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## Does repeated subcutaneous administration of sumatriptan produce an unfavorable evolution in cluster headache?

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**Abstract** Cluster headache (CH) is one of the most painful primitive headaches that exists. Since 1991, the subcutaneous administration of sumatriptan (SCS) in the treatment of acute attacks has proved to be rapid and effective. Moreover, SCS has an excellent safety-efficacy ratio. To date, there is no information on the modalities of SCS use by CH patients, and on its possible overuse. In fact, some patients have noticed that the use of this drug on a regular basis modifies the evolution of attacks. We retrospectively studied, in 67 patients admitted for CH, the modalities of self-administering SCS the subjective feeling of medication overuse and its repercussions on attacks. A total of 47 patients used exclusively SCS as an acute treat-

ment, 30 of whom had used more than two injections daily. Four patients whose use of SCS was the highest had also been drug addicts. Twenty-two patients using exclusively SCS thought that sumatriptan could have modified the evolution of attacks: 20 patients thought that the attacks occurred more frequently; 11 commented that the attacks became more intense, and the remaining 11 patients stated that sumatriptan had become less efficient. In CH, overuse of sumatriptan could aggravate the evolution of attacks. Further research is needed to corroborate this argument.

**Key words** Cluster headache • Subcutaneous sumatriptan • Medication overuse • Tachyphylaxis

### Introduction

The prevalence of cluster headache (CH) is about one in 1000 [1]. Although CH has a severe and excruciating intensity, little is known of its mechanisms. Recently, however, May et al. [2] showed that the posterior ipsilateral region of the hypothalamus was involved in the process. At present, two acute treatments do exist: subcutaneous administration of sumatriptan (SCS) and oxygen inhalation. The first article depicting the efficacy of SCS in CH was published in 1989 [3]. Since then, sumatriptan has

become the medication of choice in the treatment and management of acute attacks. Overall, 74% of attacks are relieved and this relief appears 15 minutes after subcutaneous administration [4].

It is believed that overuse in this context cannot develop in patients with CH, as is the case in patients with migraine or tension-type headache. However, in some patients, the persistent use of SCS during a bout modified this pathology, bringing about an increase in the frequency or duration of attacks, or a decrease in the treatment efficacy. For this reason, we decided to study the use of sumatriptan in patients admitted

for CH to the Neurology Unit between 1995 and 2000. Our aim was to quantitatively describe the use of SCS, the patients' feelings of overuse, and the possible influence of overuse on the evolution of attacks. A patient's feeling of overuse is personal and subjective, but the patient is the most able to describe if a drug has an influence on the course of a disease. Patients usually know the typical evolution of the disease and the spontaneous rhythm of the attacks.

## Patients and methods

We retrospectively consulted hospital data concerning all patients admitted for CH to the Neurology Unit at the Bordeaux University Hospital between 1995 and 2000. The investigation was done with the aid of the French medical coding system called *Programme de Médicalisation du Service d'Information* (PMSI), which permitted us to identify patients on entering a key word for a given disease. These patients were administrated the following phone interview concerning the disease, the modalities of using sumatriptan, and the influence of SCS on the frequency and severity of attacks:

1. When you have a bout, do you regularly and exclusively use subcutaneous sumatriptan?
2. What is the maximum number of injections you have ever used per day?
3. When you use subcutaneous sumatriptan during a bout, do you ever feel that you overused this drug?
4. If the answer is yes, why?
  - Pharmaceutical recommendations permitted no more than

2 injections daily.

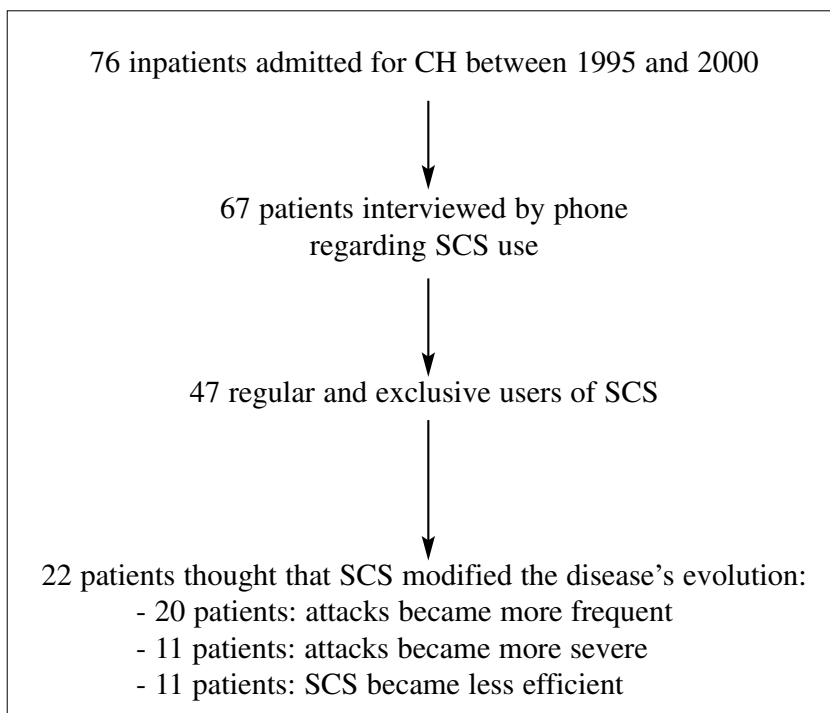
- A rebound effect occurred.
  - The treatment was used in anticipation (subcutaneous injection done before painful headache).
6. Do you feel that overuse modified the evolution of the attacks?
  7. If yes, how?
    - Attacks became more frequent.
    - Attacks became more intense.
    - Sumatriptan became less effective.

