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Pilot Study of Flesinoxan, a 5-HT1A Agonist, in Major Depression: Effects on Sleep REM Latency and Body Temperature

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Flesinoxan is a highly potent and selective 5-HT1A full agonist, active in several models of depression. In this pilot open study, flesinoxan (4 mg/d) was administered orally for 4 weeks in 16 major depressive, mostly treatment-resistant inpatients exhibiting a score of at least 19 on the Hamilton depression sale. Weekly ratings included Hamilton depression scale, Montgomery and Asberg depression scale (MADRS), and Clinical Global Impressions (CGI). Results showed considerable improvement in depressive symptomatology, with mean MADRS scores (SD) dropping from 35·7 (10·0) to 13·0 (11·9) and CGI-illness severity from 5·69 (1·14) to 2·73 (1·62) after 4 weeks of treatment. Moreover, 13 patients were classified as much or very much improved on the CGI-global improvement. The tolerance of flesinoxan was excellent, with only four patients exhibiting side-effects. In contrast to acute studies with 5HT1A agonists, flesinoxan induced no significant decrease in daily oral temperature over the 4-week period. In eight melancholic patients, the mean REM latency (SD) of respectively 35·6 (15·9) and 40·2 (17·9) min during two baseline nights significantly increased to 51·9 (20·9) min during a double-blind challenge night with flesinoxan 1 mg as compared to 42·0 (16·1) min with placebo, and to respectively 55·6 (29·9) and 55·6 (30·2) min during the last two treatment nights. All these findings encourage further developments of flesinoxan as a promising antidepressant.

KEY WORDS—Flesinoxan, 5-HT1A agonists, antidepressant, major depression, REM latency, body temperature.

INTRODUCTION

Flesinoxan is a highly potent and selective 5-HT1A full agonist ($Ki = 1·7$) surpassing both buspirone, gepirone, and ipsapirone in receptor affinity and with at least 80-times weaker affinity for any other receptor (Shipper *et al.*, 1991). Flesinoxan is active in several animal models, is more potent and longer acting than classical antidepressants (Shipper *et al.*, 1991; Hest *et al.*, 1992). Flesinoxan, like most antidepressants, down-regulates the beta-adrenergic system by uncoupling the receptor from the second messenger, probably via 5-HT1A post-synaptic receptors (Shipper *et al.*, 1991). Flesinoxan, a *full* post-synaptic 5-HT1A agonist, could exhibit a faster onset of action and/or a higher antidepressant efficacy compared to partial 5-HT1A agonist such as gepirone, ipsapirone, and buspirone. Flesinoxan was initially developed as an antihypertensive drug (Wouters *et al.*, 1988); clinical trials however did not support its antihypertensive efficacy but showed an excellent tolerance (De Voogd and Prager, 1990).

A shortening of rapid eye movement (REM) sleep latency has been proposed as a biological correlate of major depression (Kupfer, 1976). In addition, most antidepressants, such as amitriptyline, desipramine, clomipramine, trazodone, fluvoxamine and fluoxetine, are responsible for a lengthening in REM latency, which has been correlated with their clinical efficacy (review in Kupfer *et al.*, 1987).

Acute studies in animals and in humans have shown that activation of 5-HT1A receptors causes a reduction in core temperature (Hjorth, 1985; Goodwin *et al.*, 1987; Anderson *et al.*, 1990; Lesch *et al.*, 1990). Studies in rats showed similar activity for flesinoxan (Wouters *et al.*, 1988). Little is known however about the influence of 5-HT1A agonists on body temperature after chronic administration.

In this context, the purpose of our study was threefold: first, to evaluate the antidepressant efficacy and the tolerance of flesinoxan in a selected group of major depressive inpatients; second, to

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assess the influence of flesinoxan on the shortened REM latency characteristic of major depression; and third, to assess the influence of flesinoxan on body temperature after chronic intake.

METHODS

Subjects

Sixteen inpatients, representing consecutive admissions to the Psychiatric Unit of the University Hospital of Liège who fulfilled DSM-III-R criteria for a major depressive episode (American Psychiatric Association, 1987) and had a score of at least 19 on the 17-item Hamilton depression scale (Hamilton, 1960) were included in the study: one man and 15 women, with age ranging from 33 to 64 years and a mean age (SD) of 49·9 years (10·1). A subsample of eight DSM-III-R melancholic patients were included in the sleep protocol: one man and seven women, with age ranging from 43 to 64 years and a mean age (SD) of 54·5 years (8·8). This subsample fulfilled DSM-III-R criteria for melancholic type, had a score of at least 21 on the Hamilton depression scale, and a REM latency shorter than 90 min on at least one of two baseline sleep recording nights (Ansseau *et al.*, 1985). Patients presenting any evidence of serious or uncontrolled medical illness, as evidenced by history, physical examination, EKG, chest-X ray, EEG and laboratory tests were excluded from the study. All patients were included after a drug-free period of at least 1 week.

