A placebo controlled study of the propentofylline added to risperidone in chronic schizophrenia


Psychiatric Research Center, Roozbeh Psychiatric Hospital, Tehran University of Medical Sciences, Tehran, Iran
Department of Epidemiology and Biostatistics, School of Public Health, Tehran University of Medical Sciences, Tehran, Iran
Departement of Psychiatry, Zanjan University of Medical Sciences, Zanjan, Iran
Razi Psychiatric Hospital, Welfare Sciences University, Iran
Semnan University of Medical Sciences, Garmsar, Iran
National Iranian Oil Company, Central Hospital, Tehran, Iran

Received 10 August 2007; received in revised form 9 November 2007; accepted 17 November 2007
Available online 23 November 2007

Abstract

Impaired activity of the purinergic system is a plausible common factor that could be responsible for many aspects of schizophrenia. Based on the purinergic hypothesis of schizophrenia, pharmacological treatments enhancing adenosine activity could be effective treatment in schizophrenia. Propentofylline is a novel xantine derivative which is being developed for treatment of degenerative and vascular dementia. It enhances extracellular adenosine level via inhibition of adenosine uptake. The purpose of the present investigation was to assess the efficacy of propentofylline as an adjuvant agent in the treatment of chronic schizophrenia in an 8-week double blind and placebo controlled trial. Eligible participants in this study were 50 patients with chronic schizophrenia. All patients were inpatients and were in the active phase of the illness, and met DSM-IV-TR criteria for schizophrenia. Patients were allocated in a random fashion, 25 to risperidone 6 mg/day plus propentofylline 900 mg/day (300 mg TDS) and 25 to risperidone 6 mg/day plus placebo. The principal measure of the outcome was Positive and Negative Syndrome Scale (PANSS). Although both protocols significantly decreased the score of the positive, negative and general psychopathological symptoms over the trial period, the combination of risperidone and propentofylline showed a significant superiority over risperidone alone in the treatment of positive symptoms, general psychopathology symptoms as well as PANSS total scores. The means Extrapyramidal Symptoms Rating Scale for the placebo group were higher than in the propentofylline group over the trial. However, the differences were not significant. The present study indicates propentofylline as a potential adjunctive treatment strategy for chronic schizophrenia. Nevertheless, results of larger controlled trials are needed, before recommendation for a broad clinical application can be made.

© 2007 Elsevier Inc. All rights reserved.

