Psychopharmacology (1996) 127 : 231–237

ORIGINAL INVESTIGATION

J.A. Bruijn · P. Moleman · P.G.H. Mulder
W.W. van den Broek · A.M. van Hulst
R.C. van der Mast · B.J.M. van de Wetering

A double-blind, fixed blood-level study comparing mirtazapine with imipramine in depressed in-patients

Received: 12 January 1996/Final version: 15 May 1996

Abstract Antidepressant effects of mirtazapine and imipramine were compared in a randomized, double blind, fixed blood-level study with in-patients in a single centre. Patients with a DSM-III-R diagnosis of major depression and a Hamilton (17-item) score of ≥ 18 were selected. After a drug-free and a placebo-washout period of 7 days in total, 107 patients still fulfilling the HRSD criterion of ≥ 18, started on active treatment. The dose was adjusted to a predefined fixed blood level to avoid suboptimal dosing of imipramine. Concomitant psychotropic medication was administered only in a few cases because of intolerable anxiety or intolerable psychotic symptoms. Eight patients dropped out and two were excluded from analyses because of non-compliance; 97 completed the study. According to the main response criterion (50% or more reduction on the HRSD score) 11/51 (21.6%) patients responded on mirtazapine and 23/46 (50%) on imipramine after 4 weeks' treatment on the predefined blood level. Such a dramatic difference in efficacy between antidepressants has not often been reported before. The selection of (severely ill) in-patients, including those with suicidal or psychotic features, may have significance in this respect. Optimization of treatment with the reference drug imipramine through blood level control, exclusion of non-compliance for both drugs, exclusion of most concomitant medication and a low drop-out rate may also have contributed. It is concluded that imipramine is superior to mirtazapine in the patient population studied.

Key words Mirtazapine · Imipramine · Fixed blood-level monitoring · Study design · Antidepressant effect · Major depression · In-patients

J.A. Bruijn ✉ · W.W. van den Broek · A.M. van Hulst
R.C. van der Mast · B.J.M. van de Wetering
Department of Psychiatry, University Hospital Rotterdam "Dijkzigt", Dr. Molewaterplein 40, 3015 GD Rotterdam, The Netherlands

P. Moleman
Moleman Research, Burg. v.d. Boschstr. 11, 3958 CA Amerongen, The Netherlands

P.G.H. Mulder
Department of Epidemiology and Biostatistics, Erasmus University Rotterdam, Dr. Molewaterplein 50, Rotterdam, The Netherlands

Introduction

Mirtazapine, a new piperazinoazepine, is a strong antagonist of central α_2-adrenoreceptors, H_1(histamine)-receptors, $5HT_2$-receptors (de Boer et al. 1988) and $5HT_3$-receptors (Kooyman et al. 1994) and a weaker antagonist of muscarine and α_1-adrenoreceptors (de Boer et al. 1988). Mirtazapine has recently been registered as an antidepressant. Efficacy and safety have been explored in controlled clinical trials (Smith et al. 1990; Claghorn and Lesem 1995; Marttila et al. 1995; Richou et al. 1995; Van Moffaert et al. 1995; Zivkov and De Jong 1995). In all trials tolerance and safety of mirtazapine were satisfactory. In out-patients efficacy of mirtazapine was reported to be significantly superior to placebo (Smith et al. 1990; Claghorn and Lesem 1995) and to trazodon (Van Moffaert et al. 1995); no significant differences between mirtazapine and amitriptyline (Smith et al. 1990; Zivkov and De Jong 1995), clomipramine (Richou et al. 1995) and doxepin (Marttila et al. 1995), respectively, have been found.

Some authors have expressed doubt whether efficacy of the "newer" antidepressants equals the efficacy of "older" antidepressants (DUAG 1986; Bech 1988; Potter and Rudorfer 1989; DUAG 1990), in spite of the fact that most clinical trials show no differences in efficacy. The methodology of such trials may not always be suitable to detect differences. Possible confounding

factors involved include (Angst et al. 1989; DUAG 1990):
1. High placebo response rates in trials without a placebo control group;
2. "Unblinding" due to different side-effect profiles;
3. Treatment with suboptimal doses of the reference drug;
4. Non-compliance and drop-out, especially if not equally distributed over the different treatment groups;
5. High error variance in multicentre trials;
6. Concomitant treatment with other psychotropic drugs.

