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Double-Blind Randomized Controlled Pilot Study of the Efficacy and Tolerability of Pirlindole, a Reversible Inhibitor of Monoamine Oxidase A, and Mianserin, in the Treatment of Depression

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This double-blind randomized pilot study aimed to compare the efficacy and the tolerability of pirlindole (150–225 mg/day), a reversible inhibitor of monoamine oxidase A, and mianserin (60–90 mg/day) in the treatment of major depression. Forty patients were included in the trial (20 pirlindole and 20 mianserin) and 38 patients (18 pirlindole and 20 mianserin) completed the whole study (28 days of administration). Both treatments exhibited highly significant improvements in the Hamilton Depression Rating Scale score (HDRS), the Hamilton Anxiety Rating Scale score (HARS) and the Beck auto-evaluation scale score (BECK) from day 7 up to day 28. The evolution of the HDRS score in the two groups did not differ significantly. The evolution of the HARS and BECK scores taken separately and the evolution of the combined total score (HDRS + HARS + BECK) significantly differed between the two groups, pirlindole producing a significantly higher decrease than mianserin in the two separate scores on day 28 and on days 21 and 28 in the case of the combined total score. Two patients experienced adverse reactions, one in the pirlindole group complained of sleep disturbances and one in the mianserin group suffered from dry mouth. The results of this study attest to the efficacy and tolerability of pirlindole in the treatment of depression.

KEY WORDS — depression; antidepressant; reversible inhibitor of monoamine oxidase A (RIMA); pirlindole; mianserin

INTRODUCTION

Until recently, monoamine oxidase inhibitors (MAOIs) were considered as 'secondary drugs' for the treatment of depression relative to the tricyclic antidepressants due to three main reasons. Hepatotoxicity was a problem with the early MAOIs, such as iproniazid. Secondly and probably most important was the cheese effect, the interaction between MAOIs and foods rich in tyramine, leading to hypertensive episodes with eventual serious consequences, including cerebral haemorrhage or even death. Thirdly, in true depressions, MAOIs were considered less efficacious than tricyclic antidepressants (Versiani *et al.*, 1989). During the 1980s, controlled studies provided evidence that MAOIs are very effective in the treatment of so-called therapy-resistant depressions, atypical depressions, phobias, panic disorders and anxiety states (Davis, 1985; McGrath *et al.*, 1986). In addition, low cardiotoxicity, absence of anticholinergic side-effects and mood-activating properties may be factors in favour of MAOIs as compared to tricyclic antidepressants (Laux *et al.*, 1990).

The discovery of two distinct subtypes of MAO (MAO-A) and MAO-B) and the resulting development of reversible (i.e. short-acting) and selective inhibitors of MAO-A has led to a resurgence of interest in the use of MAO inhibitors for the treatment of depression (Amrein *et al.*, 1993). By competitively and selectively inhibiting MAO-A, the enzyme primarily responsible for deamination of those monoamines (noradrenaline and serotonin) implicated in the aetiology

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of depression, while leaving MAO-B unaffected, these compounds are expected to combine antidepressant activity with a reduced risk of hypertensive crisis (Fitton *et al.*, 1992).

Among new selective reversible inhibitors of MAO-A (RIMAs), moclobemide has certainly been the most studied (Da Prada *et al.*, 1985; Kettler *et al.*, 1990). Its efficacy and safety have largely been demonstrated in placebo-controlled studies (Casacchia *et al.*, 1984; Versiani *et al.*, 1989) and in comparative trials versus reference therapies (Versiani *et al.*, 1989; Guelfi *et al.*, 1992; Bakish *et al.*, 1992; Bougerol *et al.*, 1992; Lonnqvist *et al.*, 1994; Reynaert *et al.*, 1995) and confirmed in clinical use (Chen and Ruch, 1993).

Pirlindole is a tetracyclic compound that has been characterized as a potential antidepressant drug in preclinical studies (Martorana and Nitz, 1979; Mashkovsky and Andrejeva, 1981; Maj *et al.*, 1986) and for which interest has appeared due to its marked selectivity as RIMA (Schraven and Reibert, 1984). In clinical trials, the efficacy and safety of pirlindole have been demonstrated in comparison to reference standard drugs such as maprotiline (Pöldinger, 1984), imipramine (Saletu *et al.*, 1983; Schäpperle *et al.*, 1983), amitriptyline (Schäpperle *et al.*, 1983; Renfordt, 1983; Blaha, 1983) and desipramine (Lehmann *et al.*, 1983). More recently, the superiority of pirlindole has been demonstrated versus placebo (De Wilde *et al.*, 1996) and a therapeutic equivalence in terms of efficacy and adverse reactions has been found versus moclobemide (Tanghe *et al.*, submitted for publication).

