Short communication

Pilot study of milnacipran in panic disorder

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Summary — Ten outpatients with panic disorder were treated over an 8 week-period with milnacipran, an antidepressant active on both noradrenergic and serotonergic systems, at a dose between 100 and 150 mg/d. Clinical assessments included the Hamilton Anxiety Scale and the Cottraux Rating Scale for phobias, panic attacks, and generalized anxiety. Results showed very significant improvements in the frequency and intensity of panic attacks and in the level of generalized anxiety. A good or excellent response was noted in 7 patients. Only 3 patients complained of side-effects, mostly of the digestive type. These promising results of milnacipran in panic disorder need to be confirmed in controlled studies.

milnacipran / panic disorder

Introduction

There is circumstancial evidence for the involvement of noradrenergic as well as serotonergic neuronal systems in the pathogenesis of panic disorders (Uhde *et al*, 1985; Charney and Heninger, 1986). Milnacipran is a new antidepressant selected for its equipotent inhibition of noradrenaline and serotonin uptake and its lack of effect on postsynaptic receptors (Moret *et al*, 1985). Double-blind studies have demonstrated an antidepressant efficacy at least similar to that of amitriptyline in severely depressed inpatients, associated with a better tolerance (Ansseau *et al*, 1989a, 1989b).

Therefore, the purpose of this pilot study was to test the activity of milnacipran in panic patients. Indeed, the activity of the compound on both noradrenergic and serotonergic systems and its lack of anticholinergic side-effects could represent a therapeutic improvement in panic disorders.

Subjects and Methods

Subjects

Ten outpatients meeting DSM III-R criteria for panic disorder entered the study. In addition, patients had to present a score of at least 8 on the Covi Scale for anxiety, higher than the associated score on the Raskin Scale for depression (Lipman, 1982) and a lack of clinical improvement at the end of a 7-day placebo course. Eight patients were classified as "panic disorder with agoraphobia" (300.21) and 2 patients as "panic disorder without agoraphobia" (300.01). Patients were 7 men and 3 women, aged 20 to 52 years (mean age, 35.7 ± 9.1 years). The duration of the current symptomatology ranged from 1 to 25 months (mean 7.9 months ± 9.3). Seven patients had previously been treated with benzodiazepines, but none with antidepressants. Patients presenting any evidence of serious or uncontrolled medical illness were excluded from the study.

The protocol was approved by the Ethical Committee of the University of Liège Medical School and all patients gave informed consent.

Methods

After a single blind course of at least 7 days on placebo, patients were treated with milnacipran at a daily dose, with a dose of 100 mg being reached on day 6, with 50 mg from day 1 to day 3 and 75 mg on days 4 – 5. The treatment was administered in 2 daily intakes (morning and evening). The daily dose could be increased to 150 mg at day 14 in case of insufficient improvement (global evolution rated not better than minimally improved on the Clinical Global Impressions) and good tolerance. The duration of the study was 2 months, with clinical assess-

ments 1 week before inclusion, at inclusion, and after 2, 4, and 8 weeks of treatment. Associated psychotropic drugs, including benzodiazepines, were excluded.

Assessments

Each assessment included the Hamilton Anxiety Scale (Hamilton, 1959) and the Rating Scale for Phobias, Panic Attacks, and Generalized Anxiety (Cottraux *et al*, 1985). This recently developed scale assesses over the previous week the frequency and intensity of panic attacks, the level of diffuse anxiety, as well as the level of anxiety and avoidance associated with the phobic stimuli. All symptoms occurring or increasing in severity during the treatment period and which could be related to milnacipran were recorded as side-effects. They were either spontaneously reported by the patients or elicited by general questions about the major body functions. In the absence of a control group, a systematic checklist was not used. Blood pressure and pulse rate were also recorded. In addition, the final evaluation included an overall assessment of both the therapeutic effect and tolerance.

Data analysis

Statistical analysis used multivariate analysis of variance with repeated measures (SAS programs). Four periods were systematically studied: from day 0 to day 7, 14, 28 and 56.

Results

Hamilton Anxiety Scale

The total score on the Hamilton Anxiety Scale decreased significantly during the study ($F(4,6) = 5.78$; $P = 0.03$), with a significant improvement already noted after 2 weeks of treatment ($P = 0.004$) (table I).

Cottraux Rating Scale for Phobias, Panic Attacks, and Generalized Anxiety

The frequency of panic attacks presented a significant decrease with time: $F(4,5) = 8.00$; $P = 0.002$, with a trend already present after 1 week ($P = 0.005$) and a significant change after 1 month ($P = 0.03$) (table I). The intensity of panic attacks also decreased significantly with time: $F(4,6) = 4.70$; $P = 0.05$, with a trend already noted after 1 week ($P = 0.06$) and a significant improvement after 2 weeks ($P = 0.05$) (table I). The rated level of generalized anxiety decreased significantly ($F(4,6) = 10.37$, $P = 0.007$), with a trend already noted after 1 week ($P = 0.08$) and a significant improvement after 2 weeks ($P = 0.005$) (table I). Last, the rated level of anxiety and avoidance associated with the main phobic stimulus presented a trend toward significant decrease ($F(3,5) = 4.64$; $P = 0.07$) but was significantly improved after 1 month ($P = 0.03$) (table I).

Side-effects

Three patients complained of digestive side-effects (nausea) respectively from day 7 to day 56, from day 1 to day 28, and from day 2 to day 14, associated in the latter case with drowsiness from day 1 to day 7. An anti-emetic drug (metoclopramide) was needed in the first case. Reducing the dose of milnacipran or dropping-out of the study was never necessary.

The pulse rate exhibited a trend toward significant decrease with time ($F(4,6) = 4.09$; $P = 0.06$) while the systolic and diastolic blood pressures were unchanged.

Table I. Mean initial scores and decrease (%) during milnacipran treatment.

	Day−7	Initial score	Decrease (%)			
			Day 7	Day 14	Day 28	Day 56
Hamilton Anxiety Scale	24.1	25.0	5.2	22.4**	43.2*	54.4*
Cottraux Scale:						
Frequency of attacks	6.2	6.6	7.6	20.0	47.9*	57.6*
Intensity of attacks	5.6	5.7	8.8	19.3*	47.4*	57.9*
Generalized anxiety	5.2	5.4	5.6	16.7**	25.9**	48.1**
Phobic anxiety/avoidance	7.0	7.1	0.0	5.3	35.1*	50.9

* $P < 0.05$; ** $P < 0.01$.

Global assessments

Overall, 7 patients were considered as responding to treatment (much or very much improved on the Clinical Global Impressions) and wished to pursue the same treatment. Among those 7 patients showing positive results, 4 had already improved after 2 weeks. After 2 weeks of milnacipran the daily dose was increased from 100 to 150 mg in 8 patients and rated as useful in 75% of the cases.

The treatment was globally rated as well tolerated in all cases.

Discussion

The results from this pilot study have shown the beneficial activity of a new antidepressant, milnacipran, in patients with panic disorder. Indeed, 7 of 10 patients with panic disorder presented good or excellent results and the intensity of panic attacks as well as the level of generalized anxiety dropped. The phobic symptoms were also improved yet to a lesser degree. It is worth noting that none of the patients included in this study had previously been treated with antidepressants but that 7 of them had taken benzodiazepines, including alprazolam 1.5 mg/day in one case, without any improvement.

The use of a higher dose of milnacipran could have improved its therapeutic results. Indeed, we recently demonstrated in double-blind comparisons with amitriptyline that a daily dose of 200 mg of milnacipran was substantially more beneficial than a 100 mg daily dose in severely depressed inpatients (Ansseau *et al*, 1989a, b).

The predominance of men in our sample does not correspond to the general sex distributions of panic disorder patients in clinical populations; panic disorder without agoraphobia is about equally common in men and in women, while panic disorder with agoraphobia is about twice as common in women as in men (American Psychiatric Association, 1987).

An important pitfall in this type of open study is linked to the possible placebo effect or to the spontaneous evolution of the illness. Concerning the placebo effect, the fact that the patients received placebo in a single-blind protocol for 1 week before inclusion without any improvement can be taken as indicative of a true pharmacological effect of milnacipran; concerning a possible spontaneous improvement of panic symptoms with time, it should be noted that the mean duration of the illness was about 8 months without any spontaneous improvement.

As predicted by the pharmacological properties, we found milnacipran to be effective in panic disorder. Clinical efficacy was associated with a tolerance unusual for an antidepressant. Obviously, these promising pilot results need to be confirmed in larger controlled comparisons with standard compounds such as imipramine or phenelzine.

Acknowledgment

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