An open multi-centre Swiss study on efficacy, safety and tolerability of oral sumatriptan in the treatment of migraine under practice conditions

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Summary

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The objectives of this open study were to determine the efficacy, safety and tolerability of 50 mg and 100 mg oral doses of sumatriptan in migraineurs under practice conditions in Switzerland. Among the patients (n = 163) treated with 50 mg tablets for the first 2 attacks, half (n = 81) were aiming for a higher efficacy and switched to 100 mg for the subsequent 2 attacks. With 50 mg tablets, 2 hours after intake, 63% of the attacks were treated successfully, and 75% after 4 hours. Response rates with the 100 mg treatment (n = 81) were similar: 59% (2 h) and 69% (4 h). Both dosages were well tolerated, with no serious adverse events. The study confirms the dose dependent efficacy of oral sumatriptan. For some patients, the switch from 50 mg to 100 mg single doses appears to be a promising option. The results seem to be fairly comparable to those obtained in other countries, in well controlled studies, and under clinical conditions.

Keywords: sumatriptan; migraine; treatment; oral; efficacy; open multi-centre study

Introduction

Efficacy, safety and tolerability of sumatriptan as a selective agonist at the vascular 5-hydroxytryptamine ($5HT_{1B/1D}$) receptor are well documented for various application routes (sc, oral, nasal, rectal) [1–6].

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This is an extensive investigation of sumatriptan as an oral antimigraine medication under practice conditions. The open trial was done by neurologists, with a view to determining potential differences between the efficacy of sumatriptan in previous trials, compared to that in widely scattered specialists' offices in Switzerland. An individual response to attack-medication is a common experience with migraine-sufferers, not only in terms of efficacy, but also concerning the adverse effects. The dosages, used for a single oral administration, range from 25 to 100 mg. In addition to dose-related effects, the treatment results may be under question for a variety of influences, like conditions and habits in a particular health system, level of medical institution and competence (i.e. accuracy of diagnosis), and sociocultural background. In spite of the already abundant confirmation of the overall usefulness of oral sumatriptan, there still remains a challenge to refine treatment recommendations, not only for every single patient, but also for a given population with its medical providers.

Material and methods

Design and setting: This was an open, multi-centre study conducted in 43 centres in Switzerland between March 1995 and June 1996.

Patients: Enrolled in the study were 18- to 65-year-old community-based patients suffering from migraine without and/or migraine with aura, and with 1 to 6 migraine attacks per month. All patients met the diagnostic IHS criteria [7]. Exclusion criteria were pregnancy and breast-feeding, cardiovascular disorders and arterial hypertension (systolic blood pressure >160 mm Hg and/or >95 mm Hg diastolic blood pressure), substance abuse (including ergotamine), and patients with previous sumatriptan treatment.

Treatment assignment: Patients treated themselves at home for 2 migraine attacks with 50 mg sumatriptan tablets in single doses (treatment 1 [T1]). For those patients who found satisfactory

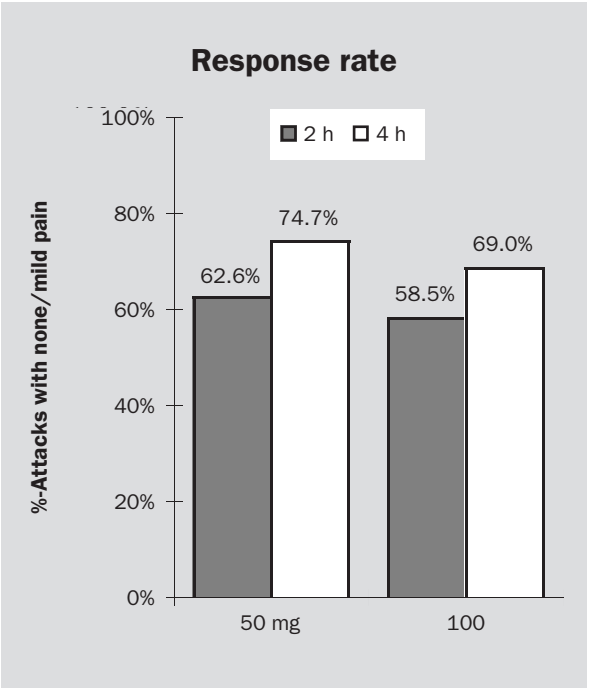
Table 1 Overview of number of patients included in the study.

