Effectiveness of ipsapirone, a 5-HT-1A partial agonist, in major depressive disorder: support for the role of 5-HT-1A receptors in the mechanism of action of serotonergic antidepressants

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Abstract
Desensitisation of serotonin 1A (5-HT-1A) receptors is a leading hypothesis for the mechanism of action of antidepressants which block serotonin reuptake. This hypothesis predicts that direct-acting 5-HT-1A agonists should also exhibit anti-depressant properties. Here we report the results of the first large-scale controlled study of the efficacy and tolerability of a 5-HT-1A partial agonist in outpatients with major depressive disorder (MDD). Three hundred and seventy-three subjects meeting DSM-III-R criteria for MDD participated in this randomised, double-blind comparison of the 5-HT-1A partial agonist ipsapirone (5 mg, 7.5 mg and 10 mg t.i.d.) to placebo t.i.d. Improvement in depressive symptoms relative to placebo, as measured by the Hamilton Depression Rating Scale, occurred in the ipsapirone (7.5 mg t.i.d.) group with a magnitude of effect (D = −2.53 points) that was statistically significant (p = 0.010). Adverse events occurred in 76% of the placebo patients and 92% of the ipsapirone patients. A dose-related increase in the incidence of adverse events led to discontinuation of treatment with the 10 mg t.i.d. Results of this study demonstrate that ipsapirone, at a dose of 7.5 mg t.i.d., is an effective antidepressant agent in the treatment of MDD, supporting the hypothesised role of 5-HT-1A receptors in the mechanism of action of serotonin reuptake inhibitors. However, as a potential therapeutic agent for depression, ipsapirone shows only a modest magnitude of drug-placebo differences as well as a side-effect profile less favorable than many of the newer antidepressants.

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Key words: Ipsapirone, 5-HT-1A receptor agonist, depression, azapirone, serotonin.

Introduction
Increased serotonergic neurotransmission is a leading hypothesis for the mechanism of action of numerous antidepressants (Blier et al., 1987; Stahl, 1996). The serotonin selective reuptake inhibitors (SSRIs) increase serotonergic neurotransmission by causing the desensitisation of presynaptic somatodendritic serotonin 1A (5-HT-1A) autoreceptors (Blier et al., 1987, 1993; Stahl, 1996). Blocking serotonin reuptake leads to an immediate increase of serotonin at these receptors, desensitising them over time (Blier et al., 1987, 1993; Stahl, 1996).

These neurochemical changes are hypothesized to explain not only the mechanism of antidepressant efficacy of the SSRIs but also the delay in onset of these actions. This hypothesis predicts that direct-acting 5-HT-1A agonists should also exhibit antidepressant properties (Blier et al., 1987, 1993; Stahl, 1996; Stahl et al., 1992).

Ipsapirone is an azapirone selective for the 5-HT-1A receptor with anxiolytic, anti-depressant, and anti-aggressive properties in animal models (De Vry et al., 1992; Pollard and Howard, 1990). It is structurally related to the clinically effective anxiolytic buspirone, as well as to the investigational anxiolytic/anti-depressant agents tandospirone and gepirone (De Vry et al., 1992; Stahl, 1992). Although numerous 5-HT-1A agonists, including ipsapirone, have been shown to be effective in the treatment of generalised anxiety disorder (GAD) in several multi-centre placebo-controlled trials (Cohn et al.,
In terms of buspirone, one placebo-controlled study of 140 patients from a single site suggested efficacy in treating patients manifesting MDD with concomitant anxiety (Fabre, 1990). Robinson (1991) and Robinson et al. (1989), summarised the efficacy of buspirone from several preliminary studies of patients with MDD, suggesting superior efficacy relative to placebo. Gammans et al. (1992), as well as Sramek et al. (1996) similarly reported the greater efficacy of buspirone compared to placebo in patients with GAD and concomitant depressive symptoms in multi-centre trials.