The aim of this pilot phase III study was to compare the efficacy and the tolerability of pirlindole and mianserin according to a double-blind randomized controlled design in hospitalized patients suffering from an endogenous minor or major depression.

MATERIALS AND METHODS

Study design

This was a double-blind, prospective pilot clinical trial, conducted in two Belgian centres (St-Denijs-Westrem and Sleidinge). Two randomized parallel groups of 20 inpatients were treated with either pirlindole or mianserin. The study drug was administered for 28 days, immediately following a washout period of 6 days.

Subjects

The subjects eligible for the study were men or women aged between 20 and 65 years, inpatients, fulfilling the criteria of a major depression. A total score of 24 or more on the Hamilton Depression Rating Scale (HDRS 21 items) was also required. Exclusion criteria were: previous antidepressive treatment within 4 weeks before the ongoing trial, electroconvulsive therapy during the last 6 months, organic brain syndrome, including ischemic brain disease and epilepsy, need of psychotropic medication, treatment with lithium or corticosteroids, repeated hyperglycemia of more than 130 mg/dl or diabetes, acute hepatitis within the last 3 months, posthepatitis syndrome, glaucoma, renal insufficiency, pregnancy or lactation. The study was carried out in accordance with the Declaration of Helsinki amended in Tokyo, Venice and Hong Kong. Patients were included after giving written informed consent. The study protocol was approved by an Ethical Committee.

Drug treatment

Patients received capsules, identical in appearance, containing either a 30-mg mianserin tablet or a 75-mg pirlindole tablet and filled up with lactose. Doses could be adjusted individually between 60 and 90 mg/day for mianserin and 150 and 225 mg/day for pirlindole. The relation between medication intake and meals was not specified and patients were not required to avoid tyramine-rich food. The use of concomitant psychotropic medication was prohibited, with the exception of chloral hydrate (at a maximum dose of 2000 mg/day), if judged necessary by the investigator.

Assessments

Assessments were made on day -6, 0, 7, 14, 21 and 28. Efficacy was evaluated on the basis of scores on the Hamilton Depression Rating Scale (HDRS 21 items), Hamilton Anxiety Rating Scale (HARS 14 items) and the Beck auto-evaluation scale (BECK 21 items). A global score was calculated by adding the three scores. Compliance was judged satisfactory when at least 80 per cent of the capsules had been taken. Tolerability was evaluated on the basis of the number of adverse events (reported on each visit), vital signs (blood pressure, heart rate, body weight) (reported on each visit), laboratory values and ECG (obtained before and after 28 days of treatment).

Statistical methods

Comparability of the two groups was assessed on day 0 using the chi-square test for discrete variables and the Student's t-test for continuous variables. The effects of mianserin and pirlindole on continuous variables, such as HDRS, HARS, BECK and the global score, were compared using an analysis of variance for repeated measurements with the factor 'treatment', 'time' and the interaction 'time–treatment'. A standard analysis (per protocol analysis), including completer patients was conducted. When the interaction was significant, *post-hoc* intragroup comparisons were made using paired t-tests and between-group comparisons were made using independent t-tests. The effects of mianserin and pirlindole specifically on sleep disorders (HDRS items 4 to 6, HARS item 4, BECK item 16) were compared using the Friedman test and the Mann–Whitney U test. Side-effect percentages were compared using the chi-square test. A probability of less than 5 per cent (two-tailed) was taken as indicative of statistical significance. Calculations were undertaken using the SPSS statistical package.

RESULTS

Description of the study population

Forty patients were included in this study, 20 in the mianserin group and 20 in the pirlindole group. Two patients of the pirlindole group stopped the treatment prematurely, one after 14 days because of a shift to mania and one after 21 days because the treatment was judged ineffective. The 40 patients were considered for the efficacy and tolerability analyses. The two groups did not differ significantly from each other for all the baseline (day 0) characteristics (Table 1).

Concomitant medication

One patient in the pirlindole group took chloral hydrate while no patient in the mianserin group took the allowed concomitant medication.