Keywords: Adenosine; Propentofylline; Schizophrenia

1. Introduction

Schizophrenia is a devastating neurobiologic disorder that typically strikes the brain function of adolescents and young adults, occurring in about 1 of every 100 people worldwide (Jablensky et al., 1991; Mohammadi and Akhondzadeh, 2001). The pathophysiology of schizophrenia remains puzzling (Anderson, 2000;
Akhondzadeh, 2006). Inadequate response to both typical and atypical antipsychotics occurs in 30–40% of patients. Of these patients, 40–60% may then respond to the atypical antipsychotic clozapine (Akhondzadeh, 2006). Atypical antipsychotic medications are often distinguished from conventional antipsychotics based on clinical advantages such as a low potential for causing extrapyramidal symptoms, efficacy for the negative symptoms of schizophrenia, and a greater potential for efficacy in cases of treatment-resistant schizophrenia (Akhondzadeh, 2006). However, these agents are not a magic bullet and are associated with their own attendant treatment complications, such as weight gain, diabetes and hyperprolactinemia. Although the dopamine hypothesis of schizophrenia remains the leading neurochemical hypothesis, other neurotransmitter receptors may also be involved in the pathogenesis of schizophrenia (Akhondzadeh, 2006). Over the past 25 years a general consensus has been reached on the crucial role of adenosine in the CNS as a modulator of neurotransmission and a neuroprotective agent against ischemic- and seizure-induced neuronal injury (Erfurth and Schmauss, 1995; Guieu et al., 1996; Brundege and Dunwiddie, 1997; Stone, 2005). Adenosine has also been proposed to be a potent regulator of cerebral blood flow. Besides its more general involvement in cellular metabolism, specific actions of adenosine in the CNS as neuroprotective are believed to be mediated through specific receptors, which have been cloned and classified as A_1, A_2A, A_2B and A_3 receptors (Erfurth and Schmauss, 1995; Guieu et al., 1996; Brundege and Dunwiddie, 1997). There is a large amount of data showing that adenosine plays a role opposite to dopamine in the brain (Darlsson et al., 1999). Adenosine agonists and antagonists produce behavioral effects similar to dopamine antagonists and dopamine agonists, respectively. Preclinically, adenosine and its analogs exert antipsychotic, anxiolytic, sedative, anticonvulsant and anti-aggressive effects (Erfurth and Schmauss, 1995; Guieu et al., 1996). Similarly to amphetamine and NMDA receptor antagonists, caffeine and theophylline produce hyperlocomotor responses in rodents, which can be reversed by antipsychotics. In healthy subjects, high doses of adenosine antagonists can produce psychosis (Lara et al., 2006). Allopurinol, a well-known hypouricemic drug that inhibits xantine oxidase, has been used as add-on drug in the treatment of poorly responsive schizophrenic patients. Indeed, the neuropsychiatric effects of allopurinol in schizophrenia have been suggested to be secondary to its inhibitory effect of purine degradation, enhancing adenosinergic activity (Lara et al., 2001; Akhondzadeh et al., 2005; Brunstein et al., 2005, 2007). Unfortunately, direct or indirect adenosine agonists with clear effects on the brain are not yet available for human use. Propentofylline is a xantine derivative which was developed for treatment of degenerative and vascular dementia (Kittner et al., 1997; Marcusson et al., 1997; Noble and Wagstaff, 1997; Mielenk et al., 1998). Nevertheless, the European agency for the evaluation of medicinal products did not approve propentofylline for treatment of dementia due to lack of strong data. Therefore, it is still considered as investigational drug and is not marketed. It enhances extracellular adenosine level via inhibition of adenosine uptake, and prevents the enzymatic degradation of cyclic adenosine monophosphate and cyclic guanosine monophosphate through inhibition of cyclic nucleotide phosphodiesterases (Noble and Wagstaff, 1997). Few details of pharmacokinetic properties of propentofylline are available. Administration of propentofylline 100 mg 3 times daily for at least four weeks produced a mean plasma concentration of 43.3 μg/L in 5 elderly patients with organic brain disorders (Noble and Wagstaff, 1997). The purpose of the present investigation was to assess the efficacy of propentofylline as an adjuvant agent in the treatment of chronic schizophrenia in an 8-week double blind and placebo controlled trial.

2. Methods

2.1. Setting

This investigation was a prospective, 8-week, double blind study of parallel groups of patients with chronic schizophrenia and was undertaken in three Psychiatric Hospitals in Iran, from October 2005 to May 2007.

2.2. Participants

Eligible participations in the study were 50 patients with chronic schizophrenia (19 women and 31 men) age ranging from 19 to 47 years. All participants were inpatients, who were recently admitted in an acute exacerbation, and met DSM-IV-TR criteria for schizophrenia (American Psychiatric Association, 2000). The minimum score of 60 on Positive and Negative Syndrome Scale (PANSS) was required for entry into the study (Kay et al., 1987). The PANSS includes 30 items on three subscales (scoring range 1 to 7), 7 items covering positive symptoms, 7 items covering negative symptoms and 16 covering general psychopathology. In addition, a total score presents all three parts. The patients did not receive neuroleptics from a week prior to entering the trial or depot neuroleptic at least two months before the study. Patients were excluded from the study if they had a clinically significant organic and neurological disorder, concurrent Axis I DSM-IV-TR diagnosis, current abuse or dependence on drugs within 6 months, serious psychotic disorders other than schizophrenia, use of any medications identified as contradicted with propentofylline and history of allergic reaction to propentofylline. Pregnant or lactating women and those of reproductive age without adequate contraception were also excluded. The trial was performed in accordance with the Declaration of Helsinki and subsequent revisions (World Medical Association, 2000) and approved by each institutional review board. Written informed consents were obtained before entering into the study.

