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Sertraline versus amitriptyline in the prophylactic therapy of non-depressed chronic tension-type headache patients

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Abstract Patients with chronic tension-type headache (CTTH) are the most difficult to treat. Tricyclic antidepressants are the first-line therapeutic agents, but their anticholinergic side effects limit their usage. Selective serotonin reuptake inhibitors (SSRI) with fewer side effects than tricyclic antidepressants have also been used in treatment of CTTH, but the results are conflicting. In this study, prophylactic action of sertraline in treatment of non-depressed patients with CTTH was investigated and compared with amitriptyline in a prospective, randomized, open label, parallel-group study. A 4-week baseline period was followed by a 12-week treatment period with either 50 mg sertraline (n=41 patients) or 25 mg amitriptyline (n=44 patients). Efficacies of treatments were determined by using a headache diary, in which patients recorded the occurrence, number, intensity and duration of headaches in days, analgesic drug consumption and any adverse events. Both drugs reduced headache symptoms and analgesic drug consumption at the first, second and third months of treatment compared to baseline values. There was significant superiority of amitriptyline in the headache symptoms and drug consumption reductions versus sertraline at the second and third months of treatment. Side effects were more favorable in the sertraline-treated patients, but dropouts were similar in both groups. These results suggest that both drugs were effective in the treatment of non-depressed patients with CTTH, but in comparison between groups, amitriptyline was more effective than sertraline.

Key words Chronic tension-type headache • Prophylaxis • Sertraline • Amitriptyline

Introduction

Chronic tension-type headache (CTTH) requires head pain to be present for at least 15 days per month for at least 6 months [1]. Remarkably little is known about its pathophysiology and treatment availability is limited [2]. Various medications including tricyclic antidepressant agents and other antidepressants, non-steroidal anti-inflammatory agents, antiepileptic drugs and muscle relaxants have been used in prophylaxis of CTTH [1, 3]. Several years ago, the tricyclic antidepressant drug amitriptyline was proven particularly effective in the prophylactic treatment of CTTH, inhibiting the presynaptic re-uptake of noradrenaline and 5HT [4–6]. However, its side effects, especially sedation and dry mouth, are not uncommon and are poorly accepted by patients, causing limitation of its use [4, 5]. Other medications for CTTH also have their own limits. Current theories of the

pathophysiology of headaches suggest a disturbance in serotonin neurotransmission, providing a rationale for treatment [7, 8]. Furthermore, an ascending serotoninergic pain modulation pathway from the dorsal raphe nucleus to the parafascicular nucleus of the thalamus has recently been discovered and appears to be of particular relevance to headache syndromes [7, 8]. In consideration of the possible pathological mechanisms of CTTH, it is thought that serotonin-specific reuptake inhibitors may be helpful.

There are some conflicting reports on the efficacy of serotonin-specific reuptake inhibitors on CTTH. Sertraline, a non-tricycle antidepressant, acts more specifically, blocking the presynaptic uptake of 5HT and it also boosts the plasma levels of the B-endorphins [9, 10]. The aim of this study was to evaluate the efficacy of the selective serotonin reuptake inhibitor sertraline (50 mg/day) in comparison with amitriptyline (25 mg/day) in the prophylactic treatment of non-depressed patients with CTTH, in a prospective, open-label, parallel and randomized clinical trial. Main outcome measures were the headache index (which was considered as the overall measure of headache activity, due to its combination of frequency, intensity, and duration measures), analgesic medication consumption and the number of patients reporting side effects. To our knowledge, this is the first study of sertraline in the prophylactic treatment of headache.

Subjects and methods

A total of 120 patients, aged 19–65 years, who met the criteria for CTTH according to International Headache Society [11, 12] were initially selected for study while attending our headache outpatients clinic for the first time. They were enrolled depending on the time of presentation. The study was conducted in accordance with the Declaration of Helsinki and the patients were included in the study after informed consent was obtained. Every patient underwent a complete physical and neurological examination as well as laboratory screening tests.