The results of the survey were kept confidential.

## Results

A total of 76 patients were admitted to the Neurology Unit for cluster headache (IHS criteria) between 1995 and 2000 (Fig. 1). Of these, 67 responded to the questionnaire by phone, while 9 were lost to follow-up. These 9 patients were not demographically different from the 67 others. The mean age at onset of the disease was 29.7 years (range, 12–80 years). The mean age of patients at the time of the study was 44.9 years. There were 59 men and 8 women. The gender ratio was 7/1. In terms of diagnosis, 58 patients (86.6%) had an episodic form of the disease and nine (13.4%) had a chronic form. Four patients were or had been addicted to heroin.

Regarding the modalities of using sumatriptan, 47 patients (70.1%) used exclusively subcutaneous sumatriptan during



**Fig. 1** Results of the phone interview on the use of subcutaneous sumatriptan (SCS) for cluster headache (CH) treatment

each cluster period to relieve the attack. Among patients not exclusively using SCS, we found patients using either sumatriptan and oxygen inhalation, and patients being frightened of using the subcutaneous route. The age factor made it impossible for others. The distribution of the maximum daily number of subcutaneous injections is given in Figure 2.

Seventeen patients never has used more than two subcutaneous injections daily. For 22 of the 47 patients who exclusively used sumatriptan, the maximal number of daily subcutaneous injections varied from 3 to 6. Eight patients used 8 or more injections daily, with a maximum of 12 injections per day for 2 patients and 13 injections per day for one patient. Among these 8 patients, 4 were or had been drug addicts.

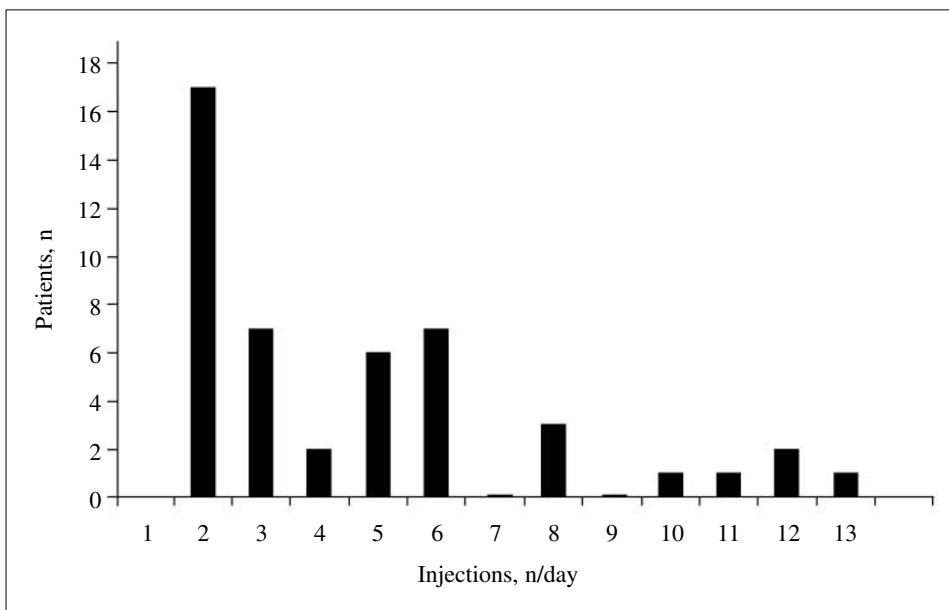
All patients who has used more than two injections daily knew that they overused SCS. Twenty-six patients thought they had a rebound effect (faster onset of the following attack after repeated administration of SCS). Four patients assumed sumatriptan before the attacks became severe. Twenty-two patients out of 47 (46.8%) thought sumatriptan could modify and exacerbate the evolution of attacks: 20 responded that the attacks were more frequent, 11 indicated that the attacks became more severe, and 11 noted that the treatment became less effective.