2.3. Intervention

Patients were randomly allocated, 25 to risperidone 6 mg/day plus propentofylline 900 mg/day (300 mg three times per day) and 25 to risperidone 6 mg/day plus placebo for an eight week, double-blind, and placebo controlled study. Patients were randomized to receive propentofylline or placebo in a 1:1 ratio using a computer-generated code. Throughout the study, the person who administered the medications, the rater and the patients were blind to assignments. Pharmaceutical form of propentofylline was film-coated tablet and purchased from Aventis Pharma. Starting dosage of risperidone was 2 mg/day and was increased to 6 mg/day with
2 mg increments in daily dosage for the first two days. Starting dosage of was propentofylline 300 mg three times per day. Patients in the placebo group received three tablets similar to propentofylline in terms of size and color. During the washout period, the patients received benzodiazepines if necessary. Lorazepam was the drug of choice. Patients also received biperiden if they had faced extrapyramidal symptoms. The patients did not receive any psychotropic medications except the trial protocol during the study. Patients were assessed by a psychiatrist at baseline and after 2, 4, 6 and 8 weeks after the medication started. Side effects were systematically recorded throughout the study and were assessed using a checklist administered by a resident of psychiatry on day 7, 14, 28, 42 and 56 (Table 3).

2.4. Outcome

The principal measure of the outcome was the PANSS. The rater used standardized instructions in the use of PANSS. The mean total and subtotal PANSS scores were used as the main outcome measure. The extrapyramidal symptoms were assessed using the Extrapyramidal Symptoms Rating Scale (ESRS) (part one: parkinsonism, dystonia, dyskinesia; sum of 11 items) (Chouinard et al., 1980).

2.5. Statistical analysis

A two-way repeated measures analysis of variance (time-treatment interaction) was used. The two groups as a between-subjects factor (group) and the five measurements during treatment as the within-subjects factor (time) were considered. This was done for positive, negative, general psychopathology subscales and PANSS total scores. A Greenhouse–Geisser correction was used for sphericity. To compare the two groups at baseline and the outcome of two groups at the end of the trial, an unpaired Student’s t-test with a two-sided p value was used. To compare the demographic data and frequency of side effects between the protocols, Fisher’s exact test was performed. Results are presented as mean±SD. Differences were considered significant with p<0.05. To consider, α=0.05, and the final difference between the two groups at least score of 5 on the PANSS rating scale, S=5 and power=0.8 (according to the pilot study of this research), the sample size was calculated at least 15 in each group. Intention to treat (ITT) analysis with last observation carried forward (LOCF) procedure was performed. Effect size was calculated from partial eta (Cohen, 1988). Statistical significance required two-tailed p<0.05. Data were analyzed by using commercially available statistical packages (SPSS 13.00. Chicago, IL, USA).

3. Results

Eighty one patients were screened for the study and 50 were randomized to trial medication (25 patients in each group) (Fig. 1). No significant differences were identified between patients randomly assigned to the group 1 or 2 condition with regard to basic demographic data including age, age of first
onset of illness, gender, marital status, level of education, mean duration of illness and number of life-time hospitalization (Table 1). Although the number of dropout in the placebo group was higher than the propentofylline group (1 in the propentofylline group and 2 in the placebo group), no significant difference was observed in the two groups in terms of dropout.

3.1. Positive symptoms

The mean±SD scores of two groups of patients are shown in Fig. 2. There were no significant differences between the two groups at week 0 (baseline) on the PANSS ($t=0.16$, df=48, $p=0.87$). The difference between the two treatments was significant as indicated by the effect of group, the between-subjects factor (Greenhouse–Geisser corrected: $p=0.03$; partial eta: 0.087 and $f=0.31$). The behavior of the two treatment groups was similar across time (groups-by-time interaction, Greenhouse–Geisser corrected: $F=2.43$, df=1.79, $p=0.09$). In addition, a one-way repeated measures analysis of variance showed a significant effect of both treatments on the positive subscale scores of PANSS rating scale ($p<0.0001$; partial eta=0.04, $f=0.20$). In the propentofylline and placebo group, post hoc comparisons showed a significant change from week 2 and 4 respectively. The difference between the two treatments was significant at the endpoint (week 8) ($t=2.03$, df=48, $p=0.04$).