Efficacy

The mean doses were 191 mg/day and 75 mg/day in the pirlindole and mianserin groups respectively. Evaluation of efficacy was carried out for completers only ($n = 38$). Compliance was judged excellent in all patients. Both treatment groups exhibited highly significant improvements in their HDRS, HARS and BECK scores over time ($p < 0{\cdot}001$, ANOVA), the decrease being significant from day 7. The evolution of the HDRS score in the two groups did not differ significantly ($p > 0{\cdot}05$, ANOVA) (Table 2). A classification of patients who received the complete treatment in three categories was established on day 28 according to their HDRS score: $\leqslant 7$ = no depression, $\geqslant 8$ and $\leqslant 15$ = minor depression and $\geqslant 16$ = major

Table 1. Description of the study population ($n = 40$)

	Pirlindole (n = 20)	Mianserin (n = 20)	Probability
Age (years)	52·5 ± 13.2	50·5 ± 13·5	$p > 0{\cdot}05$
Sex:			
M	25%	25%	$p > 0{\cdot}05$
F	75%	75%	
HDRS score	26·8 ± 6·0	28·3 ± 6·2	$p > 0{\cdot}05$
HARS score	22·3 ± 2·0	23·6 ± 5·4	$p > 0{\cdot}05$
BECK score	56·1 ± 9·1	57·0 ± 8·9	$p > 0{\cdot}05$

Results are given as means ± standard deviation; Student's *t*-tests for continuous variables and chi square for discrete variables.

Table 2. Evaluation of the Hamilton Depression Rating Scale (HDRS), Hamilton Anxiety Rating Scale (HARS) and auto-evaluation Beck (BECK) scores as a function of time and treatment for completer patients

Parameters	Pirlindole ($n = 18$)	Mianserin ($n = 20$)
HDRS		
Day 0	26·7 ± 6·2	28·2 ± 6·2
Day 7	23·1 ± 5·8*	24·7 ± 6·0*
Day 14	17·1 ± 7·9*	19·5 ± 7·2*
Day 21	11·6 ± 7·4*	15·5 ± 8·2*
Day 28	8·4 ± 8·9*	13·7 ± 10·3*
HARS		
Day 0	22·3 ± 2·1	23·6 ± 5·4
Day 7	20·9 ± 3·1*	21·0 ± 3·5*
Day 14	15·4 ± 3·0*	17·4 ± 4·1*
Day 21	10·7 ± 5·2*	14·6 ± 5·3*
Day 28	7·3 ± 6·9*†	13·2 ± 7·7*
BECK		
Day 0	55·5 ± 9·4	57·0 ± 8·9
Day 7	50·9 ± 85*	54·4 ± 9·4*
Day 14	42·3 ± 9·4*	47·9 ± 10·3*
Day 21	34·8 ± 10·3*	43·2 ± 13·1*
Day 28	31·2 ± 11·7*†	40·4 ± 14·7*

Results are given as means ± SD; *$p < 0{\cdot}01$ comparisons versus baseline and †$p < 0{\cdot}05$ between-group *post-hoc* comparisons when ANOVA interaction was significant.

depression (Danish University Antidepressant Group, 1986). In the pirlindole group the repartition in the three categories was 61·1 per cent, 16·7 per cent and 22·2 per cent respectively. In the mianserin group the repartition was 25·0 per cent 35·0 per cent and 40·0 per cent respectively. The difference between the two groups was significant ($p = 0{\cdot}049$; Mann–Whitney). The evolution of the HARS and BECK scores in the two groups differed significantly ($p = 0{\cdot}015$ and $p = 0{\cdot}021$ respectively; ANOVA). For both scores a significant difference in favour of pirlindole was measured on day 28 ($p < 0{\cdot}05$; *post-hoc t*-test) (Table 2). An improvement superior or equal to 50 per cent in the HARS score was measured in 72·2 per cent against 30·0 per cent of patients in the pirlindole and mianserin groups respectively ($p < 0{\cdot}01$, chi square). An improvement superior or equal to 50 per cent in the BECK score was measured in 55·6 per cent against 15·0 per cent of patients in the pirlindole and mianserin groups respectively ($p < 0{\cdot}01$, chi square). The evolution of the global score (HDRS + HARS + BECK) in the two groups differed significantly ($p = 0{\cdot}036$; ANOVA). A significant difference in favour of pirlindole was measured on day 21 and 28 ($p < 0{\cdot}05$; *post-hoc t*-test) (Figure 1). Both treatment groups exhibited highly significant improvements in sleep disorders over time ($p < 0{\cdot}001$, Friedman test), the decrease being significant from day 7. The two treatments did not differ significantly with an exception on day 14 where the difference was in favour of pirlindole ($p < 0{\cdot}05$, Mann–Whitney *U* test) (data not shown).

Tolerability

Side-effects occurred in one patient in each group: one patient in the pirlindole group complained about sleep disturbances and one patient in the mianserin group suffered from dry mouth. There was no relevant evolution of body weight, blood pressure, heart rate and ECG during the trial. There was no evidence of clinically important drug-related changes in laboratory values. Physical examination findings were not affected to a clinically and statistically relevant degree in either treatment group.