The presence or absence of major depression was evaluated according to criteria of DSM IV [13] which define this disorder as a condition characterized by the presence of at least five items from a list of symptoms occurring within the same 2-week period, with at least one of the symptoms pertaining to a depressed mood or loss of interest or pleasure. In this interview, we assessed depressed mood, loss of interest in pleasurable activities, weight changes, insomnia or hypersomnia, psychomotor agitation or retardation, fatigue, feeling of worthlessness or excessive guilt, diminished cognitive capacity, and preoccupation with death or suicide. If depression symptoms were present, the patient was sent to the psychiatry clinic and was not included in this study. Patients also completed the Beck depression inventory-II (BDI-II) [14] and we completed the Hamilton scale for depression [15] at the time of enrollment. Patients were excluded from the study if they took antidepressants as prophylactic therapy in the previous year, scored more than 15 points on the Hamilton scale, scored more than 13 on the BDI-II (the suggested cutoff score for mild depression [14]), had other neurological conditions, medical disorders that might interfere with drug absorption, debilitating conditions or any significant abnormality at laboratory screening tests or severe hypertension, or were pregnant or breast-feeding. All patients chosen were compliant with following instructions, completing diaries and giving informed consent.

All patients who enrolled in this study were allocated a 4-week screening period. In this period, patients did not received any prophylactic drug, but they used analgesic drugs for their headache. After a 4-week run-in period, 90 patients whom continued to meet the inclusion and exclusion criteria were randomly allocated to two groups, taking either sertraline (40 women, 4 men) or amitriptyline (39 female, 7 male) for 12 weeks.

Amitriptyline was introduced during the first week at a dosage of 10 mg sid, and thereafter it used a dosage of 25 mg sid. Sertraline was introduced at 50 mg as a morning dose. Patients were instructed to continue their usual analgesic regime. Permissible analgesics included simple analgesics (e.g. aspirin, acetaminophen and non-steroidal anti-inflammatory drugs).

Follow-up visits were performed at 4-weeks intervals. At each visit, the headache diary was checked, and side effects reported by the patients were recorded. Compliance was assessed by counting the number of used or remaining drug units in the amitriptyline bottle or the sertraline blister at each monthly visit. Participants were defined as compliant with the treatment if they had adhered to the drug regimen (more than 80% of the tablets taken as scheduled during each treatment period) and had given complete data in the diary.

Using a self-assessment questionnaire, patients recorded the number and duration of headaches in days, the name, number and dose of analgesic drug used, and any adverse events. Headache intensity was scored on a visual analogue scale, in which 0 is no headache and 10 is extremely bad headache. Headache duration was recorded as the numbers of hours of the headache each day. One unit of analgesic drug was equivalent to 500 mg aspirin. All participants were advised to contact a doctor if any problems arose. Using the patients' diaries, overall headache index (headache frequency x average intensity x duration/28) was computed. The percentage of reduction in headache index compared with baseline was computed as ([baseline headache index-third month headache index]/baseline headache index) x 100. A reduction greater than 50% was considered to be effective treatment.

Statistical analysis of results was done with SPSS for Windows. All values were displayed as mean and SD. Visual and statistical examination of the measures met criteria for a normal distribution and statistical analysis relied on parametric measures. Data was compared between amitriptyline and sertraline groups using chi-square test for categorical variables and Student's *t* test for continuous variables. Pre-post comparisons of all outcome measures (headache indices and drug consumptions) were made for each group, using analysis of variance for repeated measures. If the overall analysis for repeated measures was significant, then post hoc comparisons of run-in period measures to weeks 0–4, weeks 5–8 and weeks 9–12 were made using paired *t* tests. For three comparisons, acceptable significance level was $p<0.0167$ ($p<0.05$ divided by three planned comparisons). Hypothesis tests were two-tailed with a significance level of $p<0.05$.

Results

Of 90 patients who participated in the study, 84 (37 women, 4 men in the sertraline group and 38 women, 5 men in the amitriptyline group) completed the study and provided efficacy measurements (Table 1). Twenty-two patients also met the criteria for co-existing migraine (8 in amitriptyline group; 14 in sertraline group). The age distribution was from 19 to 64 years (40.4±11.4 years) in the amitriptyline group and from 19 to 65 years (37.8±12.2 years) in the sertraline group. The time since the onset of headaches ranged from 1 to 25 years (11.7±7.1 years in amitriptyline group, 10.8±7.5 years in sertraline group). No significant difference was seen between the groups for gender, age or time of headache from the onset. There was no significant difference between amitriptyline and sertraline groups regarding Hamilton score (4.60±2.98 in sertraline group; 5.04±3.40 in amitriptyline group, p=0.53). At the beginning of the study, the number of the enrolled patients with a Hamilton score >8 and <15 was 24 (11 in sertraline group; 13 in amitriptyline group; χ^2, p=0.813).