We have performed a study designed to avoid these methodological problems. The present study, comparing mirtazapine with imipramine, included:
1. A drug-free and a placebo wash-out period of 7 days, to exclude early placebo-responders;
2. Dose adjustment to a fixed blood-level to avoid suboptimal dosing of imipramine;
3. Allowing no concomitant psychotropic medication except in case of intolerable anxiety or intolerable psychotic symptoms;
4. No monitoring of side-effects by the investigators to avoid unblinding;
5. Inclusion of in-patients only;
6. Single centre design.

Materials and methods

General outline (Fig. 1)

Patients on the in-patient Depression Unit of the Department of Psychiatry of the University Hospital Rotterdam "Dijkzigt" were enrolled into the study from December 1989 to December 1993. This Unit has a regional function for treatment of uncomplicated depressed patients and a supraregional function for treatment of therapy-resistant depressed patients. Routinely psychotropic drugs are discontinued after admission. Depressed patients were screened for inclusion and exclusion criteria. Eligible patients had to be drug free for at least 3 days before baseline assessment. After giving written informed consent placebo was administered single blind for 4 days. At the end of this period patients were again assessed on the Hamilton Rating Scale for Depression (HRSD; Hamilton 1960) and those still meeting inclusion criteria (HRSD ≥ 18) were randomly allocated to a double-blind treatment with either imipramine or mirtazapine. Doses of both drugs were adjusted to obtain fixed blood levels. Outcome was assessed 4 weeks after attaining these predefined blood levels.

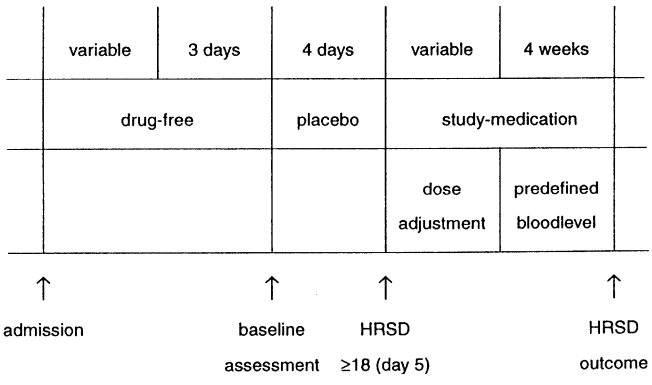

Fig. 1 General outline of the study design

Patient selection

Patients were examined for inclusion and exclusion criteria before the initial placebo period and the HRSD was administered again at the end of this period. *Included* were patients aged 18–65 with a "major depressive episode" according to a checklist with the DSM-III-R criteria (APA 1987) and an HRSD score ≥ 18. *Excluded* were patients with psychotic depression with hallucinations, schizophrenia, paranoid psychosis, organic brain syndrome, chronic drug or alcohol abuse, clinically relevant renal, hepatic, cardiovascular, or endocrine disease, presence of absolute contraindication for either imipramine or mirtazapine, and pregnancy or the risk to become pregnant.

All *assessments* were done by one research psychiatrist (JB), except the SADS (Schedule for Affective Disorders and Schizophrenia; Spitzer and Endicott 1978/79), which was performed in the presence of a second psychiatrist. In a clinical interview, demographic data (age, sex, level of professional training, profession and marital status), psychiatric history (previous affective disorders, course, duration and treatment of the current episode), and family history (depression, suicide, alcohol abuse, antisocial behavior, anxiety disorders, drug dependency and other psychiatric disorders) were obtained. The depression part of the SADS was administered at baseline by one psychiatrist in the presence of a second psychiatrist to obtain RDC diagnoses (Research Diagnostic Criteria; Spitzer et al. 1978) and to confirm the DSM-III-R diagnosis, obtained using the checklist at inclusion; scoring was based on consensus between both psychiatrists. To measure severity at baseline and response during treatment, we performed two depression rating scales. The HRSD which is internationally the most widely accepted depression scale was scored at baseline (before and at the end of the placebo period) and at 2 and 4 weeks after attaining the predefined blood level of study medication. The MADRS (Montgomery Asberg Depression Rating Scale; Montgomery and Asberg 1979), which is composed of ten depression symptoms which have proven to be most sensitive to change during treatment, was scored at baseline and weekly thereafter.