Gepirone, another azapirone closely related to buspirone and ipsapirone, has also been reported to be efficacious in treating MDD. However, all of these studies, as reported by Robinson (1991), Robinson et al. (1989), and Jenkins et al. (1990), suggested gepirone’s superiority relative to placebo in treating depressed patients with anxiety symptoms. One criticism of the findings regarding both buspirone and gepirone studies to date is the difficulty in dissociating the known anxiolytic efficacy from the postulated antidepressant efficacy of the 5-HT-1A agonists. Efficacy of ipsapirone in treating depression has been suggested from the results of a small German trial of 34 patients with the International Classification of Diseases 9 (ICD-9) diagnosis of neurotic depression (Heller et al., 1990). This preliminary clinical information, combined with the animal behavioural and biochemical models of ipsapirone action, suggested that a prospective trial be conducted in order to determine whether the 5-HT-1A agonist ipsapirone is effective in treating MDD. Demonstrating antidepressant efficacy of a direct-acting 5-HT-1A agonist would also support the hypothesis that SSRIs exert their antidepressant action via indirect agonist action on 5-HT-1A receptors. Reported here are the results of the first large-scale, multi-centre, placebo-controlled trial demonstrating that a 5-HT-1A agonist exhibits antidepressant action in MDD.

Materials and methods

Study design

This ten-centre, randomised, double-blind, placebo-controlled, parallel group study was designed to determine the efficacy, safety, and tolerability of three fixed doses of ipsapirone-HCl (5, 7.5 and 10 mg t.i.d.) versus placebo for an 8-wk treatment period in outpatients with moderate to severe MDD (single episode or recurrent) as defined by the Diagnostic and Statistical Manual of Mental Disorders (1987). Third Edition, Revised (DSM-III-R). The original protocol was amended to eliminate the 10 mg ipsapirone group because of a high incidence, relative to both the placebo group and phase III GAD study observations, of premature terminations due to adverse events. The protocol, amendment, and informed consent were approved by an Institutional Review Board at each study centre. Patients who met the inclusion criteria were enrolled after complete psychiatric and medical histories were taken, physical examinations were performed, and appropriate laboratory tests and electrocardiograms (ECGs) were conducted and evaluated. Written, informed consent was obtained from each patient prior to enrolment in the study. Efficacy was evaluated based on serial results of standard tests. The Hamilton Depression Rating Scale (HAM-D) and the Montgomery and Asberg Depression Rating Scale (MADRS) were used for evaluation of depression. Ratings for anxiety were obtained using the Hamilton Anxiety Scale (HAM-A), and global assessment ratings were performed using the Clinical Global Impressions Scale (CGI). Patient self-reports were evaluated using the Symptom Checklist-76 item (SCL-76). Assessments for efficacy were obtained at screening, during study participation, and at the end of treatment. Ratings were performed by investigators or experienced study co-ordinators at each of the ten sites. Inter-rater reliability was established at a training session of all raters prior to initiation of the study.

Tolerability and safety were evaluated based on the following: results of adverse event and concurrent illness assessments, complete physical examinations, blood pressure and heart rate assessment, electrocardiograms (ECGs), and laboratory tests performed at screening, during study participation and at the end of treatment.

Treatment

At the screening visit, all eligible patients received a supply of single-blind placebo capsules sufficient for 10 days of treatment. Patients were instructed to take one capsule three times daily for one week. At the end of that week, the placebo medication was collected and evaluated for compliance. Compliance, defined as the apparent number of capsules taken divided by the number of capsules prescribed, must have been no less than 80% and no greater than 120% during the placebo run-in phase. Interim exclusion criteria were reassessed at the end of the single-blind phase. Patients were excluded who no longer attained a score of 20 or more on the HAM-D (21-item), or 8 or more on the Raskin Depression Scale (RDS), or who showed a reduction of greater than 20% from the
HAM-D score obtained at screening. Patients meeting the criteria for compliance who developed no medical or psychiatric exclusions were randomised to one of four treatment groups and, subsequent to the amendment, to one of three treatment groups according to a computer-generated randomisation code. During the 8-wk treatment phase, all patients initially received placebo or 2.5 mg t.i.d. of ipsapirone. Those patients receiving ipsapirone were titrated to the appropriate fixed dose using an initial, gradual, forced titration. The schedule of the titration was as follows: all ipsapirone-treated patients received 2.5 mg t.i.d. on treatment days 1 and 2, and 5 mg t.i.d. on days 3 and 4; patients randomised to the ipsapirone 7.5 and 10 mg groups received 7.5 mg t.i.d. on days 5 and 6, while those patients randomised to the ipsapirone 10 mg group received 10 mg t.i.d. on day 7. Once having received the appropriate ipsapirone dose (5, 7.5 or 10 mg t.i.d.), patients continued on the fixed-dose regimen until the end of the 8-wk double-blind treatment period. Patients randomised to the placebo group received placebo t.i.d. throughout the study.