3.2. Negative symptoms

The mean±SD scores of two groups of patients are shown in Fig. 3. There were no significant differences between the two groups at week 0 (baseline) on the PANSS ($t=0.32$, df=48, $p=0.74$). The difference between the two treatments was not significant as indicated by the effect of group, the between-subjects factor (Greenhouse–Geisser corrected: $p=0.62$; partial eta=0.005 and $f=0.20$). The behavior of the two treatment groups was similar across time (groups-by-time interaction, Greenhouse–Geisser corrected: $F=0.86$, df=1.81, $p=0.41$). In addition, a one-way repeated measures analysis of variance showed a significant effect of both treatments on the negative subscale scores of PANSS rating scale ($p<0.0001$; partial eta=0.04, $f=0.20$).

Table 1

Baseline data

<table>
<thead>
<tr>
<th></th>
<th>Propentofylline group</th>
<th>Placebo group</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>Male: 16, female: 9</td>
<td>Male: 15, female: 10</td>
<td>ns</td>
</tr>
<tr>
<td>Age (mean±SD)</td>
<td>33.12±7.17 (year)</td>
<td>34.24±7.59 (year)</td>
<td>ns</td>
</tr>
<tr>
<td>Marital status</td>
<td>Single: 14, married: 8, divorced: 3</td>
<td>Single: 16, married: 7, divorced: 2</td>
<td>ns</td>
</tr>
<tr>
<td>Level of education</td>
<td>Under diploma: 16, diploma: 6, higher diploma: 3</td>
<td>Under diploma: 15, diploma: 8, higher diploma: 2</td>
<td>ns</td>
</tr>
<tr>
<td>Time since diagnosis</td>
<td>93.12±66.01 (month)</td>
<td>90.00±48.86 (month)</td>
<td>ns</td>
</tr>
<tr>
<td>Type of schizophrenia</td>
<td>Paranoid: 15</td>
<td>Paranoid: 13</td>
<td>ns</td>
</tr>
<tr>
<td></td>
<td>Disorganized: 5</td>
<td>Disorganized: 6</td>
<td>ns</td>
</tr>
<tr>
<td></td>
<td>Undifferentiated: 5</td>
<td>Undifferentiated: 6</td>
<td>ns</td>
</tr>
<tr>
<td>Number of life-time</td>
<td>4.20±0.40</td>
<td>4.16±0.34</td>
<td>ns</td>
</tr>
<tr>
<td>hospitalization (Mean±SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medications history</td>
<td>Typical antipsychotic(haloperidol) and atypical antipsychotics (risperidone or olanzapine): 19</td>
<td>Typical antipsychotic(haloperidol) and atypical antipsychotics (risperidone or olanzapine): 17</td>
<td>ns</td>
</tr>
<tr>
<td></td>
<td>Only atypical antipsychotics (risperidone or olanzapine): 6</td>
<td>Only atypical antipsychotics (risperidone or olanzapine): 8</td>
<td>ns</td>
</tr>
</tbody>
</table>

Fig. 2. Mean±SD of the two protocols on the positive subtotal scores of the PANSS. ns=non-significant and *$<0.05$.

Fig. 3. Mean±SD of the two protocols on the negative subtotal scores of the PANSS. ns=non-significant.
showed a significant effect of both treatments on the negative subscale scores of PANSS rating scale \((p<0.0001; \text{partial } \eta^2=0.01 \text{ and } f=0.1)\). In both groups post hoc comparisons showed a significant change from week 4. The difference between the two treatments was not significant at the endpoint (week 8) \((t=0.63, \text{df}=48, p=0.52)\).