DISCUSSION

The present pilot study was designed to evaluate the efficacy and tolerability of pirlindole, a selective and reversible monoamine oxidase A inhibitor, in comparison to mianserin in the treatment of major depression. A marked antidepressant effect was noted in both treatment groups from the seventh up to the 28th day of administration. As far as the

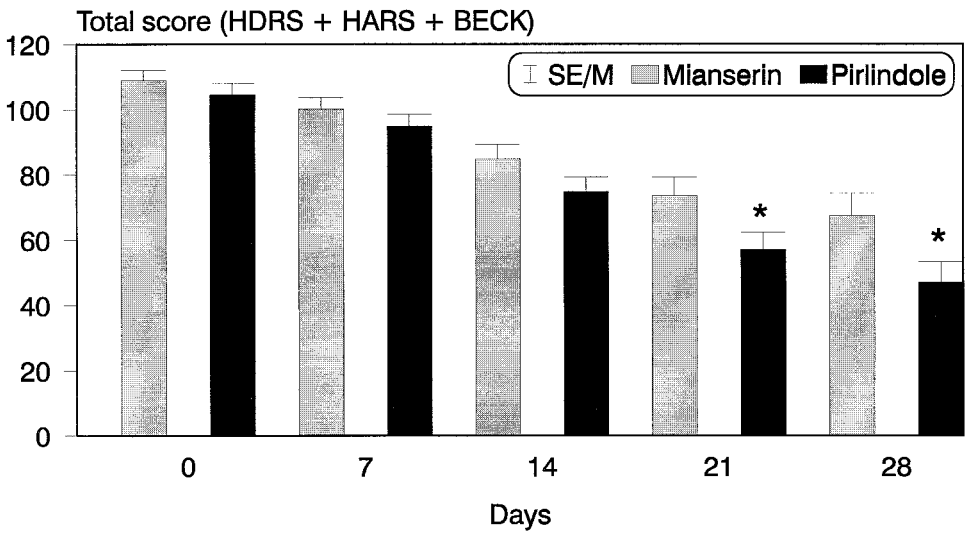

Figure 1. Evolution of the global score (HDRS + HARS + BECK) for completer patients ($n = 38$, pirlindole $n = 18$ and mianserin $n = 20$). Results are given as means ± standard errors on the mean (SEM). All the differences versus baseline were statistically significant from day 7 up to day 28 in both groups ($p < 0{\cdot}01$; paired *t*-tests). *$p < 0{\cdot}05$ between-group comparison using *post-hoc t*-test

evolution of the HDRS score is concerned, no significant difference was noted between the two treatments. However the percentage of cured patients (HDRS score $\leqslant 7$ according to the Danish University Antidepressant Group (1986) was significantly higher in the pirlindole group (61·1 per cent against 25·0 per cent in the mianserin group). The superiority of pirlindole over mianserin was significant ($p < 0{\cdot}05$) after 28 days of treatment for the HARS ($7{\cdot}3 \pm 6{\cdot}9$ in the pirlindole group against $13{\cdot}2 \pm 7{\cdot}7$ in the mianserin group), BECK ($31{\cdot}2 \pm 11{\cdot}7$ in the pirlindole group against $40{\cdot}4 \pm 14{\cdot}7$ in the mianserin group) and after 21 ($57{\cdot}0 \pm 22{\cdot}2$ in the pirlindole group against $73{\cdot}5 \pm 25{\cdot}7$ in the mianserin group) and 28 ($46{\cdot}9 \pm 26{\cdot}9$ in the pirlindole group against $67{\cdot}3 \pm 31{\cdot}7$ in the mianserin group) days for the global score. These results tend to corroborate those obtained in previous double-blind and open studies with pirlindole demonstrating that it is an efficacious antidepressive drug, superior to placebo (De Wilde *et al*., 1996) and at least comparable to amitriptyline (Schäpperle *et al*., 1983), imipramine (Saletu *et al*., 1983), desipramine (Lehmann *et al*., 1983), maprotiline (Pöldinger, 1983) and moclobemide (Tanghe *et al*., submitted for publication). As already demonstrated in other studies (De Wilde *et al*., 1996; Tanghe *et al*., submitted for publication), pirlindole seems to be very active on the anxious components of depression. The two drugs appeared relatively equivalent for the treatment of sleep disturbances. As far as tolerability is concerned, the frequency of side-effects did not differ significantly between the two treatment groups. One patient in the pirlindole group complained of sleep disturbances and one patient in the mianserin group suffered from dry mouth.

In conclusion, this pilot phase III clinical trial confirms the potential interest of a RIMA such as pirlindole for the treatment of major depression.

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