**Patient selection**

Men and women between 18 and 65 years of age with a primary diagnosis of MDD and a score of at least 20 on the HAM-D and at least 8 on the RDS were eligible to participate in this study. Women of child-bearing potential as well as pregnant or lactating women were excluded.

Patients who had previously received anti-depressant or anxiolytic pharmacotherapy must have been entirely free of drug treatment for 14 days prior to the screening visit. The presence of clinically significant concurrent medical conditions, laboratory or ECG abnormalities, or treatment with any investigational drug within 30 days of screening warranted medical exclusion from the study. Patients with a positive urine drug screen at the screening visit were also excluded. Psychiatric exclusion criteria included a history of, or current, symptoms that met DSM-III-R criteria for the following: bipolar disorder, cyclothymia, schizophrenia or schizophreniform disorder, delusional disorder, schizoaffective disorder, psychotic disorder not otherwise specified or other evidence of delusions or hallucinations on examination. Patients who met DSM-III-R criteria for the following disorders within 6 months of the screening visit were also excluded: panic disorder, obsessive-compulsive disorder, post-traumatic stress disorder, generalized anxiety disorder, somatoform disorders, eating disorders, uncomplicated bereavement, substance use disorders, any organic mental syndrome or disorder or personality disorders. Additionally, those patients considered to be at a significant risk for suicide or with a score greater than 2 on the HAM-D question for suicide (item 3), requiring or likely to require treatment with additional psychotropic drugs, or receiving other forms of psychotherapy during the study period (except for patients in psychotherapy for more than 3 months prior to screening) were excluded. Patients who had received electroconvulsive therapy (ECT) within the past year or who were likely to require ECT during the course of study participation were also excluded from trial participation.

**Evaluations for efficacy and safety**

The primary efficacy variable was the reduction from baseline (end of single-blind treatment) to week 8 with the last observation carried forward (LOCF) in the HAM-D (21-item) total score. Secondary efficacy assessments included reductions from baseline in Core Depression items (i.e., the subtotal from the HAM-D on the following items: (1) Depressed mood, (2) Feelings of guilt, (3) Interest in work and activities, and (4) Psychomotor retardation), the CGI, the MADRS, the Symptom Checklist-76, and the HAM-A.

Each patient was evaluated by a physician at each visit in order to determine adverse events and concurrent illnesses or injuries. Changes in physical health and general medical status were evaluated through physical examinations and ECGs performed at screening and the end of treatment. Complete laboratory evaluations were performed at screening, week 4 and the end of treatment. Blood pressure, heart rate and weight were recorded at all visits.

**Statistical analyses**

For each efficacy variable, the change from baseline was analysed. However, for CGI Improvement, the value itself was used. The HAM-D total score was also analysed secondarily as a percent change from baseline.

All significance tests were two-tailed and performed at the 5% significance level. In addition, to protect the 5% significance level, for the efficacy analyses, the overall comparison of treatment groups needed to be significant before a pairwise comparison of an ipsapirone dose to placebo could be claimed as significant.

Regarding continuous variables, an analysis of variance (ANOVA) model with effects for centre, treatment, and centre-by-treatment interaction was used; if the interaction effect was not significant, it was deleted from the model. From models generated in this way, least squares (LS) means were calculated for each treatment group. All pairwise comparisons of the ipsapirone doses with placebo were performed with one-at-a-time t tests. Because the ipsapirone 10 mg group was discontinued from the study,
it was not included in the statistical analysis of efficacy variables; only summary statistics for efficacy variables were evaluated for this treatment group.

In general, two-level categorical data were analysed with Fisher’s exact test (generalized to \( r \times 2 \) tables) or the \( \chi^2 \) test, depending on cell sizes. Categorical demographic data were analysed with the \( \chi^2 \) test.