3.3. General psychopathological symptoms

The mean±SD scores of two groups of patients are shown in Fig. 4. There were no significant differences between the two groups at week 0 (baseline) on the PANSS \((t=0.60, \text{df}=48, p=0.54)\). The difference between the two treatments was significant as indicated by the effect of group, the between subjects factor (Greenhouse–Geisser corrected: \(p=0.05\); partial \(\eta^2=0.07 \text{ and } f=0.27\)). The behavior of the two treatment groups was not similar across time (groups-by-time interaction, Greenhouse–Geisser corrected: \(F=5.22, \text{df}=1.65, p=0.01\)). In addition, a one-way repeated measures analysis of variance showed a significant effect of both treatments on the general psychopathological symptoms subscale scores of PANSS rating scale \((p<0.0001; \text{partial } \eta^2=0.09 \text{ and } f=0.32)\). In both groups post hoc comparisons showed a significant change from week 2. The difference between the two treatments was significant at the endpoint (week 8) \((t=2.71, \text{df}=48, p=0.009)\).

3.4. PANSS total scores

The mean±SD scores of two groups are shown in Fig. 5. There were no significant differences between the two groups at week 0 (baseline) on the PANSS \((t=0.35, \text{df}=48, p=0.72)\). The difference between the two treatments was significant as indicated by the effect of group, the between-subjects factor (Greenhouse–Geisser corrected: \(p=0.01\); partial \(\eta^2=0.11 \text{ and } f=0.35\)). The behavior of the two treatment groups was not similar across time (groups-by-time interaction, Greenhouse–Geisser corrected: \(F=4.25, \text{df}=1.57; p=0.02\)). In addition, a one-way repeated measures analysis of variance showed a significant effect of both treatments on the total scores of PANSS rating scale \((p<0.0001; \text{partial } \eta^2=0.11 \text{ and } f=0.35)\). In both groups post-hoc comparisons showed a significant change from week two. The difference between the two treatments was significant at the endpoint (week 8) \((t=2.46, \text{df}=48, p=0.01)\).

3.5. Extrapyramidal symptoms rating scale

Although the means ESRS for the placebo group were higher than propentofylline group over the eight weeks of trial, the differences were not statistically significant (Table 2). No significant difference was observed between the overall mean biperiden dosages (mg) in two groups (109.04±113.12 and 139.04±80.19 for propentofylline and placebo group respectively; mean±SD) \((p=0.28; \text{df}=48)\). The cumulative dose of biperiden in the propentofylline and placebo group was 2726 mg and 3300 mg respectively. Moreover, the difference between the two treatments in terms of the number of days of biperiden treatment was not significant \((18.47±18.95 \text{ and } 23.55±13.37 \text{ for propentofylline and placebo group respectively; mean±SD})(p=0.27; \text{df}=48)\).

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Extrapyramidal symptoms based on extrapyramidal symptoms rating scale</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean±SD</td>
</tr>
<tr>
<td></td>
<td>propentofylline group</td>
</tr>
<tr>
<td>Week 0</td>
<td>1.16±2.79</td>
</tr>
<tr>
<td>Week 1</td>
<td>4.58±5.50</td>
</tr>
<tr>
<td>Week 2</td>
<td>7.00±9.94</td>
</tr>
<tr>
<td>Week 4</td>
<td>4.80±3.40</td>
</tr>
<tr>
<td>Week 6</td>
<td>3.40±3.46</td>
</tr>
<tr>
<td>Week 8</td>
<td>2.36±2.34</td>
</tr>
</tbody>
</table>