total number of patients included in the study	188
number of patients not treated with the study medication	19
total number of patients treated with sumatriptan	169
protocol violators, lacking data	6
evaluable patients (per protocol)	163

Table 2 Demographic characteristics of evaluable patients treated with the 50 mg (n = 163) and the 100 mg (n = 81) sumatriptan tablets.

	treatment with 50 mg (n = 163)	treatment with 100 mg (n = 81)
sex, n (%)		
male	32 (19.6%)	15 (18.5%)
female	131 (80.4%)	66 (81.5%)
age (years)		
mean	39.2	39.9
std. dev.	11.1	9.7
min.–max.	18.5–63.3	21.7–63.3

Figure 1
Proportion of successfully treated attacks with the 50 mg tablet (n = 163) and the 100 mg tablet (n = 81), 2 and 4 hours after intake of sumatriptan.



relief of symptoms, the study was terminated. Patients who were not content with the alleviation of migraine symptoms and those who had taken more than two 50 mg tablets aiming to improve relief, were allowed to treat the 2 following attacks with 100 mg sumatriptan tablets in single doses, (treatment 2 [T2]). The maximum daily intake was limited to 300 mg for both dosages. Sumatriptan was provided by Glaxo Wellcome Switzerland in film-coated tablets.

Evaluation of efficacy, safety and tolerability: Headache relief was examined as the primary endpoint for analysis. Patients were advised to quantify the severity of their headaches using a diary card with a four-point scale (0 = no, 1 = mild, 2 = moderate, 3 = severe) at specified times after ingesting sumatriptan (i.e. 1/2, 1, 2, 3, 4 and more hours) and to describe the course of each attack. To be evaluable for the primary analysis, the headache severity prior to treatment had to be a grade 2 or 3. The response rate was defined as a reduction in headache severity by at least 2 grades (from 3 or 2 to 1 or 0). The secondary endpoint was the mean headache severity score change. Safety data were obtained by monitoring all the adverse events, changes in concurrent medication, as well as measurements of vital signs (blood pressure and pulse) at the beginning and end of the study. Tolerability was qualitatively ranked by patients.

Statistical analysis: Descriptive statistics are presented for continuous data. The nonparametric Wilcoxon Signed Rank Test was used for the comparison of headache severity before and 30 minutes after the intake of sumatriptan. Comparison between T1 (50 mg tablet) and T2 (100 mg tablet) was solely performed with the subgroup of patients who made both treatments, using the Wilcoxon Signed Rank Test.

Results

Patients: Of a total of 188 patients, 25 were identified as drop outs (13.3%): for never treating an attack with the study medication (19), protocol violation (5), and lacking data (1). Of the remaining 163 patients, with a mean age of 39.2 years, 131 (80.4%) were female (table 1 and 2). The mean duration of the migraine was 15.8 years, with an average frequency of 3.0 attacks per month. Forty patients (24.5%) sometimes or regularly experienced an aura.

Efficacy of the 50 mg tablet (T1): A total of 163 patients treated 2 attacks with the 50 mg dose. According to the primary endpoint (fig. 1), 62.6% and 74.7% of the attacks were treated successfully upon definition after 2 and 4 hours respectively. As a secondary endpoint, the reduc-

tion in headache severity is also demonstrated as the mean score change (fig. 2). The degree of the headache severity was significantly reduced after 30 minutes ($p < 0.0001$). After 2 hours, the patients rated the intensity of their headaches approximately half as strong as before beginning therapy.

Figure 2 Reduction of the mean headache severity score with the 50 mg tablet at various times after intake of sumatriptan (n = 163).