The protocol specified criteria for the inclusion of patients in safety and efficacy analyses. Patients were included in the safety analysis if they received at least one dose of randomised study drug and had any follow-up safety information collected. Patients were included in the intent-to-treat efficacy analysis if they were valid for safety analysis, had any baseline and post-baseline efficacy data collected, and met DSM-III-R criteria for MDD. Patients were considered valid for efficacy analysis if they met the intent-to-treat criteria and the following requirements:

1. Patient did not take any excluded antidepressant drugs between baseline and end of treatment.
2. Patient took the randomised study drug for at least 14 days.
3. Patient had data from a valid week 2 visit or beyond.

Visits were excluded from the analysis of patients valid for efficacy for the following reasons:

1. If a patient took less than 70% of the prescribed dose, the follow-up visit was invalidated.
2. If a patient stopped study medication for greater than or equal to 3 days before the study visit, that visit was invalidated.
3. If a patient received the wrong study drug, all following visits were invalidated.

Results

Patient demographics

In all, 373 patients were randomised into this study. There were 111, 111, and 112 patients randomised to the placebo, ipsapirone 5 and 7.5 mg groups, respectively. Thirty-nine patients were randomised to the ipsapirone 10 mg group prior to the discontinuation of this dose group from the study. The completion rate in this study was 59, 60 and 61% for the placebo, ipsapirone 5 and 7.5 mg groups, respectively. The completion rate in the ipsapirone 10 mg group was lower at 44% (see ‘Adverse events’ section below). Three patients assigned to the placebo group and one patient assigned to the ipsapirone 5 mg group were lost to follow-up after the baseline visit. Since no on-treatment data were collected for these patients, they were excluded from all further analyses.

The demographic and background variables were similar among the treatment groups. The difference in the number of males participating in the study, 228 (61.7%), compared to the number of females, 141 (38.2%), was believed to be due to the FDA restrictions in place at the time that prohibited clinical trial participation by females of child-bearing potential.

Efficacy results

Approximately 89% of the placebo and ipsapirone 5 and 7.5 mg patients valid for efficacy were treated for at least 4 wk and approximately two-thirds were treated for at least 8 wk. The duration of treatment in the ipsapirone 10 mg group was somewhat shorter than that in the other groups. The mean duration of treatment in patients valid for efficacy was 7.1, 7.2, 7.1 and 6.3 wk in the placebo through ipsapirone 10 mg groups, respectively.

Table 1 summarises the baseline efficacy measurements for all patients.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo (n = 93)</th>
<th>5 mg (n = 92)</th>
<th>7.5 mg (n = 97)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HAM-D</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total score</td>
<td>24.6</td>
<td>24.6</td>
<td>24.7</td>
</tr>
<tr>
<td>Core Depression items subtotala</td>
<td>8.4</td>
<td>8.3</td>
<td>8.5</td>
</tr>
<tr>
<td>Depression itemb</td>
<td>2.8</td>
<td>2.8</td>
<td>2.9</td>
</tr>
<tr>
<td>CGI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severity of Illness</td>
<td>4.2</td>
<td>4.2</td>
<td>4.3</td>
</tr>
<tr>
<td>MADRS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total score</td>
<td>28.5</td>
<td>28.6</td>
<td>29.2</td>
</tr>
<tr>
<td>Apparent Sadness itemc</td>
<td>3.5</td>
<td>3.7</td>
<td>3.7</td>
</tr>
<tr>
<td>Symptom Checklist 76</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total score</td>
<td>165</td>
<td>163</td>
<td>158</td>
</tr>
<tr>
<td>Depression dimension subtotald</td>
<td>36.0</td>
<td>34.3</td>
<td>34.1</td>
</tr>
<tr>
<td>HAM-A</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total score</td>
<td>16.8</td>
<td>16.6</td>
<td>16.5</td>
</tr>
</tbody>
</table>

Abbreviations: Ham-D = Hamilton Depression Rating Scale (21 item), CGI = Clinicians Global Impressions, MADRS = Montgomery–Asberg Depression Rating Scale, Ham-A = Hamilton Anxiety Rating Scale.