Fig. 4. Mean±SD of the two protocols on the general psychopathology subtotal scores of the PANSS. ns=non-significant and **⁎⁎⁎<0.001.
The therapeutic benefit of adjunctive propentofylline in schizophrenia is probably due to adenosine-glutamate interactions (Lara et al., 2006). Adenosine has been shown to inhibit synaptic activity and the release of several neurotransmitters, such as glutamate, acetylcholine and serotonin, by acting on presynaptic A1 receptors. Moreover, both A1 and A2a adenosine agonists prevent behavioral and neurophysiological effects of NMDA antagonists (Lara et al., 2006). Extrapyramidal side effects measured by the ESRS did not show any differences between the two groups over the trial. The use of biperiden was greater in the group receiving risperidone+placebo but the difference was not statistically significant. It is suggested that a free radical scavenger activity of propentofylline may be involved in this effect (Noble and Wagstaff, 1997). In addition, therapy with 900 mg/day of propentofylline was well tolerated, and no clinically important side effects were observed. Gastrointestinal disturbances, dizziness and headache were most common events during the trial with propentofylline. The therapeutic benefit of the combined therapy has to be attributed to effects of propentofylline. To best of our knowledge, this study is the first clinical study that suggests the potential use of propentofylline as adjunctive treatment and therefore it is not possible to draw any comparisons with other trials. Nevertheless, it is in line with recent studies that showed the beneficial effects of dipyridamole (an adenosine uptake inhibitor) and allopurinol (an inhibitor of xantine oxidase), as adjunctive therapy for schizophrenia (Akhondzadeh et al., 2000; Lara et al., 2001; Akhondzadeh et al., 2005; Brunstein et al., 2005). The limitations of the present study, including the short period of study and using only a fixed dose of propentofylline, should be taken into account and this indicates the need for further research. In addition, from a scientific viewpoint, the therapeutic effects of propentofylline without an additional neuroleptic drug would be more interesting. However, since neuroleptics are effective in antipsychotic treatment, ethic committees would not approve a study with propentofylline as the only drug for acutely ill schizophrenic patients. The present study indicates propentofylline as a potential adjunctive treatment strategy for chronic schizophrenia. Nevertheless, results of larger controlled trials are needed, before recommendation for a broad clinical application can be made.

4. Discussion

There is no doubt that atypical antipsychotics are effective against the acute psychotic symptoms of schizophrenia and in preventing relapse. Nevertheless, atypical antipsychotics are less than perfect and there is still a lot of room for improvement in the treatment of schizophrenia (Akhondzadeh, 2006). Impaired activity of the purinergic system is a plausible common factor that could be responsible for many aspects of schizophrenia (Lara and Souza, 2000). Based on purinergic hypothesis of schizophrenia, pharmacological treatments enhancing adenosine activity could be effective treatment in schizophrenia (Lara and Souza, 2000; Brunstein et al., 2007). Drugs that indirectly increase adenosine levels, such as propentofylline could stimulate A1 and A2A receptors simultaneously (Noble and Wagstaff, 1997). Indeed, propentofylline inhibits reuptake of the neuromudulator adenosine, resulting in extracellular accumulation of this molecule and potentiation of the neuroprotective effects which it exerts via adenosine A1 and A2 receptors (Noble and Wagstaff, 1997).

As expected, both groups of patients showed significant improvement on the Positive and Negative Syndrome Scale and on all subscales during the 8 weeks of treatment with risperidone. In agreement with our hypothesis, the propentofylline group had significantly greater improvement in the positive symptoms, general psychopathological symptoms and PANSS total scores over 8 weeks trial. No significant differences were observed between the means of the two groups on the negative scores. Clinical characteristics of the schizophrenic patients, such as sex, age and duration of illness, did not differ between groups and can not explain differences in the therapeutic outcome. In addition, to our knowledge, pharmacokinetic interaction with propentofylline leading to higher plasma level of risperidone, has not been reported. Moreover, a relatively high dose of risperidone in this study suggests that the extra effect of propentofylline is independent of risperidone’s mechanism.
Acknowledgment

This study was Dr. Samarand Salimi’s postgraduate thesis toward the Iranian board of psychiatry. This study was supported by a grant from Tehran University of Medical Sciences to Dr. Shahin Akhondzadeh.

References

Noble S, Wagstaff AJ. Propentofylline. CNS Drugs 1997;8:257–64.