Assessments

Assessments included weekly Montgomery and Asberg Depression Scale (MADRS; Montgomery and Asberg, 1979) and Clinical Global Impressions (CGI) (Guy, 1976), vital signs, and signs and symptoms of any possible adverse events, and Hamilton depression scale at baseline and end of the study. Moreover, EKGs, laboratory tests, and body weight were recorded during the screening period and at the end of the study.

For the subjects participating in the sleep study, whole-night sleep EEGs were recorded, using Oxford Medilog 900 portable devices, during two baseline nights, during two placebo-controlled challenge nights with flesinoxan 1 mg or placebo given at 20·00 h in double-blind and cross-over conditions as well as during the two final nights of the study and scored according to the criteria of Rechstaffen and Kales (1968). Sleep onset was defined by the first min of stage II sleep that was followed by at least 10 min of stage II sleep, interrupted by no more than 2 min awake or in stage I sleep and REM latency was defined as the time between sleep onset and the first REM period (which had to last at least 3 min), minus any intervening wake time (Reynolds *et al.*, 1983).

Body temperature was measured orally every morning at 08·00 h, using a Philips electronic device with a 0·01°C accuracy.

Design of the study

Flesinoxan was administered orally bid in a stepwise fashion: 0·5 mg in the evening on day 1, 0·5 mg bid on day 2, 0·5 mg in the morning and 1 mg in the evening on day 2, 1 mg bid on days 4–5, 1 mg in the morning and 2 mg in the evening on day 6 and then 2 mg bid for the remaining of the 4-week study period. No other psychotropic drugs were allowed during the study period, except the occasional intake of low-dose hypnotic benzodiazepine in patients not involved in the sleep protocol.

Data analysis

Changes over time in severity rating and in body temperature were analysed using multivariate analysis of variance (MANOVA's) with repeated measures. Comparisons of REM latencies used Student *t*-test(two-tailed).

RESULTS

Dropout

One patient dropped out of the study after 2 weeks for inefficacy.

Efficacy

Flesinoxan induced a very significant improvement on the MADRS, the Hamilton depression scale and the CGI (Table 1). On the CGI of improvement, six patients were rated as very much improved, seven as much improved, one as minimally improved and two as unchanged.

Adverse events

Adverse events were noted in only four patients: nausea and vomiting, insomnia, irritation of the mouth, and gastric pain and insomnia. Blood pres-

Table 1. Efficacy of flesinoxan in 16 major depressive inpatients (mean and SD)

	Baseline	Wk 1	Wk 2	Wk 3	Wk 4	*F*	*p*
MADRS	35·7 (10·0)	30·1 (11·3)	24·9 (13·2)	18·0 (11·6)	13·0 (11·9)	31·17	0·0001
Hamilton depression scale	31·4 (8·3)	—	—	—	13·7 (11·5)	7·31	0·0001
CGI-severity	5·69 (1·14)	5·00 (1·41)	4·37 (1·71)	3·53 (1·60)	2·73 (1·62)	30·15	0·0001
CGI-improvement	—	3·31 (0·95)	2·87 (0·96)	2·20 (0·94)	1·80 (0·86)	13·50	0·0001

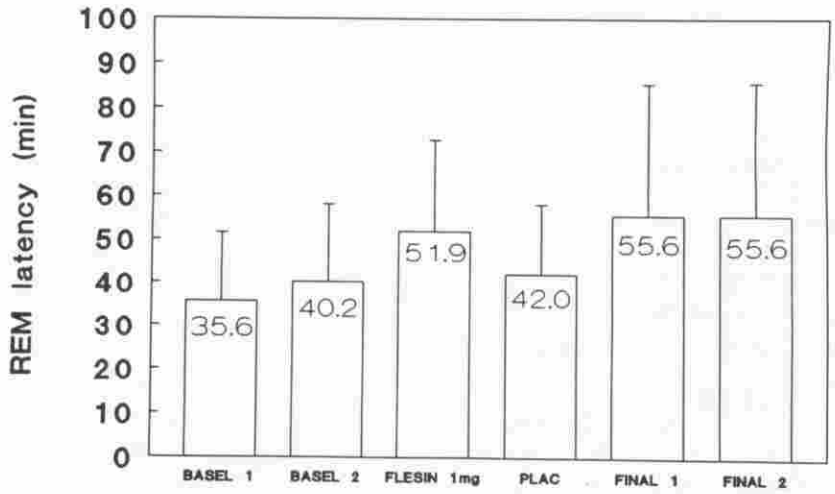

Figure 1. Influence of flesinoxan on REM latency in eight melancholic patients: after two baseline nights (BASEL 1 and 2), 1 mg flesinoxan (FLESIN 1 mg) or placebo (PLAC) was administered in double-blind and crossover conditions during two challenge nights; REM latency was also recorded at the end of the 4-week treatment period with flesinoxan 4 mg/d (FINAL 1 and 2).

sure, pulse rate, and weight did not exhibit any significant changes over time. Finally, no significant alteration in the EKGs and in the laboratory tests were noted.

REM latency and body temperature

Baseline REM latencies significantly increased during the flesinoxan challenge night ($t = 4{\cdot}13$, $df = 7$, $p < 0{\cdot}005$) and at the end of the treatment period ($t = 2{\cdot}31$, $df = 7$, $p < 0{\cdot}05$) (Figure 1). During the challenge nights, REM latencies were also significantly longer with flesinoxan than with placebo ($t = 3{\cdot}65$, $df = 7$, $p < 0{\cdot}005$). Body temperature did not exhibit any significant evolution throughout the study ($F = 1{\cdot}57$, $df = 27$, n.s.).

DISCUSSION

The results of the present pilot study suggest excellent efficacy and tolerance of flesinoxan in this group of severely depressed inpatients. Indeed, 13 out of 16 patients (81 per cent) were rated as 'much/very much improved' and 12 out of 16 patients (75 per cent) did not exhibit any adverse events. These findings support the antidepressant potential of 5-HT1A agonists already demonstrated for buspirone (Rickels *et al.*, 1990), gepirone (Jenkins *et al.*, 1990), and ipsapirone (Heller *et al.*, 1990). In comparison with these previous compounds, flesinoxan behaves as a *full* agonist instead of as a *partial* agonist at the 5-HT1A receptor and is far more potent, which could represent clear advantages in terms of antidepressant efficacy.

Flesinoxan was responsible for a lengthening in REM latency which supports its antidepressant potential. A single blind study using buspirone 5 mg in eight anxious outpatients also found an increase in REM sleep latency but at a statistically nonsignificant level; by the end of the 3-week trial, all patients had returned to baseline values (De Roeck *et al.*, 1989). These differences between flesi-

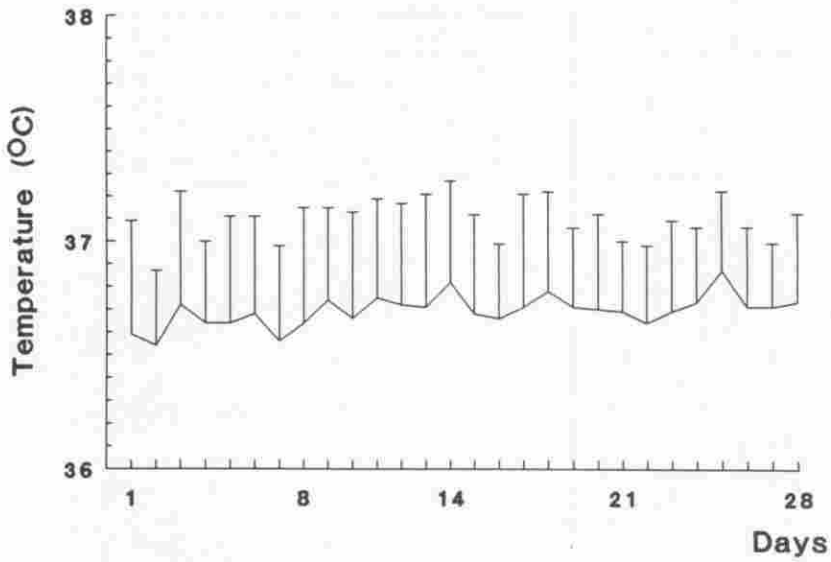

Figure 2. Changes over time in mean oral temperature (± SD) in 16 depressive inpatients treated with flesinoxan.

noxan and buspirone could also result from the distinction between these compounds in their 5-HT1A agonistic properties. They could indirectly support more antidepressant potential for flesinoxan (Kupfer *et al.*, 1987).

Flesinoxan did not induce significant changes in body temperature. This finding contrasts with the acute influence of 5-HT1A agonists which lower body temperature both in animals and in humans (Hjorth, 1985; Goodwin *et al.*, 1987; Anderson *et al.*, 1990; Lesch *et al.*, 1990; Ansseau *et al.*, 1992). These negative data could result from adaptative mechanisms which regulate the influence of 5-HT1A agonists after chronic intake. It should be noted that flesinoxan was initiated in a stepwise fashion which could have favoured these adaptative changes. Moreover, most of our patients were premenopausal women and the influence of the menstrual cycle on body temperature could have blurred the effect of flesinoxan.

In total, this pilot trial encourages further developments of flesinoxan as a promising antidepressant.

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