* Includes patients with data at baseline and Visit 8 with Last Observation Carried Forward.

a Core Depression items = the subtotal from the Ham-D on the following items: depressed mood, feelings of guilt, interest in work and activities, and psychomotor retardation.

b Depression item = Ham-D item no. 1.

c Apparent Sadness item = MADRS item no. 1.

d Depression dimension subtotal = SCL-76 item nos. 5, 12, 13, 16, 18, 22, 25, 26, 27, 28, 48, 63, and 70 subtotal.
Table 2. Efficacy variables: mean change from baseline at end of treatment (visit 8) with last observation carried forward

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo</th>
<th>5 mg</th>
<th>7.5 mg</th>
<th>Overall p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HAM-D</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total score</td>
<td>−7.92</td>
<td>−8.83</td>
<td>−10.45</td>
<td>0.010</td>
</tr>
<tr>
<td>Total (% change)</td>
<td>−33.1</td>
<td>−36.1</td>
<td>−42.7</td>
<td>0.016</td>
</tr>
<tr>
<td>Core Depression items subtotal</td>
<td>−2.98</td>
<td>−3.00</td>
<td>−3.74</td>
<td>0.060</td>
</tr>
<tr>
<td>Depression item</td>
<td>−0.92</td>
<td>−0.98</td>
<td>−1.23</td>
<td>0.048</td>
</tr>
<tr>
<td>CGI</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Global improvement</td>
<td>2.86</td>
<td>2.64</td>
<td>2.44</td>
<td>0.011</td>
</tr>
<tr>
<td>Severity of Illness</td>
<td>−0.87</td>
<td>−0.97</td>
<td>−1.22</td>
<td>0.022</td>
</tr>
<tr>
<td>MADRS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total score</td>
<td>−8.14</td>
<td>−9.54</td>
<td>−11.64</td>
<td>0.009</td>
</tr>
<tr>
<td>Apparent Sadness</td>
<td>−1.10</td>
<td>−1.32</td>
<td>−1.59</td>
<td>0.015</td>
</tr>
<tr>
<td>SCL-76</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total score</td>
<td>−16.0</td>
<td>−16.2</td>
<td>−25.2</td>
<td>0.110</td>
</tr>
<tr>
<td>Depression dimension subtotal</td>
<td>−4.34</td>
<td>−3.98</td>
<td>−6.66</td>
<td>0.140</td>
</tr>
<tr>
<td>HAM-A</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total score</td>
<td>−4.27</td>
<td>−5.63</td>
<td>−5.66</td>
<td>0.122</td>
</tr>
</tbody>
</table>

Abbreviations: Ham-D = Hamilton Depression Rating Scale (21 item), CGI = Clinicians Global Impressions, MADRS = Montgomery–Asberg Depression Rating Scale, SCL-76 = Symptom Checklist 76, Ham-A = Hamilton Anxiety Rating Scale. Numbers in parentheses are p-values for the comparison to placebo. p-values are underlined when less than 0.05 and when the overall test comparing the three treatments was significant.

* Patients valid for efficacy.
† For CGI Global improvement there is no baseline and the value itself was analysed.

Effectiveness of ipsapirone

for all patients. Table 2 summarises the results for the primary time point, week 8, with the last observation carried forward (LOCF) in patients valid for efficacy. Within the valid-for-efficacy sub-sample, the ipsapirone 7.5 mg group demonstrated a significantly greater improvement for the primary efficacy variable, the HAM-D total score (LOCF), at week 8 when compared to the placebo group (p = 0.010). The magnitude of the treatment-effect for the 7.5 mg dose was approximately 2.5 points versus placebo. This ipsapirone group also demonstrated significantly greater improvement on the HAM-D total score (LOCF) within the intent-to-treat subsample when compared to the placebo group (p = 0.002), with a magnitude of effect of −2.9 points. The results for the HAM-D total percent change support the results for the analysis of change. The trends for the Core Depression items subtotal and the Depression item are consistent with the HAM-D total score results, but the results did not reach statistical significance. The ipsapirone 7.5 mg dose was significantly better than placebo for CGI Global Improvement (p = 0.011) and for the MADRS total (p = 0.009). The results for the SCL-76 variables and HAM-A total score favoured the ipsapirone 7.5 mg group over the placebo group but did not achieve statistical significance. The results for the ipsapirone 5 mg group, which were generally intermediate to those for the placebo and ipsapirone 7.5 mg groups, were not significantly different from those of the placebo group. Group mean HAM-D total scores are depicted graphically in Figure 1.

