Eur J Clin Pharmacol (1994) 47: 305–309

PHARMACOEPIDEMIOLOGY AND PRESCRIPTION

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Adverse reactions attributed to sumatriptan

A postmarketing study in general practice

Received: 31 March 1994 / Accepted in revised form: 4 August 1994

Abstract There are several reports on cardiac adverse reactions attributed to the antimigraine drug sumatriptan in the recent literature. In order to assess the frequency and the character of adverse reactions to sumatriptan, a postmarketing cohort study was performed one year after registration of the drug in The Netherlands.

With assistance of 86 % of the drug dispensing general practitioners in The Netherlands, 1727 patients who had received sumatriptan were traced in July, 1992. Via their general practitioners, a questionnaire about use of sumatriptan, adverse reactions and other medication was sent to the patients in December 1992. During the study period, seven patients were lost to follow-up. Of the 1720 remaining patients, 1202 (70 %) responded to the questionnaire, of whom 1187 had actually used sumatriptan.

The most frequently reported suspected adverse reactions were paraesthesiae (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 %), and according to the close temporal relationship with the intake of sumatriptan and a positive rechallenge, a causal relationship was probable in most of those patients. The frequency of chest pain attributed to sumatriptan was higher in females (9.0 % vs 4.6 %; relative risk 1.9, 95 % CI 1.1–3.4). Age and hypertension were not associated with chest pain attributed to sumatriptan. Dyspnoea attributed to sumatriptan was reported by 26 patients (2.2 %), and was associated with obstructive lung disease (relative risk 5.4 95 % CI 1.7–16.9).

Thus, in view of the high frequency of chest pain after use of sumatriptan and reports in the literature of cardiac disturbances, including myocardial infarction, cautious use of the drug is advised.

Key words Sumatriptan, Migraine; pharmacoepidemiology, adverse reaction, angina pectoris, postmarketing surveillance, general practitioner

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The serotonin-1 (5HT-1) agonist sumatriptan is a new anti-migraine drug, which has been registered in several European countries and recently in the United States, too [1]. It has been demonstrated that sumatriptan is highly effective, rapidly 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]. Reports from several 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 ischaemia had been 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 abnorm-

Table 1 Characteristics of the study population

	Patients (number)	(%)
Males	284	(24)
Females	918	(76)
Mean age (years)	43	(11[a])
Obstructive lung disease	28	(2.4)
Hypertension	49	(4.1)
Diabetes mellitus	4	(0.3)

[a] Standard deviation

alities in the ECG, after sumatriptan 6 mg SC [9, 10], a young female developed acute myocardial infarction after SC administration of sumatriptan [11], and two cases were reported of serious ventricular arrhythmias after its use [12]. Furthermore, two small angiographic studies demonstrated a significant reduction in coronary artery diameter in humans both after IV and SC administration of sumatriptan [13, 14].

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

Patients and methods

Patients

In July 1992, an enquiry was held involving 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, 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 it. They were also 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, no adverse reactions were specified in the questionnaire, and the general practitioners were not informed about our particular interest in chest pain. Chest pain was defined as pain or pressure feelings, located substernally or in the chest. The enquiry was sent to the patients in December 1992. The physicians none of whose patients had responded received a reminder in March 1993. Patients were classified as diabetic if they were taking anti-diabetic drug therapy, and 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 β-adrenoceptor 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 χ^2 test was used to assess differences between proportions, with 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 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 the 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 due to change of residence. Of the 1720 remaining patients, 1202 (70 %) returned the questionnaire.

The basic characteristics of this study population are summarized in Table 1. It comprised 284 males with a mean age of 44 years and 918 females with a mean age of 43 years. Fifteen patients (2 males, 13 females) had not yet used sumatriptan, and were excluded from further analyses.

