observed the adverse reaction each time they administered sumatriptan. The most commonly suspected adverse reactions reported by the 1187 patients who had used sumatriptan, were paraesthesia in 139 patients (95% CI 9.9% - 13.5%) and dizziness in 96 patients (95% CI 6.5% - 9.7%). Chest pain after use of sumatriptan was reported by 94 patients (7.9 %, 95% CI 6.4% - 9.4%).

Neither the GPs nor the patients reported serious adverse reactions such as death or hospital admission. A marked difference was present in frequency of adverse reactions as reported by patients and as reported by their GPs. Any adverse reaction was reported by 654 patients (54%), while according to the GPs this occurred in only 185 patients (11%, $p < 0.001$). Of the 185 patients on whom the GPs reported an adverse reaction, 52 patients (28%) had more than one adverse reaction, whereas of the 654 patients 285 (44%) reported more than one adverse reaction ($p < 0.001$). Differences between the most commonly reported adverse reactions to sumatriptan by GPs and patients are depicted in figure 2.

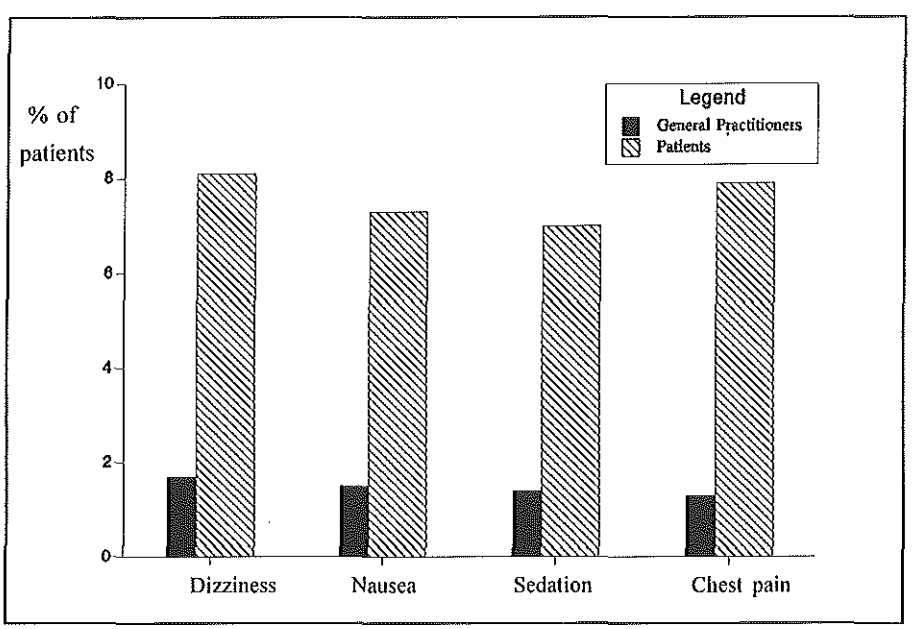

Figure 2 - *Differences in frequency of the most common adverse drug reactions reported by general practitioners and by patients*

Although it was not possible to link the results of the two questionnaires in each patient on an individual level, there was clearly a marked differential reporting between patients and GP's. Of the 30 patients on whom the GP reported dizziness, two patients reported paraesthesia and two other patients reported flushing. Of the 26 patients with, according to their GP, vomiting/nausea after use of sumatriptan, three patients reported chest pain, one patient dysphagia, and three patients dizziness. Of the 23 patients with, according to their GP, chest pain after use of sumatriptan, one patient reported hypertension, one dyspnoea and one palpitation.

Discussion

To investigate adverse drug reactions via drug dispensing GPs by sending questionnaires both to the GPs and to their patients using a specific drug, is a novel approach. In the Netherlands, one of the specific tasks of general practice is the role of gatekeeper (12), observing both complaints which do not require entry to secondary care services and complaints which are immediately presented to secondary services. The 687 GPs with a drug dispensing outlet in The Netherlands encompass a catchment population of approximately 1,500,000 inhabitants (10% of the total population in the Netherlands). Because they register both morbidity and drug dispensing, they are a useful source of information for studying ad hoc problems with newly marketed drugs. The fact that the patients were a little slower in responding to the questionnaires than the GPs, can be explained by the fact that mailing of questionnaires via their GP introduced an additional time delay.

Although drug dispensing GPs are mainly located in rural areas without a community pharmacist, different from the U.S. (13) in the Netherlands only moderate differences exist between cities and these rural areas regarding population parameters, disease frequencies and health care coverages.

One explanation for a difference in the reported ADRs by patients and by their GPs may be that for logistic reasons there was a few months time period between mailing the two questionnaires. We first had to know how many patients on sumatriptan each GP had, in order to send the GP the appropriate number of prestamped envelopes with questionnaires. Because of stringent privacy rules in The Netherlands (14), we sent the questionnaires not directly to the patients, but asked the GPs to do so. Still it seems unlikely that the somewhat longer use of sumatriptan explains the so much higher number of patients with adverse reactions, as at least

56% of the patients reported that they observed the adverse reaction each time they used sumatriptan, or reported an adverse reaction already at first intake. Furthermore, in our study, more frequent use of sumatriptan was not associated with a higher frequency of reported adverse reactions.

Another reason for the differences between reporting by GPs and patients may be that only non-serious adverse reactions were reported in this study. For an adverse reaction to be detected by their GP, patients have to visit the GP and complain about their experiences. If patients do not do so, the incidence of adverse reactions will be underestimated in postmarketing studies based on reports of GPs, in particular when they are not severe, albeit that reactions, sometimes considered as non-serious by patients (such as chest pain by sumatriptan) can result in serious, life-threatening situations (15).

The metaphor 'iceberg of morbidity' is used for presented morbidity as a fraction of the total morbidity (16). Knowledge of the magnitude of this 'iceberg' is important. It has been suggested that approximately 10% of all experienced complaints are reported to the GP (17, 18). In our study, any adverse reactions was reported by 54% of the patients, whereas the GP's had registered it on 11% of the patients, suggesting a sensitivity of approximately 20%. So it seems to be, that adverse drug reactions might be more readily presented to the GPs or registered by the GPs than health complaints in general.

To detect the frequency of complaints of patients by review of medical records of GPs, it is not only necessary that the patients consult their GP, but also that the GP records it in the medical file. For example, it has been demonstrated that review of the medical record about advice on smoking and alcohol given by the GP, will lead to significant underestimation of the frequency of advice given, as many advices are not recorded (19).

Although the response to the questionnaire by 70% of the patients was high, the non-response by 30% of the patients could have influenced the results. However, even if none of these patients observed an adverse reaction, the frequency of reported adverse reactions by the patients is still significantly higher than the frequency reported by their GPs.

Prescription-event monitoring (PEM) was developed in 1980 by the Drug Safety Research Unit (DSRU) in the UK, as a novel national approach for detecting adverse events occurring during drug treatment (4). In PEM the patient, drug and doctor are

identified from the prescriptions gathered by the Prescription Pricing Authority (PPA). Thereafter, simple questionnaires (green forms) are sent to the prescribing doctors 6 to 12 months after the prescription has been written, asking for all 'events' that happened since the prescription and some additional information, such as age and diagnosis. And although the majority of reported events are in fact no adverse drug reactions (but rather related to the disease being treated or co-incidental), it appears to be a useful approach. However, our study shows that the frequency of adverse reactions may be considerably underestimated if only GP records are used. An example of this phenomenon in PEM was the estimated frequency of cough with enalapril (20, 21) as discussed by Waller (22).

Because of the excellent co-operation of drug-dispensing GPs, their direct access to information on both dispensing drugs and disease data on an individual level, and the possibility to contact patients using a specific drug directly via them, we conclude that this group of physicians provides an important resource for studying acute problems with adverse reactions to newly marketed drugs. Patients experience adverse reactions significantly more frequently than are observed by their GPs, and postmarketing studies based on data from GPs, may result in a considerable underestimation of the cumulative incidence of adverse reactions.

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CHAPTER 8

DETERMINANTS OF OVERUSE OF SUMATRIPTAN

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Introduction

The serotonin-1 agonist sumatriptan is a relatively new drug used in the treatment of acute attacks of migraine and cluster headache (1). Adverse drug reactions attributed to sumatriptan in the postmarketing period include acute myocardial infarction (2, 3), depression (4), and skin reactions (5).

A characteristic feature is the recurrence of headache within 24 hours after administrating sumatriptan (6). After marketing of the drug, several patients were observed who developed an increase in the frequency of migraine attacks with consequent dependence and misuse, after use of sumatriptan (7-9). Preliminary results of a postmarketing study based on pharmacy records also showed overuse of sumatriptan by approximately 1% of the consumers (10).

We investigated the frequency of use and overuse of sumatriptan in a postmarketing cohort study, and explored characteristics of patients reporting overuse.

Methods and data analysis

In May 1991, sumatriptan was registered in the Netherlands for the treatment of acute attacks of migraine and cluster headache. In July 1992, an enquiry was held among all 687 drug dispensing General Practitioners (GP) in The Netherlands, to provide the date of birth and gender of every person to whom they had dispensed sumatriptan since marketing. Subsequently, they were asked to send a questionnaire to be completed at home, to the patients who had used sumatriptan. The questionnaires were sent via the GP in prestamped envelopes with a standard letter from our centre. In the questionnaire, the patients were asked whether they had indeed used sumatriptan, and if so, how often sumatriptan was used, what the efficacy of sumatriptan was and whether they had observed any adverse reaction after use of sumatriptan. In the questionnaire, no adverse reactions were mentioned by name. Some details of the study have separately been published previously (11, 12).

Use of sumatriptan was classified into five groups: < 1, 1-10, 11-20 and 21-30 administrations per month, and a fifth group of patients who reported daily sumatriptan use or more than 10 administrations each week. Patients in the latter group were regarded as 'over-users'.

Differences between group means were tested by Student's t test. A chi-square test was used to assess differences between proportions, with use of Fisher's exact

test if there was an expected cell value of less than 5. All calculated P values are two-tailed. Statistical significance was defined as a two-sided p-value of less than 0.05. Relative risks (RR) were calculated with 95% confidence intervals (95% CI).

Results

Of the 589 Dutch general practitioners (86%) who participated in this study, 474 had dispensed sumatriptan on at least one occasion to a total of 1727 patients (24% males, 76% females). During the study period, seven patients were lost to follow up, all by a change of residence. Of the 1720 remaining patients, 1202 (70%) returned the questionnaire. Of 952 (79%) of these patients full details of their sumatriptan intake were available.

General characteristics of the study population are summarized in table 1.

TABLE 1

General characteristics of 952 patients with information on sumatriptan consumption

Characteristic	Number or mean
Age (years)	44 (SD: 11)
Males	224 (24%)
Reported efficacy of sumatriptan	
- Good	729 (77%)
- Moderate	77 (8%)
- Poor	55 (6%)
- Not reported	91 (9%)
Route of administration	
- Oral	318 (33%)
- Subcutaneous	458 (48%)
- Both routes	82 (9%)
- Missing	94 (10%)
Average duration of headache complaints (years)	21 (SD: 13)
Any adverse reaction	529 (56%)
Headache after sumatriptan	34 (4%)

SD = Standard Deviation

A total of 34 patients (4%) reported (rebound) headache due to use of sumatriptan, 6

males and 28 females (gender distribution not significantly different from the other patients). In figure 1 the consumption of sumatriptan is depicted.

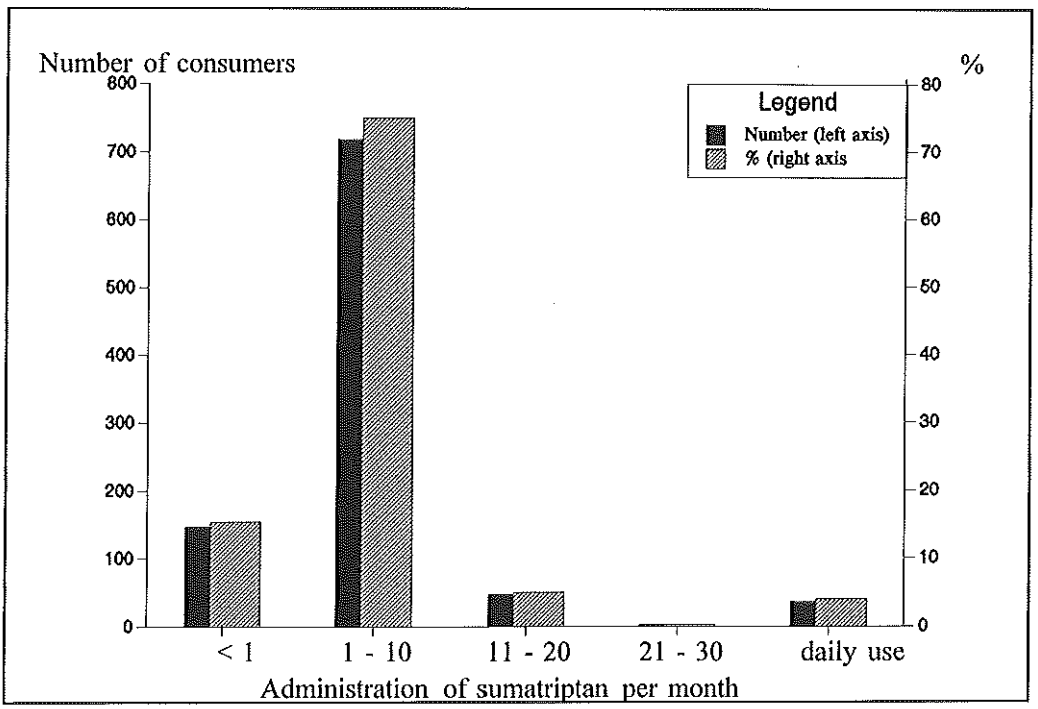

Figure 1 - *Consumption of sumatriptan in 952 patients of drug dispensing general practitioners. Consumption was classified into five groups: < 1, 1-10, 11-20 and 21-30 administrations per month and a highest group of patients who reported daily use sumatriptan or more than 10 administrations each week.*

Most patients (718, 75%) consumed sumatriptan 1-10 times each month. 36 patients (4%, 95% CI 2.8%-5.2%) used sumatriptan daily or more than 10 times each week, and were regarded as 'over-users', of whom 17 patients used sumatriptan once every day, 14 patients took sumatriptan two times each day, 3 patients three times each day, and 2 patients reported that they used sumatriptan more than 10 times each week (not specified per day). Of the 36 patients, 13 (36%) were males, which was more than in the patients who used less than 10 consumptions of sumatriptan per month (192 males, relative risk 1.9, 95% CI 1.0-3.7). There were neither differences

in age, duration of headache complaints nor in route of administration between the five groups of intake. Of the 36 patients who took sumatriptan daily or more than 10 times each week, 6 patients reported the efficacy of sumatriptan as poor, compared to 49 patients of the 916 patients who used sumatriptan less than 30 times each month (RR=3.3 95% CI 1.4-7.5). One or more adverse reactions were reported by 18 patients (50%) of the over-users, compared to 511 patients (56%) of the others (p=0.5). Headache as an adverse reaction to sumatriptan was reported by 1 'over-user' (2.8%), compared to 33 patients in the other groups (3.6%; not significantly different).

Discussion

We found that a small proportion (4%) of the consumers used sumatriptan daily or more than 10 times each week. Since sumatriptan is a drug for acute attacks of migraine or cluster headache, and not for prophylactic use, we regarded this group as 'over-users'. It has previously been recommended that patients with headaches should never take analgesics every day, and that ergotamine should not be taken more than 10 times a month (13). Overuse was in our study significantly more frequently observed in males, and in patients who reported the efficacy of sumatriptan as poor.

Analyses of medication consumption based on dispensing or reimbursement data have two major limitations: 1) no information is available on non-compliance; and 2) no information is available on drugs which are bought 'over the counter'. Furthermore, these pharmacy records based studies do not provide direct information on efficacy, clinical events or adverse drug reactions observed by consumers. In our postmarketing study we used information on drug-use obtained directly from consumers. Because of strict privacy rules in The Netherlands, we could not validate these data by evaluating the records of the drug dispensing general practitioners, We think, however, that these data give good insight into the consumption of sumatriptan in these patients, although negative misclassification may exist.

Several explanations for over-use may be considered. The most important reason for more frequent use of sumatriptan is possibly a higher attack rate of migraine or cluster headache, but information on attack rates was not available in our study. However, it was demonstrated in our study that an observed low efficacy of sumatriptan accompanied more frequent over-use. Previously, headache recurrence

after sumatriptan use was reported (14-16). It has been suggested that the rebound headache may be the underlying mechanism of over-use of sumatriptan (10, 15). However, the (rebound) headache was not associated with over-use in our study. Another explanation, more compatible with our data, is that some patients use sumatriptan in too low a dose or that in some patients the activity of sumatriptan is too short.

In conclusion, we found that 4% of patients consuming sumatriptan, used this drug daily or more than 10 times per week. Over-use was associated with a reported poor efficacy of sumatriptan and with male gender, but not with (rebound) headache after sumatriptan. Drug consumption patterns of sumatriptan have to be evaluated in all patients, but in particular in patients who report low efficacy of sumatriptan.

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CHAPTER 9

CHARACTERISTICS AND DETERMINANTS OF SUMATRIPTAN ASSOCIATED CHEST PAIN

Submitted

Introduction

The serotonin-1 (5HT-1) agonist sumatriptan is a relatively new anti-migrainous drug (1, 2). There are observations suggesting that sumatriptan also has cardiac side effects (3). Both intravenous and subcutaneous administration of sumatriptan result in a significant reduction in coronary artery diameter (4, 5), an effect which can be reversed by administration of glyceryl trinitrate (6). Furthermore, several case reports have been published in the medical literature concerning myocardial ischaemia and myocardial infarction, after administration of sumatriptan (3, 7-11).

Chest pain associated with intake of sumatriptan has been estimated to occur in up to 8% of patients treated with sumatriptan (12-16). To investigate chest pain attributed to sumatriptan in more detail, we performed a postmarketing cohort study. Primary aims of the study were to identify characteristics and independent determinants of chest pain in relation to sumatriptan use.

Patients and methods

Setting

In The Netherlands, a cohort study on adverse reactions to sumatriptan was performed with assistance of drug dispensing general practitioners (GPs), as described in detail previously (13, 16). In short, with assistance of 589 drug dispensing GPs in The Netherlands (86%), 1727 patients who had received sumatriptan were traced in July, 1992. Via their GP, a questionnaire about use of sumatriptan, adverse reactions and use of other medication was sent to these patients in December 1992. To avoid bias, in the questionnaire no adverse reactions were specified, and the GPs were not informed regarding the particular interest in chest pain. During the study period, seven patients were lost to follow-up. Of the 1720 remaining patients, 1202 (70%) responded to the questionnaire, of which 1187 had indeed used sumatriptan. Chest pain, defined as pain or pressure feelings, located substernally or at the chest, was reported by 94 patients (7.9 %, 95% CI 6.4% - 9.4%), and according to the close temporal relationship with intake of sumatriptan and the reported positive rechallenge in many, a causal relationship was probable in these patients. These 94 patients were traced from 91 GPs. The cohort for the present study consisted of all patients from these 91 GPs who had ever used sumatriptan in the study period.

Patients

The study protocol was approved by the Medical Ethics Committee of the University Hospital 'Dijkzigt' Rotterdam (MEC 140.112/1994/168), and written informed consent was obtained from all patients (n=347, 95%) who were visited at home.

Patients were eligible for the study if they were consumers of sumatriptan who reported sumatriptan associated chest pain in the questionnaires. Patients who reported chest pain both at the "open question" in the first questionnaire, and at a specific question in a second questionnaire which had been sent several weeks later were classified as patients with "probable" sumatriptan-induced chest pain. Patients who had not reported sumatriptan associated chest pain at the "open question" but only at the specific question, were classified as patients with "possible" sumatriptan-induced chest pain. Location of the pain or pressure sensations in association with intake of sumatriptan, had to be at the sternum, left thoracic wall or left shoulder. Chest pain had to occur within 6 hours after administration of sumatriptan. Determinants of probable and possible chest pain were analyzed both together and separately. A reference group was formed by consumers of sumatriptan with the same GP as the case, who reported neither at the open question nor at the specific question any type of chest pain or pressure after use of sumatriptan. The total study population consisted of 420 patients on sumatriptan, from 91 drug dispensing GPs.

Data collection and measurements

All subjects received a (second) detailed questionnaire. Non-responders received a reminder after three weeks. Furthermore, the study population was visited at home by the first author for a specific interview with regard to type of headache, presence of angina pectoris and Raynaud's phenomenon. The visit at home also included a physical examination and collection of blood samples. Physical examination consisted of measurements of length and weight, pulse, blood pressure and peak expiratory flow. All patients who were visited gave written informed consent. Finally, information from the GP was requested about the medical and drug dispensing history of the patients. The drug dispensing history was studied over the period between May 1991 (introduction of sumatriptan in The Netherlands) and January 1995.

Blood pressure measurements were made in the sitting position using an automated digital device, type Omron HEM403C (17). The heart rate was read from the digital display of the blood pressure device. Peak expiratory flow was measured with a mini

flow meter. All patients were instructed to inhale maximally and exhale maximally, not using a nose clip. They repeated this procedure three times, and the highest measurement was recorded.

Migraine was defined according to the criteria of the International Headache Society Headache Classification Committee for migraine. Angina pectoris was defined according to the Rose questionnaire (18).

Hypertension was defined as a systolic blood pressure of at least 160 mm Hg and/or a diastolic blood pressure of at least 95 mm Hg, or current use of antihypertensive medication for hypertension. The presence of Raynaud's phenomenon was considered if patients had complaints of biphasic discolorations of the digits during cold, accompanied by feeling numb (19).

Data analysis

Differences between group means were tested by Student's t test or with the Mann-Whitney test in case of non-normal distribution. A chi-square test was used to assess differences between proportions, with use of Fisher's exact test if there was an expected cell value of less than 5. All calculated P values are two-tailed. Statistical significance was defined as a two-sided p-value of less than 0.05. To adjust for possible confounders, multivariate analysis was performed, by fitting a logistic regression model, permitting calculation of odds ratios which may be interpreted as relative risks (RR), and 95% confidence intervals. Age (continuous variable) and gender and all variables which were significantly different between patients with and without chest pain attributed to sumatriptan, were included in the final multivariate model.

Stratified analyses were performed in males and females, and in patients with probable and possible sumatriptan-induced chest pain.

Results

The current study was based on 420 users of sumatriptan, who were all patients of 91 drug dispensing GPs who had at least one patient with chest pain to sumatriptan. Of these 420 patients, 372 (89%) responded to the second, detailed questionnaire. Six patients (1.6%) had not yet used sumatriptan, and were excluded from the study population. Of the 366 remaining patients, 347 (95%) were visited at home. Of 16

patients (5%) no blood sample was collected because the patient refused or because it was not possible to collect a sample for other reasons.

A total of 130 patients with chest pain attributed to sumatriptan and 217 patients on sumatriptan without chest pain were examined. General characteristics of the study population are summarized in table 1.

TABLE 1
General characteristics of the study population (N = 366)

Characteristic	Number or mean	(% or SD)
Females	293	(80)
Age (years)	43.9	(10.2)
Indication for sumatriptan:		
- Migraine	194	(53)
- Cluster headache	13	(4)
- Tension headache	6	(2)
- Combination of headaches	142	(39)
- Not stated	11	(3)
Administration of sumatriptan:		
- Subcutaneous	170	(46)
- Oral	93	(25)
- Both subcutaneous and oral	101	(28)
Systolic blood pressure (mm Hg)	129	(16.8)
Diastolic blood pressure (mm Hg)	82	(12.0)
Cholesterol (mmol/l)	6.0	(1.1)
- HDL (mmol/l)	1.7	(1.1)
- LDL (mmol/l)	4.0	(1.1)
Peak expiratory flow (l/min)	389	(81)
Body mass index (kg/m^2)	23.5	(2.9)
Current smokers	97	(27)
Raynaud's phenomenon	40	(11)
Angina pectoris	21	(6)
History of myocardial infarction	3	(1)

SD = Standard deviation

The mean age of the 137 patients with chest pain after use of sumatriptan (mean age 42 years, SE 0.86) was significantly different from patients without chest pain after

use of sumatriptan (45 years, SE 0.68 $p<0.05$). Other general characteristics dit not differ between the two outcome groups. During the follow-up period of approximately two years, 82 patients (22%) discontinued use of sumatriptan. Patients with chest pain to sumatriptan discontinued use more often (34% vs. 16%, relative risk (RR) 2.7 95% confidence interval (CI) 1.6 - 4.6).

A positive rechallenge (renewed occurrence of chest pain after renewed exposure to sumatriptan) was reported by 113 patients (80%) with sumatriptan-associated chest pain. Chest pain occurred within 30 minutes after administration of sumatriptan in 101 patients (74%), between 30 minutes and 2 hours after administration in 48 patients (35%) and between 2 and 6 hours after administration in 9 patients (7%). The duration of sumatriptan-associated chest pain was less than 30 minutes in 78 patients (57%), between 30 minutes and one hour in 35 patients (26%), between 1 and 2 hours in 18 patients (13%) and longer than 2 hours or not specified in 6 patients (4%). Differences in time relationship and duration of chest pain between oral and subcutaneous administration are shown in table 2.

TABLE 2

Differences in time relationship and duration of chest pain between oral and subcutaneous administration of sumatriptan, in 137 patients with chest pain after use of sumatriptan

	Oral administration N (%)	Subcutaneous administratio N (%)
*Temporal relationship between administration and chest pain**		
Within 30 minutes	18 (31)	83 (83)
30 minutes - 2 hours	34 (59)	14 (14)
2 - 6 hours	6 (10)	3 (3) ($p < 0.00$
Total patients in column	58	100
Duration of sumatriptan-associated chest pain$		
Less than 30 minutes	13 (35)	56 (71)
30 minutes - 1 hour	14 (38)	12 (15)
1 hour - 2 hours	8 (22)	8 (10)
Longer than 2 hours or not specifled	2 (5)	3 (4) ($p=0.003$)
Total patients in column	37	79

N = number of patients with the characteristic; % = percentage of patients in each column.

* 21 patients had chest pain after both the oral and subcutaneous administration of sumatriptan.

$ Only patients (116) with either chest pain only after subcutaneous or only after oral administration of sumatriptan.

All variables collected were compared between patients with and without chest pain

after use of sumatriptan. No differences were found in body mass index, peak expiratory flow, smoking, history of myocardial infarction, chronic obstructive lung disease, use of oral contraceptives, use of coffee or tea, concomitant use of ergot alkaloids, serum cholesterol level (including HDL and LDL fractions), or family history of migraine or sudden death. There was, however, a statistically significant difference in blood pressure, the frequency of gastrointestinal complaints, and of a family history of myocardial infarction. The mean systolic blood pressure in patients with chest pain after use of sumatriptan was 132 mm Hg (SE 1.5) and 127 mm Hg (SE 1.1) in controls ($p<0.005$). Diastolic blood pressure was 84 mm Hg (SE 1.1) in patients with chest pain and 81 mm Hg (SE 0.7) in the other group (table 3).

TABLE 3

Comparison between patients with chest pain attributed to sumatriptan and patients without chest pain after intake of sumatriptan

Characteristic	Patients with chest pain Number or mean (% or SE)	Patients without chest pain Number or mean (% or SE)	Odds ratio (95%-confidence interval)
Number	137	229	
Age (years)	42 (0.86)	45 (0.68)	0.98 (0.96 - 0.99)
Females	115 (84)	179 (78)	1.5 (0.8 - 2.6)
Males	22 (16)	50 (22)	
Route of administration:			
- Oral*	34 (25)	60 (26)	0.9 (0.6 - 1.6)
- Subcutaneous*	64 (47)	106 (46)	1.0 (0.7 - 1.6)
- Both*	39 (28)	62 (27)	1.1 (0.7 - 1.8)
Gastrointestinal complaints:			
- Dyspepsia	89 (65)	111 (48)	2.0 (1.3 - 3.1)
Raynaud's phenomenon	23 (17)	17 (7)	2.5 (1.2 - 5.2)
Angina Pectoris	13 (9)	8 (4)	2.9 (1.1 - 7.9)
AMI	1 (1)	2 (1)	
Blood pressure:			
- Systolic (mm Hg)	132 (1.5)	127 (1.1)	1.02 (1.0 - 1.03)
- Diastolic (mm Hg)	84 (1.1)	81 (0.7)	1.02 (1.0 - 1.04)
- Hypertension	34 (25)	30 (13)	2.2 (1.2 - 3.9)
Family history			
- of migraine	89 (65)	147 (64)	1.0 (0.7 - 1.7)
- of AMI < 65 years	37 (27)	33 (14)	2.2 (1.3 - 3.9)

SE = Standard Error

* compared to patients with another kind of administration(s)

As chest pain on a cardiovascular basis may show gender differences, a separate analysis was performed in males and females. Here, there was a moderate difference in total serum cholesterol and LDL fraction in males: Mean total cholesterol in males with chest pain after sumatriptan was 6.3 mmol/l, with LDL-cholesterol 4.6 mmol/l, whereas in males without chest pain after sumatriptan total serum cholesterol was 5.9 mmol/l (p=0.2), with LDL-cholesterol 4.0 mmol/l (p=0.06). Hypertension and a family history of myocardial infarction were strong predictors of sumatriptan-induced chest pain in males, relative risk 8.0 (95% CI 1.8-40) and 5.9 (95% CI 1.1-39.4) respectively.

Age (continuous variable) and gender and all variables which were significantly different between patients with and without chest pain, were included in the final multivariate model. The results of the multivariate analysis are given in table 4.

TABLE 4
Multivariate analysis of risk factors of sumatriptan associated chest pain, all patients and stratified by gender

Characteristic	Relative Risk	95% Confidence interval
All patients		
Females	1.5	0.8 - 2.7
Age (per year)	0.97	0.94 - 0.99
Dyspepsia	1.9	1.2 - 3.0
Raynaud's phenomenon	2.1	1.0 - 2.9
Hypertension	2.2	1.2 - 4.0
Family history of AMI	1.4	1.0 - 1.8
Angina pectoris	2.4	0.9 - 6.4
Females		
Age (per year)	0.97	0.94 - 0.99
Dyspepsia	2.0	1.2 - 3.3
Raynaud's phenomenon	2.4	1.1 - 5.0
Hypertension	1.6	0.8 - 3.0
Family history of AMI	1.3	0.97 - 1.7
Angina pectoris	2.1	0.7 - 6.2
Males		
Age (per year)	0.95	0.9 - 1.0
Dyspepsia	1.7	0.9 - 6.3
Raynaud's phenomenon	0.7	0.04 - 10.7
Hypertension	9.8	2.1 - 45.1
Family history of AMI	7.7	1.4 - 43.9
Angina pectoris	1.7	0.1 - 25.3

AMI = Acute Myocardial Infarction

Raynaud's phenomenon was a significant risk factor for sumatriptan-associated chest pain in females (relative risk 2.4; 95% CI 1.1-5.0) but not in males, whereas in males in particular hypertension (RR 9.8; 95% CI 2.1-45) and a family history of acute myocardial infarction (RR 7.7; 95% CI 1.4-43.9) were associated with sumatriptan-associated chest pain. When angina pectoris was excluded from the multivariate model, the risk of hypertensive males on sumatriptan-induced chest pain increased.

There were 93 patients with probable sumatriptan-induced chest pain and 44 patients with possible sumatriptan-induced chest pain. Separate analyses of risk factors in patients with probable and possible sumatriptan-associated chest pain, gave no material change of the results.

All drugs dispensed in the period between May 1991 and January 1995 were studied. In table 5 differences in use of gastrointestinal drugs between patients with and without chest pain after sumatriptan are shown.

TABLE 5

*Differences in use of gastrointestinal drugs during the study period between patients with and without chest pain after use of sumatriptan**

Drugs	Chest pain after sumatriptan N (%)	No chest pain after sumatriptan N (%)
Total	104	176
- Antacids	11 (10.6)	16 (9.1)
- H_2-antagonists	16 (15.4)	19 (10.8)
- Proton-pump inhibitors	4 (3.8)	10 (5.7)
- Cisapride	7 (6.7)	8 (4.5)
- Any of the above	26 (25.2)	32 (18.3)

* of the total of 280 patients whose information was available
No statistically significant differences

Discussion

The primary aim of this study was not to demonstrate that sumatriptan can cause chest pain, since ample support for this association has been obtained from a number of case reports, clinical trials and postmarketing studies (3). Our primary aims were to identify characteristics and independent risk factors for chest pain attributed to sumatriptan, which may contribute to better prescribing and understanding of the nature of this adverse drug reaction.

Chest pain occurred faster after subcutaneous administration than after oral administration, whereas the duration of chest pain was shorter after subcutaneous administration. These relationships suggest a dose-response relation between sumatriptan and chest symptoms, since subcutaneously administered sumatriptan has a faster peak plasma concentration which also decreases faster (1). It is of clinical importance that in almost all patients (96%) chest pain after sumatriptan disappeared within 2 hours, so if chest pain continues for longer than 2 hours this should be viewed as an unusual reaction which requires special attention. It seems prudent that in these cases electrocardiography is performed to exclude myocardial infarction.

The results of our study suggest a vascular mechanism of the chest complaints after use of sumatriptan. There also was a weak association of sumatriptan-associated chest pain and complaints of dyspepsia in our study. A gastrointestinal mechanism of chest symptoms after sumatriptan has been suggested in a recent study, in which a small group of volunteers had abnormal oesophageal contractions after a supratherapeutic dose of sumatriptan (20). However, the design and implications of this study have been challenged (21). Furthermore, a previously reported case-history described a patient with sumatriptan associated chest pain without alterations of the pressure in the oesophagus following a sumatriptan injection (22). The association of chest symptoms after sumatriptan with general complaints of dyspepsia in our study, could be compatible with a gastrointestinal mechanism in a proportion of the patients. Unfortunately, we have no detailed information on the abdominal complaints. Abdominal pain is not a feature of migraine in adults (23). Moderate, not statistically significant, differences were demonstrated in our study in use of gastrointestinal drugs between patients with and without chest pain after sumatriptan. Patients with chest pain more frequently used H_2-antagonist (15.4% vs. 10.8%), but less frequently proton-pump inhibitors (3.8% vs. 5.7%).

The association of sumatriptan-induced chest pain and hypertension, the presence of Raynaud's phenomenon, angina pectoris and a family history of myocardial infarction, suggest a vascular mechanism of the chest symptoms. A vascular mechanism of the chest symptoms, with in particular involvement of coronary arteries is suggested by a number of case reports concerning cardiac side effects after use of sumatriptan. It has been suggested that this may be mediated by endothelial dysfunction (24). Chest symptoms in our study were associated with hypertension. An

association between endothelial function and hypertension has previously been demonstrated (25-28). This may also explain the observation in our study that notably in males hypertension was a strong risk factor for sumatriptan-associated chest pain (29). However, other determinants of endothelial dysfunction, such as hypercholesterolaemia (26, 30) or smoking (31, 32), were not associated with chest pain attributed to use of sumatriptan in our study. Males with chest pain after sumatriptan had a higher cholesterol and LDL-cholesterol than males without chest pain after sumatriptan. Probably because the number of patients in these groups was small these differences were not statistically significant.

Our study has several limitations. Not all cases experienced chest pain after each administration of sumatriptan. It is possible that certain variables modify the risk of chest pain associated with sumatriptan within a patient, e.g. smoking during use of sumatriptan. This could not be studied in this study since no relevant data were collected. A case cross-over study might offer a better approach to assess potential transient risk factors during use of sumatriptan in future studies (33).

We previously demonstrated the cumulative incidence of chest pain attributed to sumatriptan to be approximately 8%, which is higher than observed in the clinical trials. It is possible that we found a higher frequency of chest pain, because in clinical trials patients with hypertension were excluded (34). Hypertension is also listed among the contra-indications in the product information of sumatriptan. However, because hypertension is often not recognized sumatriptan is probably often used by hypertensive patients with severe migraine or cluster headache. In a previous part of our study (16), 22 out of the 414 males had chest pain on one or more occasions after administration of sumatriptan (5.3%; 95% CI 3.2 - 7.5%). Conservatively based on the lower boundary of the 95% confidence interval, this would be compatible with a cumulative one-year incidence in hypertensive males of approximately 30 percent.

In conclusion, we demonstrated several characteristics and determinants of sumatriptan associated chest pain. The chest symptoms appear to have a dose-effect relationship with use of sumatriptan, whereas the duration in most patients is not longer than 2 hours. After multivariate analysis, young age, hypertension, general complaints of abdominal pain, a family history of myocardial infarction and Raynaud's phenomenon were associated with an increased risk of chest pain attributed to sumatriptan. Especially in males, hypertension and a family history of myocardial

infarction were strong risk factors. These findings are compatible with a vascular mechanism of chest pain (with possibly involvement of coronary arteries) in some patients.

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CHAPTER 10

CARDIAC EXERCISE TESTING IN PATIENTS WITH CHEST PAIN DUE TO SUMATRIPTAN

Submitted

Introduction

Sumatriptan is a relatively new drug for the treatment of acute attacks of migraine and cluster headache (1, 2). It is a serotonin-1 (5HT-1) agonist which can be administered orally or subcutaneously. It has been estimated that 3-8% of the consumers of sumatriptan experience chest pain after use of the drug (3-5). These chest symptoms have been associated with both cardiac disturbances (6-9) and abnormal oesophageal contractions (10). Both intravenous and subcutaneous administration of sumatriptan result in a significant reduction in coronary artery diameter (11, 12), an effect which can be reversed by administration of glyceryl trinitrate (13).

To assess whether chest pain attributed to sumatriptan is associated with abnormalities on cardiac exercise testing, we performed a case-control study.

Patients, methods and analysis

Patients

A cohort study on adverse reactions to sumatriptan was performed in The Netherlands with assistance of drug dispensing general practitioners (GPs) as described in detail previously (3, 5). The study protocol was approved by the Research Ethics Committee of the University Hospital 'Dijkzigt' Rotterdam (MEC 140.112/1994/168), and written informed consent was obtained from all patients.

From this cohort, cases were selected as consumers of sumatriptan who reported sumatriptan associated chest pain. Location of the pain or anginal sensations in association with intake of sumatriptan, had to be at the sternum, left thoracic wall or left shoulder, and had to occur within 6 hours after administration of sumatriptan. Cases were included if they were able and willing to perform an exercise test. They were asked about participation in (this part of) the study, during a home visit in a previous part of the study.

A reference group was selected randomly from consumers of sumatriptan with the same GP as the case, who reported no chest pain after use of sumatriptan. If possible, controls were matched for age (within 5-year groups) and gender.

Of the 130 potential cases who were visited at home, nine subjects were unable to exercise, three subjects were lost to follow-up because of a change of residence, and seven subjects refused to participate in an exercise test, resulting in a total of 111 potential cases.

For 16 cases, no control could be selected mainly because the general practitioner

of the case had only one patient (= case) on sumatriptan. This resulted in 95 potential controls.

Methods

Symptom-limited exercise tests were performed in hospitals in the neighbourhood of the subjects, with either a treadmill or bicycle ergometer, mostly using the Bruce protocol or a protocol with 20 Watts per minute workload increments respectively. Electrocardiography (ECG) and heart rate were continuously monitored, and recorded every three minutes. Blood pressure was measured and recorded every three minutes.

A horizontal or downsloping ST segment depression of at least 0.1 mV extending at 80 msec after the J point was considered as abnormal. The exercise tests were evaluated by cardiologists in the hospitals. A random sample of 10% of the ECGs were re-evaluated by a cardiologist who had no knowledge as to whether it concerned a case or a control.

Analysis

Differences between group means were tested by Student's t test. A chi-square test was used to assess differences between proportions, with use of Fisher's exact test if there was an expected cell value of less than 5. All calculated P values are two-tailed, with statistical significance defined by a two-sided p-value less than 0.05.

Results

In a total of 74 cases (67%) and 55 controls (58%) symptom-limited exercise tests were performed. General characteristics of the study population are summarized in table 1.

TABLE 1
Basic characteristics of the study population

Characteristic	Cases		Controls	
	Number or mean (% or SE)		Number or mean (% or SE)	
Number	74		55	
Age (years)	43	(1.2)	47	(1.3)#
Females	61	(82)	46	(84)
Resting blood pressure (mm Hg):				
Systolic	133	(2.3)	131	(2.5)
Diastolic	83	(1.2)	82	(1.6)
Serum cholesterol (mmol/l)	5.9	(0.14)	5.8	(0.17)
Smoking	20	(27)	15	(27)
Family history of myocardial infarction	15	(20)	10	(18)

SE = Standard Error; # $p<0.01$

In cases, non-responders more frequently had a family history of myocardial infarction (20% and 36% respectively, p=0.05), other characteristics did not differ between responders and non-responders. Besides a small difference in age, there were no differences in basic characteristics between cases and controls. In males, cases had a moderately increased resting systolic blood pressure of 134 mm Hg as against 126 mm Hg in controls, a difference which was not statistically significant (p=0.21). None of the patients used sumatriptan during the exercise test.

Two patients (both cases) had an abnormal resting ECG: one patient had left ventricular hypertrophy (LVH) and one patient had a left bundle branch block. The patient with LVH on resting ECG concerned a 42-year-old male with a medical history of chronic obstructive lung disease and hypertension.

The results of exercise testing are shown in table 2.

TABLE 2

Results of exercise testing in 74 patients with sumatriptan-induced chest pain (cases) and 55 consumers of sumatriptan without such complaints (controls)

Characteristic	Cases	Controls	
	Number or mean (% or SE)	Number or mean (% or SE)	p-value
Number	74	55	
Maximal workload (watt)	150 (4.2)	146 (6.3)	0.34
Angina pectoris	0	0	
Maximal bloodpressure (mm Hg):			
- Systolic	180 (2.9)	183 (3.4)	0.38
- Diastolic	87 (2.4)	86 (2.1)	0.92
Maximal heart rate	162 (2.5)	158 (3.0)	0.32
ST-depression	3 (4)	0	

The conclusions of the re-evaluation of the ECGs did not differ from the conclusions reached by the cardiologists in the different hospitals. None of the variables measured differed significantly between cases and controls. Three cases had ST-depression on ECG during exercise (mean age 51 years, 1 male, 2 females). During exercise, one patient (case) developed a quadrigeminy. In males, cases had a moderately higher diastolic maximal blood pressure compared to controls: 94 mm Hg (SE 3.5) and 84 mm Hg (SE 3.2) respectively (p=0.05).

Discussion

In this case-control study, no differences could be demonstrated in exercise tests results between patients with and without sumatriptan-induced chest pain. Of the 74 cases, 3 subjects had, however, ST-segment depression on ECG during exercise.

Certain limitations of our study need to be mentioned. The size of the study was relatively small, with a higher response in cases than in controls. We do not know whether the non-response of 33% (cases) and 42% (controls) has influenced our results. However, except for a family history of myocardial infarction, none of the basic characteristics were different between responders and non-responders. Furthermore, 80% of the study population was female, and the diagnostic value of stress testing in women is controversial, in particular in women with low prior probability of coronary artery disease (14, 15).

One question is whether sumatriptan-induced chest pain is associated with myocardial ischemia in a majority of the patients. It can, however, not be concluded from a normal exercise test that a subject had no myocardial ischemia during sumatriptan-induced chest pain. Previously, the case-history has been described of a patient with sumatriptan-associated chest pain and normal coronary angiography but with a positive ergonovine provocation test (16).

It has been suggested that coronary vasospasm after sumatriptan may be caused by (occult) endothelial dysfunction (17). According to this mechanism, the coronary effects of sumatriptan may be comparable to those of serotonin itself and acetylcholine (18, 19). Exercise tests are not very suitable for the investigation of such endothelial abnormalities. Future studies with use of non-invasive methods to detect endothelial dysfunction in patients with and without sumatriptan-induced chest pain may give more insight into this mechanism (20, 21).

In conclusion, the prevalence of abnormal exercise tests in patients with sumatriptan-induced chest pain is low. In future studies on sumatriptan-induced chest pain provocation tests with either sumatriptan or ergonovine accompanied by (non-invasive) methods for detecting endothelial dysfunction may be used as a potentially more sensitive predictor of this adverse reaction. Based on the results of our study we do not recommend routine performance of exercise testing in patients with sumatriptan-induced chest pain.

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GENERAL DISCUSSION

GENERAL DISCUSSION

Main findings in our studies

In this final chapter the main findings, limitations, supporting evidence from the literature, clinical importance and suggestions for further studies are briefly discussed and summarized. Through the voluntary reporting scheme of the Netherlands Centre for Monitoring of Adverse Reactions to Drugs, we became aware of several cardiovascular adverse reactions to the new antimigrainous drug sumatriptan. Firstly, several reports of chest pain attributed to use of sumatriptan were received. Secondly, there was a report about a patient who developed an acute myocardial infarction, shortly after administration of sumatriptan 6 mg subcutaneously. In view of the close temporal relationship between use of sumatriptan and these reactions, a causal relation seemed to be probable. These reports gave, however, no insight into the frequency of the adverse reactions to sumatriptan, and their risk factors.

We performed a pharmaco-epidemiologic study with assistance of drug-dispensing general practitioners (GP). Because these GPs have direct access to both data on drug dispensing and on disease and because of their excellent co-operation (response rate 86%), this group of physicians appeared a very useful resource to study acute problems with adverse reactions to newly marketed drugs. According to the GP records, chest pain was noted in approximately 1% of the consumers. According to the consumers themselves, approximately 8% had experienced chest pain after administration of sumatriptan. Furthermore, it was demonstrated that a small proportion of the consumers (4%) used sumatriptan very often, a pattern of use that was more frequent in males and in those patients with a reported poor efficacy of sumatriptan.

Chest pain to sumatriptan occurred faster after subcutaneous administration than after oral administration, whereas the duration of chest pain was shorter after subcutaneous administration. This is compatible with a dose-response relationship. In almost every patient (96%) chest pain disappeared within 2 hours. In a multivariate analysis, young age, hypertension, general complaints of abdominal pain, a family history of myocardial infarction and Raynaud's phenomenon were associated with an increased risk of chest pain attributed to sumatriptan. There were differences in the strength of the risk factors between males and females. In particular in males, hypertension and a family history of myocardial infarction were strong predictors of sumatriptan-associated chest pain.

Exercise testing in patients with chest pain due to use of sumatriptan hardly revealed any abnormalities, and is not a useful diagnostic tool for this condition.

Limitations of the studies

The sample size of our study (approximately 1700 patients) was too small to observe rare adverse reactions, for instance those with an incidence below 1 per 1000 users. It was, for example, not possible to estimate the exact incidence rate of acute myocardial infarction due to sumatriptan.

In our cohort study on the frequency of adverse reactions to sumatriptan, we did not include a reference group. For this, there were several considerations. Firstly, we were mainly interested in adverse reactions with a close temporal relationship with use of sumatriptan, and with a relatively low background incidence in the middle-aged. Sumatriptan is mostly used for short periods. As it is unlikely that many reference patients would have developed chest pain in the same short periods in which the index patients were exposed, a reference group was not deemed necessary to obtain a valid estimate of the frequency of the event. A recent postmarketing clinical trial, in which sumatriptan was compared to both placebo and aspirin, confirmed that chest pain occurred in approximately 5% of the consumers of sumatriptan but in none of the patients after administration of a placebo or aspirin (1). Secondly, as sumatriptan is contraindicated in patients with angina pectoris and variant angina, such patients might have been overrepresented in a reference group of patients with migraine.

In our study on determinants of chest pain to sumatriptan, not all cases experienced chest pain after each administration of sumatriptan. It is possible that certain variables can modify the risk of chest pain associated with sumatriptan *within* a patient, e.g. smoking *during* use of sumatriptan. However, this could not be investigated in this study since the required time specific data could not be collected.

The size of our study with exercise tests was relatively small. Moreover, if myocardial ischemia due to use of sumatriptan is associated with endothelial dysfunction rather than with coronary stenoses (2), exercise tests give only limited information.

Supporting evidence from the literature

Our reports on chest pain and acute myocardial infarction were soon confirmed by other reports in the literature (see chapter 6). Although several pre-marketing clinical studies did not mention chest pain as an adverse reaction to sumatriptan (3, 4), a post-marketing clinical trial did clearly demonstrate the occurrence of this adverse reaction (1).

There is some pharmacological evidence for myocardial ischaemia due to sumatriptan. Sumatriptan constricted isolated coronary arteries of beagle dogs (5). Human isolated basilar artery rings constricted in response to sumatriptan (6), as did human epicardial

coronary artery rings from explanted hearts. Furthermore, two small studies, in which patients undergoing diagnostic coronary arteriography were studied, demonstrated a significant reduction in coronary artery diameter after both intravenous and subcutaneous administration of sumatriptan (7, 8).

Our findings suggested a dose-response relation between sumatriptan and the occurrence of chest pain. An increasing incidence of chest symptoms with a higher dose of sumatriptan has been observed in one dose-finding study (9). This may also be of clinical importance, as a small proportion of the consumers of sumatriptan administrates sumatriptan very often, which was also observed in Denmark (10).

Clinical importance of our findings

Chest pain after use of sumatriptan seems to be a relatively common (8%) adverse reaction to this drug. Since myocardial infarction due to sumatriptan has been reported, each case of chest pain after administration of sumatriptan, requires a careful evaluation, with respect to factors such as duration of chest pain, severity of the reaction and the presence of recognized cardiovascular risk factors. If chest pain after use of sumatriptan continues for longer than 2 hours, this consists of an unusual reaction which requires special attention. Several risk factors for chest pain to sumatriptan, such as young age, hypertension, general complaints of abdominal pain, a family history of myocardial infarction and Raynaud's phenomenon, warrant careful use of sumatriptan in patients with one or more of these characteristics. Particularly in males with hypertension or a family history of myocardial infarction, there is a high probability of chest pain after use of sumatriptan.

Exercise testing is often used as a diagnostic tool in the evaluation of angina pectoris. It concerns, however, a relatively expensive and insensitive method. Based on the results of our study, we advise against routine performance of exercise testing in patients with sumatriptan-induced chest pain.

According to the potential risk of over-use of sumatriptan, it is important to evaluate the treatment of headache attacks with sumatriptan in every patient, in particular in males who report a poor efficacy of sumatriptan.

Suggestions for further studies

A number of questions merits further research. It may be interesting whether within one patient transient determinants increase the risk of chest pain after use of sumatriptan. A case cross-over study might offer a useful approach to assess potential transient risk

factors during use of sumatriptan in future studies, such as smoking during use of sumatriptan.

It is important to identify risk factors for serious (cardiovascular) adverse reactions to sumatriptan. A case-control study of patient characteristics in reports of serious cardiac adverse reactions to sumatriptan like myocardial infarction (cases), compared to characteristics in consumers of sumatriptan with mild chest pain after use of the drug (=controls), may give insight into risk factors for serious cardiac reactions after use of sumatriptan. This approach to identify risk factors for relatively rare adverse reactions has previously been described in the study on risk factors for the development of flucloxacillin associated jaundice (11).

With regard to the mechanism of sumatriptan-induced chest pain, it may be useful to assess a possible association of this adverse reaction with endothelial dysfunction. In future studies on sumatriptan-induced chest pain, a provocation test with either sumatriptan or ergonovine accompanied by (non-invasive) methods for detecting endothelial dysfunction may be used as a potentially more sensitive predictor of this mechanism to explain the adverse reaction.

It has previously been demonstrated that low-dose aspirin in-vitro reduces constriction of coronary arteries (12). In order to prevent myocardial ischaemia due to sumatriptan-induced coronary vasoconstriction, the protective effect of aspirin may be investigated in controlled clinical studies.

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SUMMARY

SUMMARY

The objective of the work presented in this thesis was to assess adverse drug reactions to the new antimigrainous drug sumatriptan in a postmarketing setting, with emphasis on the cardiovascular adverse reactions to this drug. The thesis is divided into three parts. Part I introduces the background of the project and postmarketing surveillance. Parts II summarizes case reports to the Netherlands Centre for Monitoring of Adverse Reactions to Drugs, in particular reports concerning cardiovascular adverse reactions to sumatriptan. In part III the exploration of the potential problem, chest pain and myocardial infarction to sumatriptan, is discussed.

Chapter 1 provides a general introduction and describes the outline of the project. It is emphasized that at the time of the marketing of a new drug not all adverse drug reactions can be known, and that the pharmacological effects of the drug are only studied in a selected population. A brief discussion follows about the treatment of migraine, with reference to the difference between drugs used against acute attacks of migraine, and drugs used for prophylactic use.

Chapter 2 describes postmarketing surveillance. After an introduction on this subject, several aspects of premarketing studies are discussed. Next, a brief description follows of the history of adverse drug reactions. Finally, the limitations of premarketing studies and the methods of post marketing surveillance are described.

In *chapter 3* the Netherlands Centre for Monitoring of Adverse Reactions to Drugs is introduced. The centre was initiated after the thalidomide disaster in the 60s. In the past years, an increase in the annual number of reports to the centre has been observed.

Chapter 4 gives a review of reports of drug-induced chest pain or myocardial infarction as received by the Netherlands Centre for Monitoring of Adverse Reactions to Drugs between January 1975 and January 1995. These comprised 130 reports (71%) of drug-induced chest pain and 54 reports (29%) of drug-induced myocardial infarction. The most frequently reported suspected drugs were the antimigrain drug sumatriptan (33 reports, 4 concerning myocardial infarction), the calcium antagonist nifedipine (9 reports, 2 of myocardial infarction) and nicotine (9 reports, five concerning myocardial infarction, 8

patches, 1 chewing gum).

In *chapter 5* the reports to the Netherlands Centre concerning adverse reactions to sumatriptan are discussed. Firstly, reports of chest pain attributed to use of sumatriptan are reviewed. In particular, the possibility that this concerns a symptom of myocardial ischaemia is discussed. Secondly, the case history is described of a 47-year-old woman with an acute myocardial infarction after administration of sumatriptan 6 mg subcutaneously for cluster headache.

In *chapter 6*, the published cardiovascular adverse reactions to sumatriptan are reviewed, with attention to the pharmacological profile of the drug. Furthermore, the possible relationship between migraine per se and cardiovascular disease, the association between serotonin and cardiovascular disease, and the differential diagnosis of chest pain are discussed. It is concluded that, although severe cardiovascular adverse reactions to sumatriptan may be rare, every case of chest pain after administration of sumatriptan, requires careful evaluation.

To study the incidence of cardiovascular adverse reactions to sumatriptan, a pharmacoepidemiological study was performed, which is described in *chapter 7*. Chest pain attributed to sumatriptan occurred in 1.3% of the consumers according to the general practitioners, and according to the consumers themselves in 7.9%.

In *chapter 8* the pattern of use and over-use of sumatriptan is described. A small group of patients (4%) used sumatriptan too often. A high intake was associated with both male gender and a reported poor efficacy of sumatriptan.

Chapter 9 describes characteristics and determinants of sumatriptan-associated chest pain. The findings show a dose-response relation between sumatriptan and chest pain. After multivariate analysis, young age, hypertension, general complaints of abdominal pain, a family history of myocardial infarction and Raynaud's phenomenon were associated with an increased risk of chest pain attributed to sumatriptan. There were differences in the magnitude of the risk factors between males and females. The results may have consequences for both prescribing and understanding of the possible mechanism of this adverse reaction.

Finally, *chapter 10* describes exercise tests which were performed in patients with chest pain attributed to sumatriptan and in matched controls. There were no statistically significant differences between cases and controls in results of exercise testing. Furthermore, patients with chest pain associated with use of sumatriptan have a low prevalence of abnormal exercise tests: of the 72 cases, 3 patients (4%) had ST-depression during exercise, of whom two were females. Routine performance of exercise testing in patients with uncomplicated sumatriptan-induced chest pain is not recommended.

SAMENVATTING

SAMENVATTING

Het doel van het onderzoek dat wordt beschreven in dit proefschrift, was het onderzoeken van bijwerkingen van het nieuwe anti-migraine middel sumatriptan (Imigran), zoals deze worden waargenomen in de dagelijkse praktijk. In het bijzonder de cardiovasculaire bijwerkingen werden onderzocht. Het proefschrift bestaat uit drie gedeelten. In deel I worden algemene achtergronden van het onderzoek en van 'post marketing surveillance' beschreven. In deel II wordt een samenvatting gegeven van meldingen aan het Bureau Bijwerkingen Geneesmiddelen, in het bijzonder met betrekking tot cardiovasculaire bijwerkingen van sumatriptan. In deel III wordt een farmaco-epidemiologisch onderzoek beschreven, dat werd uitgevoerd naar aanleiding van de meldingen van pijn op de borst en hartinfarct na gebruik van sumatriptan.

Hoofdstuk 1 biedt een algemene inleiding en geeft een overzicht van het proefschrift. Er wordt gesteld dat op het tijdstip van introductie op de markt van een nieuw geneesmiddel nog niet alles over mogelijke bijwerkingen bekend is, en dat de meeste farmacologische effecten van het nieuwe geneesmiddel alleen zijn bestudeerd in een geselecteerde patiënten-groep. In het hoofdstuk wordt tevens de behandeling van migraine besproken, waarbij een onderscheid dient te worden gemaakt tussen behandeling van aanvallen, en maatregelen ter voorkoming van aanvallen.

Hoofdstuk 2 geeft een beschrijving van 'postmarketing surveillance': het volgen van een geneesmiddel na het verschijnen op de markt. In dit hoofdstuk wordt onder andere een samenvatting gegeven van de geschiedenis van bijwerkingen van geneesmiddelen. Daarnaast wordt ingegaan op de beperkingen van het onderzoek vóór registratie en methoden die gebruikt worden bij de postmarketing surveillance.

In *hoofdstuk 3* wordt een beschrijving gegeven van het Bureau Bijwerkingen Geneesmiddelen. Dit landelijke meldingssysteem werd opgericht na de problemen rond thalidomide (Softenon) in de 60'er jaren. In de afgelopen jaren werd een duidelijke toename van het jaarlijkse aantal meldingen waargenomen.

Hoofdstuk 4 geeft een overzicht van de meldingen van pijn op de borst of hartinfarct

door geneesmiddelen, zoals gemeld bij het Bureau Bijwerkingen Geneesmiddelen in de periode januari 1975 tot januari 1995. Dit betrof 130 meldingen van pijn op de borst en 54 meldingen van een hartinfarct in relatie tot gebruik van geneesmiddelen. Sumatriptan was het geneesmiddel dat het meest frequent verdacht werd (33 meldingen), gevolgd door de calcium-antagonist nifedipine (9 meldingen) en nicotine (eveneens 9 meldingen. 8 betreffende de nicotine pleisters, 1 betreffende nicotine-kauwgom).

In *hoofdstuk 5* worden cardiovasculaire bijwerkingen van sumatriptan besproken, zoals deze werden gemeld bij het Bureau Bijwerkingen Geneesmiddelen. Eerst worden meldingen van pijn op de borst na gebruik van sumatriptan besproken, waarbij wordt ingegaan op de mogelijkheid dat deze bijwerking wordt veroorzaakt door zuurstoftekort van de hartspier (myocardischemie). Daarna wordt een melding besproken welke de ziektegeschiedenis betreft van een 47-jarige vrouw welke na toediening van 6 mg sumatriptan een hartinfarct kreeg. Deze patiënte had voorheen nooit last gehad van het hart, maar reeds twee keer eerder na gebruik van sumatriptan pijn op de borst gehad.

In *hoofdstuk 6* worden de in de literatuur gepubliceerde gevallen van cardiovasculaire bijwerkingen van sumatriptan besproken. Er wordt in dit hoofdstuk ook ingegaan op de farmacologische werking van sumatriptan, de mogelijke relatie tussen migraine zelf en cardiovasculaire ziekten, het verband tussen serotonine en cardiovasculaire ziekten, en de differentiaal diagnose van pijn op de borst. Er wordt geconcludeerd dat cardiovasculaire bijwerkingen van sumatriptan waarschijnlijk zeldzaam zijn maar dat iedere patiënt met pijn op de borst na sumatriptan bijzondere aandacht verdient. Verder wordt geconcludeerd dat er nader onderzoek dient te geschieden naar deze bijwerking.

Teneinde meer inzicht te krijgen in de incidentie van (cardiovasculaire) bijwerkingen van sumatriptan werd een farmaco-epidemiologisch onderzoek gestart, hetwelk wordt beschreven in *hoofdstuk 7*. Pijn op de borst trad volgens apotheekhoudende huisartsen op bij 1,3% van de patiënten na gebruik van sumatriptan. Volgens de gebruikers zelf, trad deze bijwerking op bij bijna 8%.

In *hoofdstuk 8* wordt het gebruik van sumatriptan in de onderzoeksgroep beschreven. Een kleine groep patiënten (4%) gebruikte sumatriptan erg vaak. Een (te) hoog gebruik kwam vaker voor bij mannen, en bij patiënten die weinig baat zeiden te hebben van sumatriptan.

In *hoofdstuk 9* worden enkele karakteristieken en determinanten van pijn op de borst door sumatriptan beschreven. De resultaten lijken op een dosis-respons relatie tussen deze bijwerkingen en sumatriptan gebruik te wijzen. Verschillende factoren bleken geassocieerd met pijn op de borst door sumatriptan. Met name mannen met een hoge bloeddruk of een familie geschiedenis van een hartinfarct hadden een sterk verhoogd risico op pijn op de borst na gebruik van sumatriptan. Bij vrouwen was het fenomeen van Raynaud geassocieerd met het optreden van pijn op de borst na sumatriptan.

In *hoofdstuk 10* worden de resultaten van inspanningsonderzoek beschreven bij patiënten met en zonder pijn op de borst na gebruik van sumatriptan. Er waren vrijwel geen afwijkende inspanningsonderzoeken, en de conclusie is dan ook dat een inspanningsonderzoek bij patiënten met pijn op de borst na gebruik van sumatriptan, weinig aanvullende informatie verschaft.

EPILOOG

EPILOOG

Op de laatste bladzijden van dit proefschrift wil ik graag diegenen bedanken die in welke vorm dan ook hebben bijgedragen aan de voltooiing van 'het boekje'.

In de eerste plaats ook hier nogmaals een woord van dank aan de vele apotheekhoudende huisartsen en patiënten die belangeloos hebben meegewerkt aan de totstandkoming van dit proefschrift. Zonder hun hulp en medewerking was het niet mogelijk geweest via de door ons beschreven methoden meer inzicht te krijgen in de bijwerkingen van sumatriptan.

J. Verhoeff, psychiater, Hoofdinspecteur voor de Gezondheidszorg en drs. P.H. Vree, apotheker, Hoofdinspecteur voor Farmacie en Medische Technologie, maakten het mogelijk om het onderzoek uit te voeren. Jitze en Piet, hartelijk dank voor de samenwerking en de wijze waarop jullie de geneesmiddelenbewaking behartigen.

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Professor J.H.P. Wilson dank ik voor het vertrouwen dat hij ons schonk om vanuit 'zijn' afdeling dit onderzoek te doen, alsmede voor zijn toestemming om een promotor te zoeken wiens vakgebied dichter bij het onderzoek lag.

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CURRICULUM VITAE

CURRICULUM VITAE

De schrijver van dit proefschrift werd geboren op 29 maart 1965 te Rotterdam. In mei 1983 behaalde hij het diploma ongedeeld VWO te Rotterdam, waarna hij (na uitloten voor de studie geneeskunde) een jaar werkzaam was als assistent-accountant bij Moret & Limperg, Registeraccountants Rotterdam. Gedurende dit jaar volgde hij 1 dag per week de accountants-opleiding (via NIVRA). In september 1984 begon hij de studie geneeskunde aan de Erasmus Universiteit Rotterdam. Van 1986 tot 1988 werkte hij part-time voor de Stichting Trombosedienst en Artsenlaboratorium Rotterdam. Daarnaast deed hij van 1986 tot 1991 in het Zuiderziekenhuis te Rotterdam onderzoek naar prognostische factoren na een hartinfarct, in samenwerking met de afdeling Epidemiologie & Biostatistiek van de Erasmus Universiteit. In 1988 behaalde hij zijn doctoraal-examen, en in april 1991 het arts-examen.

Van 1 mei 1991 tot 1 mei 1992 was hij als assistent-geneeskundige werkzaam op de afdeling cardiologie van ziekenhuis "De Weezenlanden" te Zwolle. In mei 1992 werd met het in dit proefschrift beschreven promotie-onderzoek begonnen, en werd hij aangesteld bij de 'farmaco-epidemiologie unit' van het instituut Interne Geneeskunde II van het Academisch Ziekenhuis Dijkzigt te Rotterdam. Tevens had hij vanaf die datum een part-time aanstelling (50%) als inspecteur voor de volksgezondheid bij de Hoofdinspectie voor de Geneesmiddelen (vanaf 1 januari 1995 de Inspectie voor de Gezondheidszorg) van het Staatstoezicht op de Volksgezondheid. Gedurende deze periode werden diverse cursussen epidemiologie gevolgd, onder meer in Boston, U.S.A.

Vanaf 1 maart 1996 volgt hij, in het kader van de opleiding tot cardioloog (opleider dr J.C.A. Hoorntje), de vooropleiding Inwendige Geneeskunde in het Academisch Ziekenhuis Dijkzigt te Rotterdam (opleider prof. J.H.P. Wilson).

Naast bovengenoemde activiteiten is hij een enthousiast beoefenaar van karate.

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