Although the ipsapirone 10 mg group was not included in the statistical analysis, summary statistics indicate that
Table 3. Incidence rates of treatment-emergent adverse events*

<table>
<thead>
<tr>
<th>Event</th>
<th>Placebo (n = 108)</th>
<th>5 mg (n = 110)</th>
<th>7.5 mg (n = 112)</th>
<th>10 mg (n = 39)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>19 (18)†</td>
<td>17 (16)</td>
<td>27 (24)</td>
<td>15 (38)</td>
<td>0.015</td>
</tr>
<tr>
<td>Palpitation</td>
<td>0 (0)</td>
<td>5 (5)</td>
<td>3 (3)</td>
<td>5 (13)</td>
<td>0.002</td>
</tr>
<tr>
<td>Nausea</td>
<td>16 (15)</td>
<td>23 (21)</td>
<td>33 (29)</td>
<td>14 (36)</td>
<td>0.014</td>
</tr>
<tr>
<td>Vomiting</td>
<td>2 (2)</td>
<td>2 (2)</td>
<td>5 (4)</td>
<td>6 (15)</td>
<td>0.006</td>
</tr>
<tr>
<td>Dizziness</td>
<td>15 (14)</td>
<td>53 (48)</td>
<td>72 (64)</td>
<td>24 (62)</td>
<td>0.001</td>
</tr>
<tr>
<td>Paresthesia</td>
<td>3 (3)</td>
<td>6 (5)</td>
<td>14 (13)</td>
<td>4 (10)</td>
<td>0.032</td>
</tr>
<tr>
<td>Sweating</td>
<td>1 (1)</td>
<td>1 (1)</td>
<td>8 (7)</td>
<td>5 (13)</td>
<td>0.001</td>
</tr>
<tr>
<td>Tinnitus</td>
<td>0 (0)</td>
<td>3 (3)</td>
<td>1 (1)</td>
<td>5 (13)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

* Patients valid for safety, events with p-value < 0.05.
† Percentages are shown in parentheses.

The results at week 8 were better for the 10 mg group than for the 7.5 mg group, while at week 8 with the LOCF, the 10 mg group was generally comparable to the 7.5 mg group. There was little indication of a treatment-by-centre interaction. The only statistically significant interactions at week 8 were for the HAM-A total score.

Adverse events

Adverse events and concurrent illnesses were reported for 82 (76%) of 108 patients treated with placebo, 101 (92%) of 110 patients treated with ipsapirone 5 mg, 103 (92%) of 112 patients treated with ipsapirone 7.5 mg, and 36 (92%) of 39 patients treated with ipsapirone 10 mg. The incidence of dizziness was increased in all ipsapirone groups compared to placebo. The 7.5 and 10 mg doses were associated with a higher incidence of headache, nausea, paresthesia and sweating. In addition, the 10 mg dose was associated with an increased incidence of palpitation, vomiting and tinnitus compared to the placebo group. These results are summarised in Table 3. There was a dose-related increase in the rate of discontinuation due to adverse events (placebo, 5%; ipsapirone 5 mg, 16%; ipsapirone 7.5 mg, 21%; ipsapirone 10 mg, 44%). As noted above, the increased incidence of premature terminations resulted in a decision to discontinue the 10 mg ipsapirone dose from the study.

There were no significant differences in the incidence of abnormal laboratory values for the ipsapirone treatment groups compared to placebo. No patients were discontinued from the study because of changes in laboratory variables.

The only significant change in ECG findings during the study was a decrease in the QT interval for the ipsapirone 10 mg group relative to placebo. The mean QT interval change from baseline in the ipsapirone 10 mg group was −16.8 ms compared to −2.4 ms in the placebo group. There is no obvious explanation for this finding, nor were there any clinically significant correlates related to this finding.