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

Some patients reported more than one adverse reaction

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
Dyspnoea	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
Paraesthesiae	139	(11.7)	9.9–13.5
Pressure in throat	39	(3.3)	2.3–4.3

The most commonly suspected adverse reactions reported by the 1187 patients who had taken sumatriptan, are shown in Table 2. The most frequent were paraesthesiae (139 patients, 11.7 %, 95 % CI 9.9 %–13.5 %) and dizziness (96 patients, 8.1 %, 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 y (range 19 to 69 y; not significantly different from the total study population). 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 1 h 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. Dyspnoea after sumatriptan was reported by 26 patients (2.2 %, 95 % CI 1.4 %–3.0 %), 21 women and 5 men, of average age 39 y. Of those 26 patients, 24 patients (92 %) experienced dyspnoea within 1 h after administration of sumatriptan, and in 22 patients (85 %) the reaction recurred after rechallenge. Of the 28 patients with obstructive lung disease, 3 patients experienced dyspnoea 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).

Discussion

Postmarketing studies of adverse reactions to drugs can provide information not available from premarketing studies, mainly because the latter are 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. The close temporal relationship between the intake of sumatriptan and chest pain, and the recurrence of the same symptoms after renewed exposure (positive rechallenge) in many patients makes a causal relationship between the use of sumatriptan and chest pain probable in most of the patients. Another interesting adverse reaction was dyspnoea, 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 novel approach. Due to the stringent privacy regulations in The Netherlands [16], we could not send the questionnaires directly to the patients, and instead we 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 remarkably high compared to other studies, e. g. those in the United Kingdom [17], and offers the opportunity for future studies. The fact that the drug dispensing general practitioners record 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 representative of the determinants in our study.

We did not include any reference group in our study for two reasons. First, we were mainly interested in adverse reactions with a close temporal relationship to the 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. And second, 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.

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

We have no direct data about the mechanism of the chest pain observed in our study group, but we cannot exclude a cardiac origin. It is possible that in some patients the chest symptoms were caused by myocardial ischaemia, due to sumatriptan-induced coronary artery spasm. It is well known that coronary artery spasm can be induced by several drugs, including the antimigraine drugs ergotamine and methysergide [18–20]. Some evidence for this hypothesis with regard to sumatriptan can be found in the literature. Isolated human basilar artery rings contracted in response to sumatriptan [21], as did normal and atherosclerotic human epicardial coronary artery rings from explanted hearts [22, 23].

Furthermore, two small studies of patients undergoing diagnostic coronary arteriography demonstrated a significant reduction in coronary artery diameter both after IV and SC administration of sumatriptan [13, 14]. Even during the early evaluation of sumatriptan, when it was administered IV, a case of possible myocardial ischaemia was recorded; the patient experienced chest symptoms accompanied by ST-segment elevation on electrocardiogram [8]. After marketing, several case reports of cardiac disturbances due to use of sumatriptan were published [9–12]. However, despite these indications for a cardiac origin of the chest symptoms, we cannot exclude some other mechanism. In general, no cardiac abnormalities were identified in 10–30 % of the patients with angina-like retrosternal chest pain [24], and oesophageal abnormalities were 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 did not include even one single case of chest pain attributable to sumatriptan, the incidence would have exceeded 5 %. It is surprising that in several studies, including 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 and the exclusion of subjects 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 about 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, it 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 is 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 than has previously been reported, may be the fact that the present patients had taken sumatriptan on several occasions during the study period. The investigation does not give any in sight into the incidence per administration of sumatriptan.

Dyspnoea as an adverse reaction to sumatriptan has previously been 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 between dyspnoea attributed to sumatriptan and obstructive lung disease was demonstrated here. The mechanism of this adverse reaction is unclear, but an increase both in pulmonary arterial pressure and pulmonary wedge pressure due to sumatriptan have been demonstrated [13, 14]. Furthermore, serotonin itself is a bronchoconstrictor, although this para-sympathetic effect is mediated by stimulation of 5-HT_2 receptors [35]. It is not clear, however, whether the dyspnoea 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 its use. In our opinion, every patient with chest pain suggestive of angina pectoris, drug-induced or not, requires careful evaluation, including a history, physical examination, electrocardiogram, and simple laboratory tests [36]. We recommend further investigation 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 questionnaires to patients via their (drug dispensing) general practitioner is a very useful source of information for studying ad hoc problems due to newly marketed drugs.

Acknowledgments We are indebted to the drug dispensing general practitioners in The Netherlands for providing data of their patients and to the patients for returning the questionnaires.

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