Study medication

Once a day at 10 p.m. either imipramine or mirtazapine was administered in identical capsules containing 37.5 or 75 mg imipramine or 10 or 2 mg mirtazapine, respectively. Treatment was started with either 75 mg imipramine or 20 mg mirtazapine. After 2 days the dose was doubled unless severe side effects were observed. Blood levels were monitored twice a week for the first 2 weeks and weekly thereafter. The results were send to an independent psychiatrist from another ward who adjusted the number of capsules on the basis of these blood levels. The predefined blood level for imipramine + desmethylimipramine was 200–300 ng/ml (Perry et al. 1987). For mirtazapine, no therapeutic levels are known. To keep the study double-blind, to exclude treatment under extremely high or low blood levels, and to ascertain treatment compliance it was decided to adjust mirtazapine doses to blood levels around the mean levels obtained with 60 mg mirtazapine per day. This dosage was advised at the time the study started by Organon for treatment of depressed patients. To obtain such levels, we performed a pilot study in 20 patients with a dose of 60 mg. The mean steady-state blood levels in this pilot study were 67.0 ng/ml (SD ± 25.4, range 33.0–123.9). On the basis of these results, predefined blood levels of 50–100 g/ml mirtazapine were chosen. The difference with predefined imipramine levels is, however, that optimal efficacy is not proven at these predefined mirtazapine levels.

Side-effects were not systematically rated by the investigators to prevent highlighting the different side-effect profiles and thus introducing a bias towards "unblinding". Side-effects were observed by treating psychiatrists and nurses not involved in the ratings for the study. Only in some drop-out patients was specific treatment for side-effects necessary according to these observations.

Evaluation of blindness

After completion of the study the research psychiatrist (J.B.) guessed the medication each of the 107 patients had received. This was correct in 46 cases and incorrect in 37 cases. In 24 cases the research psychiatrist was not able to decide on one of the two study medications.

Assay of study medication

Imipramine and desipramine assays were carried out with HPLC. Mirtazapine was assayed according to the method of Paanakker and Van Hal (1987).

Concurrent medication

Drugs for somatic complaints not interfering with study medication were continued unchanged during the study, if necessary. No psychotropic medication besides the study medication was allowed, except for 1–6 tablets a day containing 45 mg of an extract of valerian in case of anxiety or insomnia. This extract was assumed to be without antidepressant effect. In exceptional cases lorazepam, 1–5 mg a day for intolerable agitation or anxiety, or haloperidol, 1–15 mg a day in case of intolerable psychotic symptoms, respectively, had been prescribed.

Data analysis and statistical methods

The main response criterion was defined a priori as a reduction of 50% or more of the HRSD score 4 weeks after attaining the predefined blood level. The x^2-test was used for comparing outcome scores between the two treatment groups; the *t*-test for comparing continuous outcome variables. In order to increase precision of the estimated treatment effects, ANCOVAs, using multiple linear regression analyses, were also a priori planned for comparing the MADRS and HRSD post-treatment scores between the two treatment groups with the following covariables potentially taken into account: MADRS and HRSD pretreatment scores (baseline severity), duration of the present episode, number of previous depressions, manic episodes, personality, family history, previous treatments during current episode, melancholic type, psychotic features and type of depression according to RDC criteria. Adequate pretreatment during the current episode was defined as an adequate dose of an antidepressant during at least 4 weeks (Potter and Rudorfer 1989).

The difference in time-trend of the of the MADRS during 6 weeks of treatment between the two treatment groups was tested in a random coefficient model using RM-ANOVA.

Because efficacy of antidepressants may be less in the subgroup of psychotic patients, separate analysis of this subgroup was planned a priori.

Ethical considerations

The protocol was approved by the Ethics Committee of the University Hospital Rotterdam "Dijkzigt" and the Medical Faculty of the University of Rotterdam and was carried out in accordance with the ethical standards laid down in the declaration of Helsinki.

Results

Patient population and drop-outs

One hundred and seven depressed in-patients were randomized to either mirtazapine ($n = 54$) or imipramine ($n = 53$) (Table 1). Eight patients dropped out, while two patients were excluded from analyses because monitoring of blood levels showed non-compliance (Table 2). Five drop-outs on imipramine were due to side effects, compared to none on mirtazapine. Thus 97 patients (51 on mirtazapine and 46 on imipramine) completed the study.

