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LONG-TERM USE OF DAILY SUMATRIPTAN INJECTIONS IN SEVERE DRUG-RESISTANT CHRONIC CLUSTER HEADACHE

Chronic cluster headache (CCH) is a rare but severely debilitating condition.¹ Some patients have drug-resistant CCH and continue to have daily attacks using abortive agents for long periods many times per day, mainly subcutaneous sumatriptan (SS).² According to pharmaceutical company indications, the maximum SS dosage is 2 injections (12 mg) per day but these patients often use more. This limitation appears reasonable because of single case reports of cardiac arrest attributable to SS vasoconstrictive properties.^{3,4} Usually these events occur at the initial administration, and an underlying occult coronary artery disease is disclosed.^{3,4} Very little is known about the risk of serious adverse events (AEs) (i.e., stroke, TIA, ischemic heart disease including myocardial infarction, arrhythmia, and any other vascular disorders) when the drug is used 2 or more times per day for long periods.

Classification of evidence. This study provides Class IV evidence that in selected patients with CCH, the continuous use of ≥ 2 SS per day for at least 2 years does not cause serious AEs.

Methods. The aim of this study was to investigate occurrence of serious AEs in patients with CCH using ≥ 2 SS daily for at least 2 years. Fifty-three consecutive patients with CCH (table) followed between 2003 and 2014 who had daily attacks and continuously used ≥ 2 SS per day for at least 2 years were retrospectively considered for serious AE occurrence. The study was conducted in accordance with institutional review board policy, and it provides Class IV evidence. During the 2-year period, all patients were carefully followed with regular visits at our center. Headaches and SS consumption were recorded in headache diaries. ECG was obtained at least twice at 6- to 18-month intervals. Patients were questioned at each visit about serious AEs including angina and any vascular event, and these were recorded. Diagnosis of CCH was made according to International Headache Society criteria.¹ Brain MRI was normal in all patients. None of the patients had a history of stroke, TIA, ischemic heart disease, myocardial infarction, or arrhythmia, or diseases affecting systemic vessels. Main cardiovascular

risk factors are reported in the table. When indicated, arterial hypertension and hypercholesterolemia were controlled by appropriate treatment.

Results. In the 2-year study period, no serious AEs were observed and no patients needed to discontinue SS use. No ECG abnormalities were found. Patients overdosed sumatriptan despite recommendations of their physicians that included full explanation of additional risk due to the smoking habit when present. All patients needed SS full dose (6 mg). At the end of the study period, 42% noticed a subjective certain reduction of SS efficacy both in terms of latency to efficacy and on pain intensity but still considered the drug their first choice to treat the attacks.

Discussion. Safety and efficacy of SS 6 mg were assessed for a 3-month period in 138 patients with cluster headache (CH) who treated 6,353 attacks and had a maximum of 2 attacks daily.⁵ Authors reported no clinically significant treatment effects on vital signs, ECG recordings, or laboratory parameters. Tachyphylaxis was not observed. A total of 2,031 CH attacks in 52 patients (episodic and chronic CH) were recorded in a multicenter study over a period of up to 1 year.⁶ Before entering the study, 81% of the patients had 1–6 cluster attacks per day. In the study period, 36 of the 52 patients (69%) used more than 12 mg of sumatriptan in 24 hours (maximum 36 mg in 24 hours) but no increase in number or severity of AEs was observed during the course of the study. Tachyphylaxis and loss of efficacy were not reported. In a review article on sumatriptan postmarketing experience⁷ approximately 451 serious cardiac AEs within 24 hours after administration of SS, tablets or nasal spray, were reported for more than 236 million migraine attacks and more than 9 million patient exposures between 1992 and 1998. Sumatriptan has a half-life of approximately 120 minutes. The majority of patients who developed serious cardiac events within 1 to 3 hours of sumatriptan administration showed risk factors for coronary artery disease; in most cases, an underlying coronary artery disease was established. Other studies on long-term SS use confirm a low incidence of AEs, tolerance, and tachyphylaxis.^{c1–c4}

In conclusion, our results showed that in well-selected patients, long-term daily SS use did not

Supplemental data
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Table Main clinical characteristics of patients with severe drug-resistant chronic cluster headache using daily sumatriptan injections to abort acute cluster headache

No. of patients	53
Sex	43 M, 10 F
Age, y, median (min-max)	43 (24-70)
Duration of chronic cluster headache, y, median (min-max)	4 (1-27)
Pain side, n	
Right	24
Left	15
Alternating	14
No. of daily attacks, median (min-max)	5 (2-10)
No. of sumatriptan injections per day, median (min-max)	5 (2-10)
Arterial hypertension, n (%)	5 (9.4)
Smoke >10 cigarettes per day, n (%)	42 (79.2)
Hypercholesterolemia, n (%)	12 (22.6)

Four of the 5 patients with arterial hypertension had to modify antihypertensive treatment (2 dosage increase, 2 change of drug) in the study period.

induce serious AEs; this is in line with observations from previous studies with shorter observation periods.^{5,6} More data are necessary to investigate serious AEs attributable to long-term daily use of SS. In these patients, prophylaxis needs to be the main focus because sumatriptan overuse can increase attack frequency.

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