Significant decreases in headache index and drug consumption were observed in both groups as soon as the first month compared to baseline measures (p<0.001) and thereafter such significant decreases continued during the study (p<0.001).

Comparison of the headache index between the sertraline and amitriptyline groups is presented in Table 2 and Fig. 1. The overall repeated-measures ANOVA for headache index improvement over the 3 months of therapy revealed a significant trend for increasing improvement in sertraline group (F=43.7, df=3, p<0.001) and in amitriptyline group

Table 1 Main efficacy parameters in patients with chronic tension-type headache, by treatment. Values are mean (SD)

	Sertraline, 50 mg (n=41)				Amitriptyline, 25 mg (n=43)			
	Frequency (days/4 weeks)	Duration (hours/day)	VAS score (cm)	Drug consumption (number of tablets/4 weeks)	Frequency (days/4 weeks)	Duration (hours/day)	VAS score (cm)	Drug consumption (number of tablets/4 weeks)
Run-in period	17.4 (3.0)	9.7 (4.5)	5.6 (1.3)	27.6 (12.0)	20.2 (3.9)	10.0 (4.9)	4.9 (1.3)	27.2 (12.0)
Weeks 0–4	15.7 (3.3)	8.6 (4.6)	4.9 (1.4)	24.0 (11.0)	15.7 (3.3)	8.0 (3.3)	3.7 (0.9)	24.3 (10.8)
Weeks 5–8	14.2 (4.0)	7.8 (3.6)	3.7 (0.8)	23.5 (8.8)	14.4 (4.5)	6.5 (2.7)	3.0 (1.2)	18.9 (10.0)
Weeks 9–12	13.8 (4.2)	7.6 (4.0)	4.5 (1.6)	22.4 (9.5)	13.0 (5.5)	6.3 (3.9)	2.8 (1.4)	17.0 (10.6)

Table 2 Comparative efficacy of drugs for prophylaxis of chronic tension-type headache. Values are mean (SD) unless otherwise indicated

	Sertraline, 50 mg (n=41)	Amitriptyline, 25 mg (n=43)	t	df	p[a]
Headache index					
Run-in period	33.1 (20.2)	36.9 (21.8)	1.10	82	0.41
Weeks 0–4	23.4 (13.4)*	19.2 (12.5)*	0.13	82	0.14
Weeks 5–8	18.0 (11.8)*	11.4 (8.9)*	4.99	82	0.006
Weeks 9–12	17.2 (13.0)*	10.8 (11.8)*	0.29	82	0.02
Drug consumption (number of tablets/4 weeks)					
Run-in period	27.6 (12.0)	27.2 (15.5)*	3.17	82	0.9
Weeks 0–4	24.0 (11.0)*	24.3 (10.0)*	0.12	82	0.8
Weeks 5–8	23.5 (8.8)*	18.9 (10.0)*	1.05	82	0.02
Weeks 9–12	22.4 (9.5)*	17.0 (10.6)*	1.14	82	0.01
Average reduction in headache index at weeks 9–12 vs. run-in period (%)	44.4	70.3	0.19	82	0.001
Patients with 50% or more reduction in headache index at weeks 9–12, n (%)	18 (44)	31 (72)	–	1	0.009