Blood levels and doses

The mean time to reach the predefined blood levels was 10.9 days (SD ± 3.5, range 5–21) for mirtazapine and 13.6 days (SD ± 4.6, range 7–25) for imipramine. Including the 4-week treatment on this blood level, the mean total period on study medication was 38.9 days (SD ± 3.5, range 33–49) for mirtazapine and 41.6 days (SD ± 4.6, range 35–53) for imipramine. The mean daily dose during the 4 weeks on the predefined blood level for mirtazapine was 76.2 mg (SD ± 17.6, range 40–100) with a mean blood level of 69.3 ng/ml (SD ± 10.0, range 48.8–92.8), and for imipramine 235.5 mg (SD ± 90.8, range 37.5–450) with a mean blood level of imipramine + desmethylimipramine of 267.1 ng/ml (SD ± 35.9, range 199.0–400.3). Within this sum, the mean blood level of imipramine was 119.13 ng/l (SD ± 44.48, range 44.6–235.0) and the mean desmethylimipramine was 148.01 ng/l (SD ± 54.6, range 45.0–310.3).

Concomitant medication

Nine mirtazapine and seven imipramine patients were treated with the valerian extract. There were no significant differences between the two treatment groups with respect to dose and duration of valerian medication. Lorazepam was administered to six patients (four on mirtazapine and two on imipramine), which has been ignored in the analyses because of the small number of patients (6/107). Nine of the 31 psychotic patients were treated with haloperidol, seven on mirtazapine and two on imipramine. Only one of those patients (on mirtazapine) was a responder; the other eight patients were nonresponders. This indicates, that haloperidol was not instrumental in the recovery in those patients.

Table 1 Total population ($n = 107$)

	Mirtazepine ($n = 54$)	Imipramine ($n = 53$)
Age: mean ± SD (range)	45 ± 11 (23–64)	47 ± 10 (27–65)
Sex: male/female	12/42	11/42
Diagnosis: "major depressive episode" (DSM-III-R)	54	53
**Unipolar*	49	52
Not-psychotic, 1st episode	19	23
Not-psychotic, recurrent	15	14
Psychotic, 1st episode	9	10
Psychotic, recurrent	6	5
**Bipolar*	5	1
Not-psychotic	4	1
Psychotic	1	0
Melancholic type	47	45
Major depressive episode (RDC)	54	52
Retarded depression (RDC)	16	16
Agitated depression (RDC)	16	19
Endogenous depression (RDC)	53	50
Suicidal	28	32
HRSD baseline	26.1 ± 4.5 (19–37)	26.5 ± 5.0 (18–37)
MADRS baseline	37.5 ± 6.0 (25–51)	36.2 ± 6.8 (16–54)
Duration current episode		
>1 year	34	32
<1 year	20	21
Adequate pretreatment with antidepressants	28	27
Family history (1st/2nd degree)		
Depression	28	33
Suicide	10	9
Personality disorder	11	7

Table 2 Drop-outs and non-completers by non-compliance ($n = 10$)

Treatment	Reason	Day of study med.	Day after attaining predefined blood level
Mirtazapine	1. Transfer to other ward	14	–
	2. Refuse to take medication	12	–
	3. Non-compliance (plasma level ↓)	31	14
Imipramine	4. Mania	18	4
	5. Orthostasis	9	–
	6. Deterioration	19	2
	7. Fever and delirium	12	2
	8. Allergic reaction	21	7
	9. Allergic reaction	36	22
	10. Non-compliance (plasma level ↓)	28	7

Table 3 Mean HRSD-scores ± SD at baseline and endpoint (after four weeks of predefined blood level)

	Intention to treat		Completers	
	Mirtazapine ($n = 54$)	Imipramine ($n = 53$)	Mirtazapine ($n = 51$)	Imipramine ($n = 46$)
Baseline HRSD	26.1 ± 4.5	26.5 ± 5.0	26.1 ± 4.4	26.7 ± 4.9
Endpoint HRSD	19.6 ± 8.7	15.8 ± 9.6	19.2 ± 8.6	14.1 ± 9.0

Treatment effects

According to the main response criterion 11/51 (21.6%) patients were responders on mirtazapine and 23/46 (50%) on imipramine; a significant difference ($\chi^2 = 7.38$; $df = 1$; $p = 0.007$). In addition, the mean HRSD score after 4 weeks of predefined blood levels (Table 3) of the imipramine group was significantly lower than that of the mirtazapine group (mean difference = 5.1; SE = 1.8; $t = 2.83$; $df = 95$; $p = 0.006$). "Intent to treat"

analysis ($n = 107$) with the last HRSD score carried forward showed 11/54 (20.4%) responders with the mirtazapine and 23/53 (43.4%) with the imipramine group ($x^2 = 5.5$; $df = 1$; $P = 0.019$).