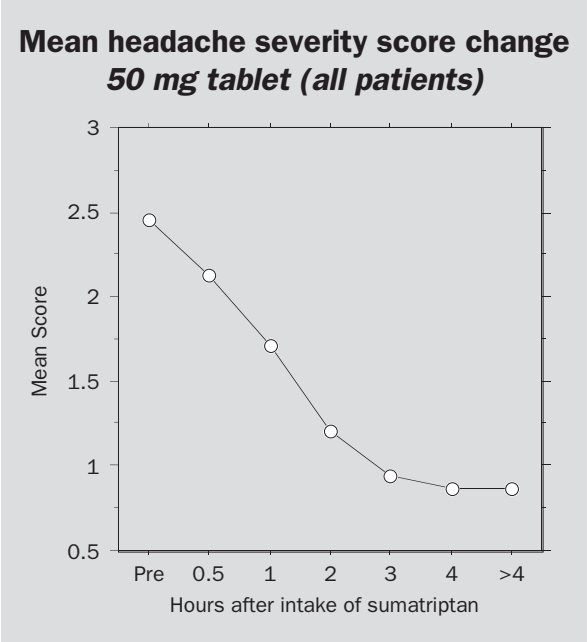
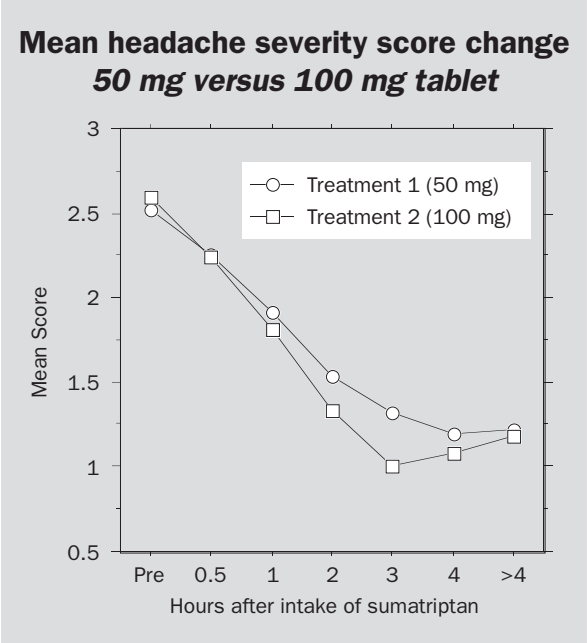


Figure 3 Reduction of the mean headache severity score with the 50 mg and 100 mg tablet at various times after intake of sumatriptan within patients treated with both dosages (n = 81).



Efficacy of the 100 mg tablet (T2): 50% of all patients (81/163) switched to the 100 mg dose, with a response rate of 58.5% after 2 hours, and 69% after 4 hours (fig. 1). With both treatments (T1, T2), a significant reduction in the degree of severity was already reached 30 minutes after intake ($p < 0.0001$). The comparison of the reduction in headache severity between the 50 mg and 100 mg treatment is demonstrated in figure 3. Both curve profiles of the mean score change after the intake of sumatriptan are very similar. There are no significant differences between the results after 2 ($p = 0.21$) and 4 ($p = 0.50$) hours. However, if solely the non responders to the 50 mg tablets were included in the analysis (n = 26), the results with the 100 mg dose were statistically significantly better ($p = 0.004$) than with the smaller dose (fig. 4).

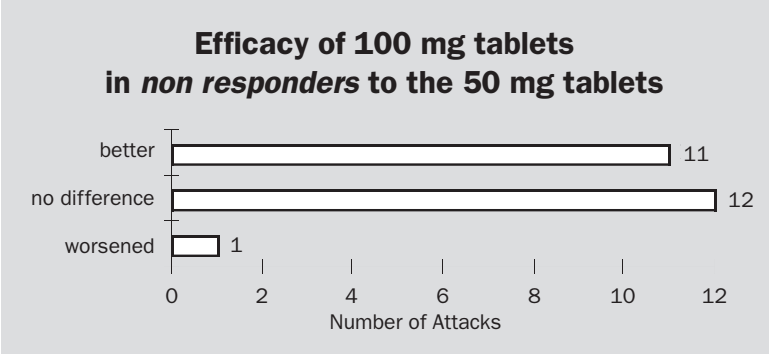
Recurrence headache and rescue medication: Recurrence headache occurred after about 1/3 of the treated attacks (T1 32.2%, T2 39.9%). The need for rescue medication registered in about 1/5 of all the attacks (T1 21.9%, T2 18.5%). Data on the efficacy of these subsequent measures have not been collected.