## Discussion

The clinical data of our sample are close to the results in the largest case series of the literature [5–7]. Our study is of interest because it reveals that many patients exceeded the legal daily dose of subcutaneous sumatriptan. Centonze et al. [11] reported one patient who took 8 injections daily. The

answers to our questionnaire did not provide sufficient information on the number of days SCS was overused, but in clinical practice, we know that many patients use regularly more than 2 injections per day, over a period of weeks. This depends on the duration of the bout. No serious adverse event (particularly cardiovascular) was reported by this group during overuse of SCS. This medication has an excellent safety-efficacy ratio, and overuse did not lead to serious adverse events, even in the 4 patients who reported using more than 10 injections daily. Patients who had already used more than 10 injections daily were male and present or former drug-addicts. Although our sample size is small, drug addiction could be a risk factor in the development of SCS overuse in CH. In addition, this study shows that SCS is not used by all patients, not only because of contraindications: 71.6% of the patients used exclusively subcutaneous sumatriptan, the others associated SCS and oxygen during a bout, or declined using SCS alone for fear of adverse events or being unsure of the subcutaneous route. Some patients had tried SCS and did not want to use it again because they were unsure of the subcutaneous route or were worried about adverse events. All regular and exclusive users of SCS defined overuse as the administration of more than 6 mg twice per day according to pharmaceutical and legal recommendations. We must emphasize that the definition of misuse in cluster headache is not as clear as in migraine: should we say that there is overuse when the legal daily dose is exceeded, or should we use this term only when there are repercussions on the evolution of attacks, as in the case of chronic daily headache and migraine?

The definition of abuse in cluster headache should be discussed. IHS criteria for abuse do exist for other types of



**Fig. 2** Maximum number of subcutaneous injections of sumatriptan per day, in 47 patients with cluster headache

headache. This abuse can develop from migraine, tension-type headache, or chronic headache de novo. IHS criteria of abuse stipulate that overuse must last for longer than 3 months, and that chronic daily headache should disappear 2 months after withdrawal. The same criteria cannot be applied to CH because of the disease's spontaneous evolution and spontaneous remissions: if improvement occurs after withdrawal it could be the result of withdrawal or due to the disease's spontaneous evolution. Moreover, the improvement after withdrawal should be faster than in migraine (maybe a few days instead of one month in the case of withdrawal in chronic daily headache with drug abuse).

The relationship between overuse of sumatriptan and modification of the evolution of attacks has been spontaneously noticed by some patients, and this fact was confirmed by our results: 20 of 47 regular users of this medication considered that the attacks were more recurrent. Eleven of 47 considered the attacks more intense and resistant to treatment. However, reports about a link between overuse of SCS and evolution of attacks are rare. SCS use in CH was reported for the first time in 1989: Krabbe [3] described 6 patients treated subcutaneously with 3 mg sumatriptan. The Sumatriptan Cluster Headache Study Group showed in 1991 [4] that the drug was efficient in 74% of the attacks during the first 15 minutes. Ekbom and colleagues confirmed the same thesis in 1992 [9] and 1993 [10] during, respectively, 480 attacks in one patient and 6353 attacks in 138 patients. In 2000, Centonze et al. [11] noticed there were no cases of tachyphylaxis. However, Goebel et al. in 1998 [12] noticed that for 13% of 52 patients, there was an increase in the number of daily attacks. Moreover, the drug was less effective for chronic cluster headache. In fact, there is only one clear report in

the literature asserting that the frequency of attacks in CH is altered during subcutaneous administration of sumatriptan [13]: in 1999, Hering-Hanit described 4 episodic CH patients treated with the drug for the first time, and who developed a dramatic increase in the frequency of their attacks. Three of them developed chronic daily headache after being put on this medication for 3–4 weeks, and two experienced a longer CH period than previously. In our series, 41.6% of the subjects described an increase in the number of attacks during the treatment period. Since this study was retrospective, patients could have overestimated the possible negative effect of SCS. Moreover patients admitted to hospital for abuse had a more severe disease. This could explain the frequent feeling of overuse in our series. We have no information about preventive medications these patients used, because of the retrospective design of the questionnaire.

The pathophysiology of modification and evolution of the attacks during SCS use in CH is unknown but down-regulation of the 5-HT<sub>1B,D</sub> receptors, psychiatric association with anxiety or tendency to addiction (tobacco, alcohol, illegal substances). Our results will have to be compared to those of prospective studies. As a preventive measure, it would be necessary to associate oxygen with sumatriptan in the case of patients with more than 2 attacks per day. Moreover a preventive treatment with verapamil should be set up at an early stage. It would be worthwhile performing dose-ranging clinical trials for sumatriptan in CH, aimed at proving if 3 mg sumatriptan administered subcutaneously is the ideal dose for obtaining relief during an attack. This information may help decrease the risk of developing overuse. More prospective research is needed. It would be interesting to know the answers about "feeling of overuse" in patients who have used a correct dose of SCS.

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