Since nine of the 31 psychotic patients were treated with haloperidol and since more patients on mirtazapine received haloperidol, we have analysed the results omitting patients receiving haloperidol. The response on imipramine, 23/44 (52.3%), differed significantly from the response on mirtazapine: 10/44 (22.7%) ($\chi^2 = 6.7$; $df = 1$; $P = 0.008$).

Figure 2A (completers) and 2B (ITT with LOCF) show the mean MADRS scores for the two groups during 6 weeks of treatment. According to the RM-ANOVA, the time-trends were significantly different between the two treatment groups (completers: $P = 0.003$; ITT: $P = 0.026$). Regression analyses with severity (HRSD score at baseline), suicidal or psychotic features (DSM-III-R), duration of current episode, previous adequate treatment of current episode with imipramine, with other classical tricyclics or with modern antidepressants, number of psychiatric admissions before the current depression, positive family history for depression and/or suicide, and personality disorder as covariables did not improve the precision of the estimated difference between the two drugs to an appreciable extent.

In the subgroup of 31 psychotic patients four dropped out (two patients on mirtazapine and two on imipramine), so 27 psychotic patients completed the study. According to the main response criterion, 4/14 (28.6%) responded on mirtazapine and 9/13 (69.2%) on imipramine ($\chi^2 = 2.98$; $df = 1$; $P = 0.084$). The mean HRSD scores after 4 weeks of predefined blood levels were significantly lower for the imipramine group than

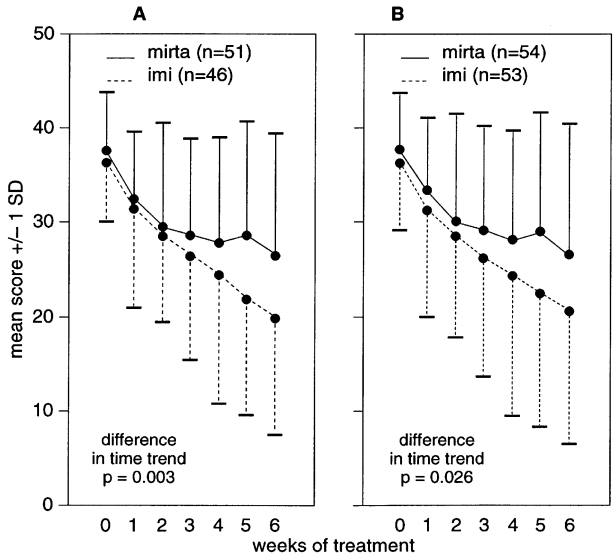

Fig. 2A, B Mean total scores on the Montgomery-Asberg depression rating scale. **A** Completers ($n = 97$); **B** all patients ($n = 107$, LOCF)

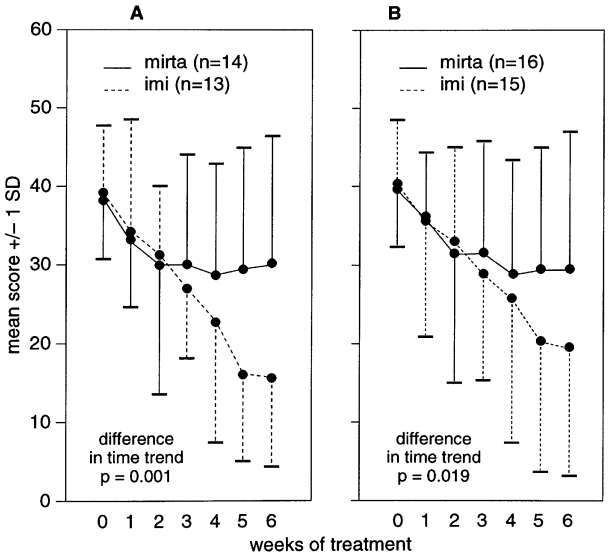

Fig. 3A, B Mean total score on the Montgomery-Asberg depression rating scale of the psychotic patients. **A** Completers ($n = 27$); **B** all psychotic patients ($n = 31$, LOCF)