Tolerability and safety: Sumatriptan was well tolerated: 77.5% of all patients rated the overall tolerability as very good or good. Only 10.9% found the treatment inappropriate, irrespective of the dosage taken. Of the 169 patients included for safety analysis, 39 patients (23%) had one or more adverse events, but none of them was serious. Of a total 66 adverse events (table 3), nausea, chest symptoms, dizziness and tingling were the most commonly reported unwanted effects. 31 of 161 patients (19.3%) reported adverse events with T1, and 15 of 82 (18.3%) with T 2.

Discussion

This open study with a total of 163 patients, suffering from severe to moderate migraine in a Swiss community-based setting, performed in neurologists' offices, reveals a high response rate for oral sumatriptan. With 50 mg tablets, 63% of the attacks were treated successfully after 2 hours and 75% after 4 hours. With 100 mg tablets, used by 50% of all the patients under investigation, we found a response rate of 59% after 2 hours, and of 69% after 4 hours. In both treatments (T1, T2) a significant alleviation of the headache severity was first noticed after 30 minutes, which may be recognised as a rapid onset of action, and after 2 hours the headache severity was rated to be only half as intense as before intake of sumatriptan.

Figure 4 Comparison of the headache severity scores in non responders (n = 26) between the 100 mg and 50 mg dose after 2 hours of treatment. Due to missing data only 24 attacks (n = 17) could be analysed.



The apparent lack of superiority of the 100 mg dose against 50 mg may be explained, at least in part, by a biasing effect: those patients who were relieved from their headaches to a satisfying extent with the smaller dose (50 mg) quit the study, thereby leaving the supposedly more severe migraine sufferers for the 100 mg trial. Beyond this, if only the non responders to the 50 mg dosage were included in the analysis, the results with the 100 mg dose were significantly superior to those obtained within the 50 mg treatment (T1). These observations allow the conclusion, as found in other trials [8–9], that for a selection of patients, failing with 50 mg, it is recommended they try the 100 mg dosage. Overall, the results seem to be rather in accordance with what is known from many investigations in various countries, done in clinical environments and under stringent modalities [3–5, 8, 10–12].

The frequency of recurrence headaches stayed within the expected range [3, 12–14], as well as the need for rescue medication.

The tolerability and safety data are roughly compatible with what is known from other studies.

Summarzing our observations, we may draw the essential conclusion that under accurate management in every day practice oral sumatriptan in 50 mg and 100 mg doses has proved to be a potent and well-tolerated antimigraine agent.

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Table 3 Adverse events in all 169 treated patients.

adverse event	no. of adverse event	frequency (per patient)	frequency (per attack)
nausea	6	3.6%	1.3%
pressure sensation (chest symptoms)	5	3.0%	1.1%
dizziness	4	2.4%	0.9%
tingling	3	1.8%	0.6%
asthenia	2	1.2%	0.4%
bad concentrating ability	2	1.2%	0.4%
dry mouth	2	1.2%	0.4%
heaviness	2	1.2%	0.4%
vomiting	2	1.2%	0.4%
burning	2	1.2%	0.4%
redness	2	1.2%	0.4%
tightness	2	1.2%	0.4%
gastritis	2	1.2%	0.4%
other[1]	30	17.8%	6.5%

[1] other (1 adverse event, 0.6%): allergy of the skin, ankylosis, anxiety, apathy, cervical syndrome, convulsing of the mouth, depersonalisation, depression, dysphagia, excitation, imprudence, irritability, migraine (increasing), numbness, palpitation of the heart, paresthesia, precordial pain, restlessness, rush, sleepiness, tickling, tiredness, trembling, vertigo; not identifiable: 6 adverse events

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