* p<0.001 in measures of both groups compared with the measures of run-in period

[a] Comparison of sertraline versus amitriptyline groups

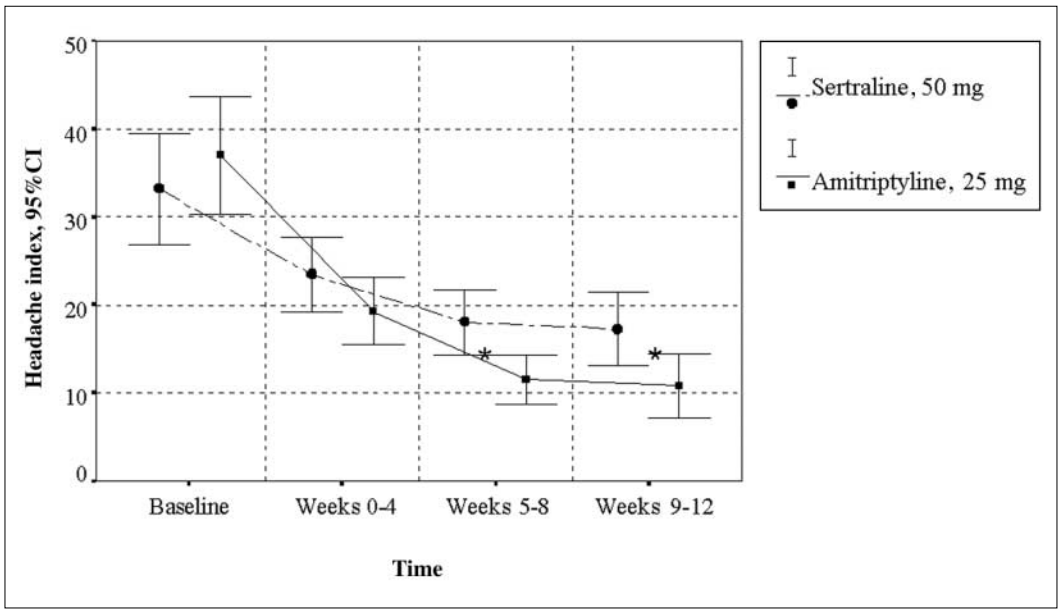

Fig. 1 Comparison between sertraline and amitriptyline in headache index reductions. *p<0.05

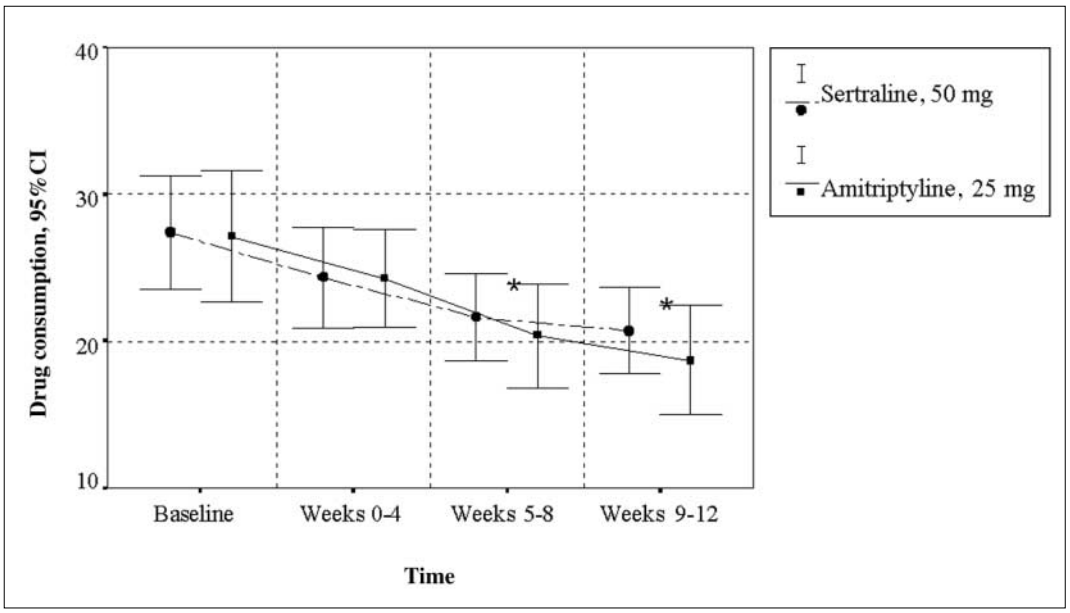

Fig. 2 Comparison between sertraline and amitriptyline in drug consumption. *p<0.05

(F=69.6, df=3, p<0.001). Headache index showed more significant improvements (p<0.05) in the amitriptyline group when compared with sertraline at the second and third months of the therapy.

Comparison of drug consumption between the sertraline and amitriptyline group is presented in Table 2 and Fig. 2. The overall repeated-measures ANOVA for drug consumption over the 3 months of therapy revealed a significant trend for decrease in sertraline group (F=7.37, df=3, p<0.001) and in amitriptyline group (F=12.7, df=3, p<0.001). Drug consumption showed a more significant decrease (p<0.05) in amitriptyline group when compared with sertraline. Significant difference between groups was seen at the second and third months of therapy.

Group x time period interactions reflected a more significant extent of headache improvement (F=6.97, df=3, p<0.001) and decrease in drug consumption (F=3.32, df=3, p=0.02) in amitriptyline group when compared to sertraline group.