for the mirtazapine group (mean difference = 9.8; SE = 3.8; $t = 2.56$; $df = 25$; $P = 0.017$). "Intent to treat" analysis in the subgroup of 31 psychotic patients showed 4/16 (25%) responders with the mirtazapine and 9/15(60%) with the imipramine group ($\chi^2 = 2.59$; $df = 1$; $P = 0.11$). If patients treated with haloperidol were regarded as drop-outs, an "intent to treat" analysis showed the following results: 3/16(18.8%) responders with the mirtazapine group and 9/15(60%) with the imipramine group. This is a significant difference ($\chi^2 = 3.95$; $df = 1$; $P = 0.046$). Figure 3A (completers) and Figure 3B (ITT with LOCF) show the MADRS scores for the two groups of psychotic patients during 6 weeks of treatment. According to the RM-ANOVA the time trends were significantly different between the two treatment groups (completers: $P = 0.001$; ITT: $P = 0.019$).

The overall response rate to treatment was rather low (50% on imipramine and 22% on mirtazapine). For this reason we performed subgroup analyses. Excluding patients with a duration of the depression longer than 1 year, the response rate on imipramine was 63.3% (19/30) and 31.3% (10/32) on mirtazapine. Excluding in this subgroup also patients with adequate pre treatment of the current episode, response rates were even higher: 69.6% (16/23) on imipramine and 37.5% (9/24) on mirtazapine. These differences between the imipramine, and mirtazapine group are not significant, most likely because of the low number of patients.

Discussion

The most obvious result in this study is the considerable difference in antidepressant efficacy between

mirtazapine and imipramine. Such a difference has not been reported in previous studies (Smith et al. 1990; Claghorn and Lesem 1995; Marttila et al. 1995; Richou et al. 1995; Van Moffaert et al. 1995; Zivkov and De Jong 1995). A possible explanation may be found in differences between the present and other trials with mirtazapine.

Previous studies on mirtazapine (Smith et al. 1990; Claghorn and Lesem 1995; Marttila et al. 1995; Richou et al. 1995; Van Moffaert et al. 1995; Zivkov and De Jong 1995) used a flexible dose design. This may lead to inappropriate dosing especially with tricyclic antidepressants because side effects preventing dose increments may occur at subtherapeutic doses/blood levels (Dawling 1982; DUAG 1990). In at least two previous studies (Smith et al. 1990; Richou et al. 1995) the mean dose of the tricyclic reference drug was rather low; 111 mg amitriptyline and 113.7 mg clomipramine, respectively. In the present patient group the mean daily dose of imipramine was 235.5 mg with a very wide range (37.5–450 mg). No fewer than nine (20%) patients were on a dose of 112.5 mg or less, and 17 (37%) patients received 300 mg imipramine per day or more. This illustrates the range of doses necessary to obtain therapeutic blood levels. It is not very likely that such doses would have been administered without blood level control. With mirtazapine it was not possible to predefine an optimal blood level because therapeutic blood levels of mirtazapine are not available. The mean mirtazapine dose of 76 mg/day was above the dose used in other studies: 53 mg/day (Zivkov and De Jong 1995) and 47 mg/day (Richou et al. 1995) in other in-patient studies. The predefined blood level of mirtazapine was based on steady-state blood levels of patients on 60 mg/day of mirtazapine, which was the recommended dose in the previous in-patient mirtazapine studies (Richou et al. 1995; Van Moffaert et al. 1995; Zivkov and De Jong 1995).

It cannot be excluded that mirtazapine has a curvilinear blood level response curve, as is the case with nortriptyline (Perry et al. 1987), and that the present dose was less effective for that reason. Dose finding or blood level response studies to clarify this point are not available. Thus, the imipramine dose in the present study was in the therapeutic range for all patients, but this is not certain for all patients on mirtazapine, which could be one explanation for the difference in efficacy between both drugs in this study.