Discussion

The statistical analysis of efficacy and safety data obtained from this study reveals several clinically important findings. Ipsapirone 7.5 mg t.i.d. was significantly better than placebo in ameliorating depressive symptoms as determined by analysis of the primary efficacy variable (HAM-D total score change from baseline) at the primary time point (Visit 8 with the LOCF). Furthermore, ipsapirone 7.5 mg t.i.d. was significantly better than placebo on the percent change in the HAM-D total score results, and the secondary efficacy variables of CGI Global Improvement and MADRS. The trends for the HAM-D Core Depression items subtotal and the Depression item supported the HAM-D total score results, but these trends did not achieve statistical significance. Additionally, the results for the CGI Severity of Illness, MADRS Apparent Sadness item, SCL-76 and HAM-A scores favoured ipsapirone 7.5 mg t.i.d. over placebo, but did not reach statistical significance.

Ipsapirone was less well tolerated than placebo at each of the doses studied. The overall incidence of adverse events/concurrent illnesses was 92% for each of the ipsapirone groups and 76% for the placebo group. Ipsapirone produced significantly more dizziness with each of the dosages studied. The ipsapirone 7.5 and 10 mg doses produced more headache, nausea, paresthesia and sweating; additionally, the 10 mg dose was also associated with an increased incidence of vomiting, tinnitus and palpitations. The incidence of adverse events correlated positively with increasing doses of ipsapirone.
such that testing with the highest (10 mg) dose was discontinued from the study. Importantly, no deaths or life-threatening adverse events occurred. Furthermore, no statistically significant changes in laboratory values or ECG abnormalities occurred in patients randomised to ipsapirone treatment versus the placebo group.

The findings in this study are consistent with the efficacy and safety findings of a randomised, double-blind, placebo-controlled trial of ipsapirone 7.5 mg t.i.d. conducted in Germany with 65 inpatients, 34 of whom were diagnosed with neurotic depression (ICD 9 300.4) as reported by Heller et al. (1990). The common adverse events identified in the present study are similar to adverse events identified in previous Phase I and II studies using the immediate-release form of ipsapirone (Stahl et al., 1992).

The results demonstrate that ipsapirone improves symptoms of MDD at doses that generally produce adverse side-effects in a majority of subjects. As these side-effects appear to be related to the stimulation of 5-HT-1A receptors, and therefore may be mechanism-based, the therapeutic index of ipsapirone may be unacceptable in an immediate-release dosage formulation such as was employed here.

In summary, ipsapirone 7.5 mg administered three times daily was significantly more effective than placebo for the treatment of MDD. This is the first reported study demonstrating the efficacy of a 5-HT-1A receptor agonist in treating MDD in a large, multi-centre trial of well-defined subjects and a fixed dose, placebo-controlled design. While no significant safety problems were identified with the ipsapirone 5 and 7.5 mg dosages, ipsapirone was not well tolerated in the present formulation. Since this could significantly restrict its use as an antidepressant agent, further development of ipsapirone as an antidepressant may be contingent upon the ability of new drug delivery technologies to preserve or enhance the efficacy observed here while simultaneously improving tolerability.

The observation that a direct acting 5-HT-1A agonist produced delayed-onset antidepressant effects in a large controlled clinical study supports the hypothesis that SSRIs produce their delayed-onset antidepressant effects via indirect stimulation of 5-HT-1A somatodendritic autoreceptors (Blier et al., 1987, 1993; Stahl, 1994, 1996 and In Press; Stahl et al., 1992; Varrault et al., 1991; Wieland et al., 1993). However, ipsapirone exhibited less robust therapeutic action in decreasing HAM-D scores compared to what is usually observed in studies of SSRIs. This might be explained by the partial agonist properties of ipsapirone (De Vry et al., 1992; Stahl et al., 1992). SSRIs, acting indirectly via the full agonist serotonin itself, may have more robust effects on 5-HT-1A receptors than the partial agonist ipsapirone (Stahl, 1994, Stahl et al., 1992; Varrault et al., 1991; Wieland et al., 1993).

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References


Harto N, Branconnier RJ (1988). Clinical profile of gepirone:


