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Drug-induced chest pain and myocardial infarction. Reports to a national centre and review of the literature

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Abstract *Objectives*: To analyse reports of drug-induced myocardial infarction and chest pain sent to a national reporting centre. To review which drugs were suspected of exhibiting these adverse events and what mechanisms were involved.
Methods: During the 20-year period 1975 through 1994, a total of 19 141 reports on adverse reactions to drugs were received by the Netherlands Centre for Monitoring of Adverse Reactions to Drugs. Of these 19 141 reports, 220 (1.1%) were concerned with drug-induced chest pain or myocardial infarction. After excluding reports in which the causal relationship was unlikely, poorly documented reports and reports on cases of overdosage, 183 reports (84%) were analysed.
Results: There were 130 reports (71%) of drug-induced chest pain and 53 reports (29%) of drug-induced myocardial infarction. A total of 104 reports concerned females (57%). The most frequently reported suspected drugs were the antimigraine drug sumatriptan (33 reports, 4 concerning myocardial infarction), the calcium antagonist nifedipin (9 reports, 2 of myocardial infarction) and nicotine [9 reports (8 patches, 1 chewing gum), 5 concerning myocardial infarction]. There were 18 reports of a fatal outcome.
Conclusions: Several drugs can produce chest pain or myocardial ischaemia. It is important to recognise drugs as a potential cause, especially in patients with normal coronary arteries.

Key words Myocardial infarction, Drug induced, Angina pectoris

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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 investigate. In spite of the low incidence, it is important to recognise when drugs are 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 summarised in Table 1. 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 ischaemia or infarction or may make the patient more susceptible to these disorders.

Although voluntary reporting systems have several disadvantages, especially under-reporting, 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 (NARD) between 1 January 1975 and 31 December 1994.

Methods

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 1 January 1975 and 31 December 1994 concerning drug-induced chest pain, myocardial ischaemia or infarction were included in this study. Only adverse

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 ischaemia/infarction
Direct: reduced coronary blood flow, thrombosis
Indirect: coronary steal, interaction with anti-anginal drugs
Pericardial disease
Haemopericarditis
Others

drug reactions due to drugs administered 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 use 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 ischaemia, 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 min; (2) characteristic changes in the electrocardiogram; and (3) peak elevation of serum enzymes [creatine phosphokinase (CPK), serum glutamic oxaloacetic transaminase (SGOT)] of at least twice 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

NARD 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. Twenty-two reports (10%) were poorly documented and in 15 reports (6.8%), the causal relationship was unlikely. The poorly documented 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 sulprostons, respectively, have previously been 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. 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 with drug-induced chest pain, drug-induced myocardial infarction was more frequently reported in males (63 vs 35%; $P < 0.001$). Eighteen patients (9.8%) died after myocardial infarction. Age was not related to myocardial

Table 2 Overview of drugs which were related to chest pain or myocardial infarction in 183 reports[a]. *NSAIDs* non-steroidal anti-inflammatory drugs

Drug group (number of reports)	Drug (number of reports)
Cardiovascular (37)	
Ca-antagonists (15)	Nifedipine (9), diltiazem (4), verapamil (2)
ACE inhibitors (6)	Captopril (1), lisinopril (2), perindopril (2), enalapril (1)
β-adrenoceptor blockers (5)	Oxprenolol (1), pindolol (1), atenolol (1), metoprolol (2)
α_1-adrenoceptor 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-migraine (35)	Ergotamine (1), sumatriptan (33), methysergide (1)
Respiratory system (15)	
β-sympatho-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), sulprostone (1), epoetin (1), desmopressin (3)
Anti-infectives (15)	
Antibiotics (10)	Nitrofurantoin (4), co-trimoxazole (1), amphotericin (1), amoxicillin (1), metronidazole (1), norfloxacin (1)
Others (6)	Mefloquine (3), niridazol (2), ketoconazol (1)
Analgesics (10)	NSAIDs (6), glafenine (2), penicillamine (1) aspirin (1)
Gastro-intestinal drugs (5)	Cisapride (2), cimetidine (2), domperidon (1)
Miscellaneous (44)	Alfuzosin (3), nicotine (9), amphetamines (2), fenfluramine (2), β-blocker containing eye drops (4), various (24)

[a] In nine reports, more than one drug was suspected

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 six patients abnormal ECGs were observed.

In 174 out of 183 reports, one drug was suspected to have caused the adverse reaction, whereas in five reports, two drugs were suspected and in four reports, more than two drugs were suspected. Chest pain or myocardial infarction were attributed to a total of 98 different drugs (Table 2). 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. Fifteen reports concerned calcium-channel blocking agents: nine reports concerning nifedipine (seven chest pain, two acute myocardial infarction), four reports concerning diltiazem (all chest pain) and two reports concerning chest pain attributed to use of verapamil. There were three reports of chest pain induced by systemic use of β-adrenoceptor blockers (oxprenolol, pindolol and atenolol). ACE inhibitors were suspected in five reports: captopril (one report of chest pain), lisinopril (one report of chest pain, one report of myocardial infarction) and perindopril (one report of chest pain, one report of myocardial infarction).

There were 17 reports of chest pain or myocardial infarction attributed to the use of antidepressants. Three of them concerned fatal myocardial infarction after use of tricyclic antidepressants (one imipramine, two amitriptyline). Of four reports concerned with myocardial infarction attributed to use of the monoamine oxidase (MAO)-A inhibitor moclobemide, two concerned a fatal reaction.

Several reports concerned chest pain or myocardial infarction attributed to drugs for respiratory problems, of which seven reports concerning β-sympatho-mimetics are of special interest.

Four reports concerned adverse reactions attributed to use of oral contraceptives (two myocardial infarction, two chest pain), whereas in three 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.

Discussion

The most common cause of myocardial ischaemia 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 ischaemia is probably low, there are several reasons why it is important to know which drugs can induce myocardial ischaemia and what mechanism is involved. Firstly, drugs which should be used cautiously can be identified, especially in patients with coronary artery disease. Secondly, it is important to consider a drug adverse event if chest pain occurs in a patient using some specific drugs, particularly 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 ischaemia or infarction may differ from patients with regular myocardial ischaemia or infarction. Finally, the pharmacological mechanisms may also provide insight into the pathophysiology of 'not-drug-induced' myocardial ischaemia.

It is, of course, important to remember that our reports of chest pain or myocardial infarction concern rare adverse reactions, and that the risk–benefit assessment of a specific drug can be only assessed in a (randomised) clinical trial.

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 for 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 three reports of chest pain induced by systemic use of β-adrenoceptor blockers (oxprenolol, pindolol and atenolol), and four reports of chest pain induced by β-adrenoceptor blocker-containing eye drops (timolol 2x, betaxolol, metipranolol). Acute myocardial infarction has been associated with propranolol [14] and

metoprolol [15]. Also β-blocker-containing eye drops have been associated with chest pain [16] and myocardial infarction [17]. The pathophysiological mechanism of β-adrenoceptor blocker-induced myocardial ischaemia is probably coronary vasospasm mediated by α-adrenoceptors [15].

A few reports concerned chest pain or myocardial infarction attributed to the 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 six fold increase in risk of fatal myocardial infarction, associated with current use of tricyclic antidepressants was demonstrated in young women [20]. In general, the cardiovascular effects of tricyclic antidepressants are considered to consist mainly of conduction disturbances, arrhythmias and orthostatic hypotension [21, 22]. Myocardial infarction was attributed to moclobemide in four reports. Recently, hypertension was described as an adverse reaction to this MAO-A inhibitor [23].

Anti-migraine drugs

In the literature, there have been several reports of cardiac ischaemia due to the antimigraine drugs ergotamine [24, 25], methysergide [26], sumatriptan [27] and isometheptene [28]. The proposed mechanism is coronary spasm. There was a large number of reports sent to our centre of chest pain (29 reports) and several reports (four) of myocardial infarction attributed to the use of the new anti-migraine drug sumatriptan. One report of myocardial infarction [29] and 13 reports of chest pain [30] were previously 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 associated with use of sumatriptan have been reported 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 β-sympathomimetics 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 β_2-adrenoceptor 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 ischaemia, even at the 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 cannot 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]. A more recently published study demonstrated a reduced risk of myocardial infarction in users of third-generation oral contraceptives [42].

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 [43].

Analgesics

Coronary spasm has been described after administration of naproxen (44) and glafenine (45): the proposed mechanism is an allergic reaction [44].

Miscellaneous

Of the reports of chest pain ($n = 4$) or myocardial infarction ($n = 5$) attributed to use of nicotine sent to the national centre one had previously been published as a case report [46]. There have been reports of serious cardiovascular adverse reactions in the literature, including acute myocardial infarction and cardiac arrest, associated with continued smoking during use of the patches [47–49].

There were two reports of acute myocardial infarction and one report of chest pain attributed to the use of alfuzosin. Alfuzosin is a relatively new drug, used for the symptomatic treatment of benign prostatic hyperplasia, which acts as an antagonist of α_1-adrenoceptors [50]. 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 to patients with a high risk of coronary diseases (elderly males). There

were also reports concerning chest pain attributed to two other α_1-adrenoceptor blockers, urapidil and prazosin, used for treatment of hypertension.

Two reports also concerned chest pain attributed to use of fenfluramine. Myocardial infarction associated with dexfenfluramine has been described previously [51].

Underreporting and selective reporting

The most important disadvantages of a spontaneous reporting system are under-reporting and selective reporting. According to the latter, it is particularly interesting that chest pain or myocardial infarction was not even in 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 [52]. Moreover, several antiproliferative drugs and/or irradiation to the mediastinum can cause cardiac damage [53–55]. These drugs include 5-fluorouracil [56], taxol [57], bleomycin and etoposide [58] and cisplatin [59].

Several cases of myocardial infarction attributed to the administration of blood coagulation factors have been documented in the literature [60–62]. In most cases, patients with haemophilia were involved.

Cases of cocaine-induced myocardial infarction were previously reviewed in the literature [63].

In conclusion, the present study, the reports of drug-induced chest pain or myocardial infarction as reported to the NARD during the period 1975 through 1994 were demonstrated. The reviewed reports give an impression of the different drugs and the different mechanisms in the difficult field of drug-induced myocardial ischaemia or infarction.

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