In the present study only a minority of patients was treated with comedication, and the difference in efficacy between imipramine and mirtazapine remained significant if these patients were excluded. In the earlier mirtazapine studies (Smith et al. 1990; Claghorn and Lesem 1995; Marttila et al. 1995; Richou et al. 1995; Van Moffaert et al. 1995; Zivkov and de Jong 1995), short acting benzodiazepines were allowed for the first 2 weeks and chloral hydrate (0.5–3 g) during the entire study. It was not reported whether the comedication was equally divided between the two treatment groups. Angst (1993) has argued that comedication with benzodiazepines increases response to placebo treatment and decreases the power of a comparative trial considerably. It may be of significance, therefore, that other studies with mirtazapine reported response percentages as high as 72% (Zivkov and de Jong 1995), 80% (Richou et al. 1995), and 78% (Van Moffaert et al. 1995), respectively.

The drop-out rate in the present study was low: 9.1% versus 17–35% in other mirtazapine studies (Smith et al. 1990; Claghorn and Lesem 1995; Marttila et al. 1995; Richou et al. 1995; Van Moffaert et al. 1995; Zivkov and De Jong 1995). A high drop-out rate may bias results of clinical trials even if analyses are based on "intent to treat" samples (Angst et al. 1989).

Patient selection may also play an important role in treatment outcome (Ansseau 1992). Similar to the present trial, three trials of mirtazapine were performed with in-patients, comparing it with amitriptyline, clomipramine, and trazodone, respectively (Richou et al. 1995; Van Moffaert et al. 1995; Zivkov and De Jong 1995). However, other selection criteria differed. Patients with active suicidal tendencies were excluded (Smith et al. 1990; Claghorn and Lesem 1995; Marttila et al. 1995; Richou et al. 1995; Van Moffaert et al. 1995; Zivkov and de Jong 1995). It is not clear whether patients with psychotic depressions and patients with a "melancholic type"-depression had been included in these studies. In the present study 29% (31/107) of the patients had psychotic depressions and 86% (92/107) fulfilled criteria for melancholic type, respectively. Out-patients (Smith et al. 1990; Claghorn and Lesem 1995) or in- and out-patients (Marttila et al. 1995) were studied in some trials, while in the three trials with in-patients (Richou et al. 1995; Van Moffaert et al. 1995; Zivkov and De Jong 1995) those with a duration of the depression longer than 6 months were excluded. In three studies (Marttila et al. 1995; Richou et al. 1995; Van Moffaert et al. 1995) none of the patients had been treated with an adequate dose of an antidepressant in the month preceding the trial.

The present results are in some respects comparable to those of the DUAG studies (DUAG 1986, 1990), in which the serotonine reuptake inhibitors citalopram and paroxetine, respectively, were compared with clomipramine. Differences in favour of clomipramine were reported in both studies. The authors suggested that this may be related to inclusion of only in-patients, rigid adherence to a fixed dose schedule and control of drug compliance by blood level monitoring.

The sub-group of psychotic patients showed an even larger superiority of imipramine over mirtazapine, response percentages being around 60–70% for imipramine and around 20–30% for mirtazapine, depending on the analysis performed. Most of these results were significant, even with the small number of psychotic patients studied. Seven patients treated with

haloperidol were on mirtazapine and only two on imipramine, also hinting at a better efficacy of imipramine.Thus the inclusion of psychotic patients may have contributed to the superiority of imipramine.

The response rate in this study was relatively low; 50% on imipramine compared to 70–80% in other studies (Potter and Rudorfer 1989). This is probably due, at least in part, to a lower response rate of patients with a current depressive episode of long duration and of patients that had been pretreated with antidepressants, since with the exclusion of these patients, the response rate was 70% (16/23) on imipramine.

In conclusion, the present study shows a considerable difference in antidepressant efficacy between the new antidepressant mirtazapine and imipramine. Optimization of treatment with the reference drug imipramine through blood level control, exclusion of non-compliance for both drugs, exclusion of most concomitant medication and a very low drop-out rate may have contributed to this result. Also, the selection of severely ill in-patients, including those with suicidal or psychotic features, may be significant in this respect, although it is difficult to ascertain differences between patient characteristics in different studies. In the patient population studied imipramine is superior in efficacy to mirtazapine.

Acknowledgement The study was supported by a grant from N.V. Organon.