The adverse effects reported by the patients are presented in Table 3. Both drugs were generally well tolerated, although amitriptyline induced significantly more side effects than sertraline. The difference between sertraline and amitriptyline was due to a higher number of patients complaining of dry mouth and sedation during amitriptyline

Table 3 Patients reporting adverse effects or ineffectiveness of the drug

Adverse events	Sertraline, 50 mg (n=44)	Amitriptyline, 25 mg (n=46)	*p*
Sedation	10	22	0.013
Nausea	9	6	0.51
Dry mouth	3	19	0.001
Constipation	2	4	0.40
Nervousness	5	6	0.80
Dizziness	8	10	0.60
Increased appetite	7	9	0.60
Sleep disturbances	5	3	0.40
Weight gain	4	4	0.97
Discontinuation due to adverse effect	1	2	0.58
Dropouts due to ineffectiveness	2	1	0.52

therapy. Nevertheless, the drop out rate caused by drug side effects was not different between the groups. Two patients in amitriptyline group and 1 patient in sertraline group discontinued drugs because of adverse effects. One patient in amitriptyline group and 2 patients in sertraline group did not continue the study because of ineffectiveness of therapy.

Discussion

In this study, the efficacy of the selective serotonin reuptake inhibitor sertraline in the prophylactic treatment of non-depressed patients with CTTH was investigated and compared with amitriptyline, a drug that is traditionally used in the prophylaxis of CTTH.

Although both drugs reduced headache index and analgesic drug consumption, amitriptyline was significantly superior to sertraline at the second and third months of therapy. Besides the reduction in headache index, the significant decrease in the number of tablets of analgesic taken was the subjective opinion of headache relief expressed.

Amitriptyline induced more side effects than sertraline but side effects were generally mild and dropouts caused by drugs were similar in both groups. The side effects were usually the most prominent in the first week of treatment and gradually decreased as the treatment took effect.

Many drugs have been used to treat CTTH. Amitriptyline was considered to be one of the most effective drugs and there have been several studies demonstrating efficacy of amitriptyline for the treatment of CTTH. On the other hand, several SSRI have been tried in the treatment of headache. Although some of these studies showed the efficacy of SSRI, even comparable with amitriptyline [16–18], some others studies contradicted this result [19, 20].

We used a fixed daily dose of 50 mg sertraline, which was the lowest dose recommended for the treatment of depression. In comparison, the dose of amitriptyline was much lower than the recommended dose for the treatment of depression [4–6, 20–22]. Even in our study, amitriptyline doses were lower than the dose used in most previous studies.

The mechanism of action of antidepressant drugs in the treatment of tension-type headache is unclear, but some clinical studies have shown that the antinociceptive effects of these drugs seem relatively independent of the antidepressant activity and the effective dosage in headache is usually much lower than that used in the treatment of depression [4–6, 23–26].

Our study supports this by the findings of an effect of low-dose amitriptyline in non-depressed patients with CTTH. Previous studies were assumed that analgesic properties of tricyclic antidepressants could be ascribed to the blockage of serotonin and noradrenalin reuptake in CNS [20, 24, 27].

The present study indicates that selective serotonin reuptake inhibition by sertraline, which has antidepressant properties comparable with the tricyclic drugs but a far better side effect profile, is less effective than nonselective reuptake inhibition by amitriptyline in management of CTTH [28]. In addition, while sertraline is only an extremely specific blocker of serotonin reuptake [27], amitriptyline also has effects on adrenergic [29], cholinergic [30], and histaminergic [31] receptors, besides the serotonin and noradrenalin reuptake inhibition [32], although this study does not allow any firm proof on this issue. In addition to the inhibition of noradrenaline and serotonin reuptake, other mechanisms also may contribute to the analgesic effects of tricyclic antidepressants.

We cannot conclude the possibility that a better effect would have been obtained with a higher dose of sertraline, but previous studies with other SSRI inhibitors in others pain disorders contradict this [5].

Our study suffers from being not blind; however, we believe that our observations may provide some useful therapeutic options.

In conclusion, amitriptyline was found to be more effective than sertraline for prophylactic treatment of CTTH. On the other hand, amitriptyline is an inexpensive drug. Despite the excellent side effect profile of sertraline, its side effect profile makes it not deserve to be the drug of choice in the treatment of non-depressed patients with CTTH. It can possibly be the drug of choice when a more effective antidepressant, for example amitriptyline, cannot be tolerated. Further placebo-controlled studies are needed to shed light on this issue.

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