References

Angst J (1993) Severity of depression and benzodiazepine comedication in relationship to efficacy of antidepressants in acute trials. Hum Psychopharmacol 8: 401–407

Angst J, Bech P, Boyer P, Bruinvels J, Engel R, Helmchen H, Hippius H, Lingjaerde O, Racagni G, Saletu B, Sedvall G, Silverstone JT, Stefanis CN, Stoll K, Woggon (1989) Consensus conference on the methodology of clinical trials of antidepressants, Zurich, March 1988: report of the consensus committee. Pharmacopsychiatry 22: 3–7

American Psychiatric Association (1987) Diagnostic and statistical manual of mental disorders, 3rd edn, revised (DSM-III-R). The American Psychiatric Association Press, Washington DC

Ansseau M (1992) The Atlantic gap; clinical trials in Europe and the United States. Biol Psychiatry 31:109–111

Bech P (1988) A review of the antidepressant properties of serotonin re-uptake inhibitors. Adv Biol Psychiatry 17:58–69

Claghorn JL, Lesem MD (1995) A double-blind placebo controlled study of Org 3770 in depressed outpatients. J Affect Disord 34: 165–171

Danish University Antidepressant Group (1986) Citalopram: clinical effect profile in comparison with clomipramine. A controlled multicentre study. Psychopharmacology 90:131–138

Danish University Antidepressant Group (1990) Paroxetine: a selective serotonin reuptake inhibitor showing better tolerance, but weaker antidepressant effect than clomipramine in a controlled multicentre study. J Affect Disord 18:289–299

Dawling S (1988) Monitoring of tricyclic antidepressant therapy. Clin Biochem 15: 56–61

De Boer Th, Mauri G, Raiteri M, de Vos CJ, Wieringa J, Pinder RM (1988) Neurochemical and autonomic pharmacological profiles of the 6-aza-analogue of mianserin, ORG 3770 and its enantiomers. Neuropharmacology 27:399–408

Hamilton M (1960) A rating scale for depression (HRS). J Neurol Neurosurg Psychiatry 23:56–61

Kooyman AR, Zwart R, Vanderheyden PML, Van Hooft JA, Vijverberg HPM (1994) Interaction between enantiomers of mianserin and ORG 3770 at 5-HT_3 receptors in cultured mouse neuroblastoma cells. Neuropharmacology 33:501–510

Marttila M, Jaaskelainen J, Jarvi R, Romanov M, Miettinen E, Sorri P, Ahlfors U, Zivkov M (1995) A double-blind study comparing the efficacy and tolerability of Org 3770 and doxepin in patients with major depression. Eur Neuropsychopharmacol 5: 441–446

Montgomery SA, Asberg MA (1979) A new depression scale designed to be sensitive to change. Br J Psychiatry 134: 382–389

Paanakker JE, Van Hal HJM (1987) Capillary gas chromatographic assay for routine monitoring of the antidepressant meperzepine in human plasma. J Chromatogr 417:203–207

Perry PJ, Pfohl BM, Holstad SG (1987) The relationship between antidepressant response and tricyclic antidepressant plasma concentrations; a retrospective analysis of the literature using logistic regression analysis. Clin Pharmacokinet 13:381–391

Potter WZ, Rudorfer MV (1989) Antidepressants: a comparative review of the clinical pharmacology and the therapeutic use of the 'newer' versus the ''older'' drugs. Drugs 37:713–738

Richou H, Ruimy P, Charbaut J, Delisle JP, Brunner H, Patris M, Zivkov M (1995) A multicentre, double-blind, clomipramine-controlled efficacy and safety study of Org 3770. Hum Psychopharmacol 10:263–271

Smith WT, Glaudin V, Panagides J, Gilvary E (1990) Mirtazapine vs amitriptyline vs placebo in the treatment of major depressive disorder. Psychopharmal Bull 26:191–196

Spitzer RL, Endicott J (1978/79) Schedule for affective disorders and schizophrenia (SADS). Research Assesment and Training Unit, State Psychiatric Institute, New York

Spitzer RL, Endicott J, Robins E (1978) Research diagnostic criteria (RDC): rationale and reliability. Arch Gen Psychiatry 35:773–782

Van Moffaert M, De Wilde J, Vereecken A, Dierick M, Evrard JL, Wilmotte J, Mendlewicz J (1995) Mirtazapine is more effective than trazodone: a double-blind controlled study in hospitalized patients with major depression. Int Clin Psychopharmacol 10:3–9

Zivkov M, De Jong G (1995) Org 3770 vs amitriptyline: a 6-week randomized double-blind multicentre trial in hospitalised depressed patients. Hum Psychopharmacol 10:173–180