Tolerability and Efficacy of Amisulpride in Elderly Chronic Psychotic Patients: A 12-week Open-labeled Study

Tzu-Ting Chen, Geng-Han Mo, Yen-Ping Liu, Shr-Shian Shiu, Yu-Yuan Wang, Mei-Lin Chen, Ling-Fen Kung, Ya-Hsin Yu, Shih-Fang Wang, Chiu-Hui Kuan, Jen-Yeu Chen*

Abstract

Objectives: To evaluate the tolerability and efficacy of treatment with amisulpride in elderly patients with chronic psychosis.

Methods: This study recruited patients of both sexes aged 60 years or older, meeting the DSM-IV criteria for psychotic disorders, and reporting psychotic symptoms severe enough to require antipsychotic medications. Subjects were selected from residents in a chronic mental hospital, who, after being treated with antipsychotics for years, were switched to amisulpride with flexible dose for twelve weeks. Safety assessment involving adverse event reporting, physical examination, ECG, laboratory tests and extrapyramidal symptoms were evaluated or monitored. Efficacy parameters were based on changes in score on the Positive and Negative Syndrome Scale (PANSS) and Clinical Global Impression-Severity (CGI-S).

Results: 45 patients (mean age: 66.7 ± 5.7 years) were recruited with 34 completing the 12-week study. 11 patients discontinued the study due to the emergence of acute psychotic episode. Mean dosage of antipsychotics in baseline is 340.4 ± 292.2 mg, and mean dosage of amisulpride at end point was 365.2 ± 204.8 mg/day. The PANSS total score mildly decreased at the end of study without significant difference. A significant improvement in the negative symptom domain of PANSS was noted at the end of study. At study endpoint, no significant baseline-to-endpoint differences were observed on total and subscales of side effect parameters. No significant changes of biochemical data, such as fasting glucose, cholesterol, and triglyceride between baseline and end point was found except decrease in body weight.
Conclusion: Amisulpride is generally well tolerated in elderly patients with psychosis and shows some efficacy in the study population.

(Taiwan Geriatr Gerontol 2009; 4(3): 179-186)

Key words: amisulpride, elderly, psychosis, tolerability

Introduction

With a rising of elderly patients suffering from mental disorders or conditions, psychiatric conditions including psychotic disorders or behavioral and psychological symptoms of dementia (BPSD) are expected to increase [1]. Psychotic symptoms like agitation, verbal and physical aggression, sleep disturbances and wandering can decrease the quality of life for elderly patients and their caregivers. In addition, high occurrence of medical morbidity and excess mortality have long been associated with chronic mental conditions. Although some neuroleptic medications have been proven to be effective in treating BPSD and psychotic symptoms, adverse effects are commonly reported in the elderly and may be related to the administration of antipsychotics. Unfortunately, 90% of the published reports concerning antipsychotics have largely ignored elderly patients [2]. The paucity of studies examining the safety and efficacy of antipsychotics in the elderly may increase unfavorable risks or limit its efficacy.

Antipsychotics, both first and second generation, represent the treatment of choice for schizophrenia and related psychotic disorders at any age while first-generation antipsychotics (FGAs) are associated with extrapyramidal side effects (EPS) and tardive dyskinesia (TD). These agents render elderly patients more susceptible to events like orthostatic hypotension and are less effective for negative symptoms or cognition[3]. Though the second-generation antipsychotics (SGAs) sustain less such side effects, they are not free from motor side effect, and several drawbacks have been identified, such as metabolic syndromes [2].

Amisulpride, a substituted benzamide derivative, is a SGA characterized by a selective affinity for dopamine D2 and D3 receptors without any affinity to other receptors, in particular to the adrenergic, cholinergic, histaminergic and serotoninergic receptors. Amisulpride is effective and well-tolerable in double-blind studies on several symptoms
of acute and chronic schizophrenia [4]. Amisulpride usually demonstrates a satisfactory global safety profile within the range of suggested doses [5]. Therefore, the purpose of the study is to evaluate the tolerability and efficacy of amisulpride in chronic psychotic elderly.

Method & Materials

This was a prospective, open-labeled, 12-week study conducted in a chronic mental hospital in the east of Taiwan. The study was reviewed and approved by Hospital Institutional Review Board and was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Reporting Practice. Written informed consent was obtained from each patient.

Subjects

The study included patients of both sexes aged 60 years or older, meeting the DSM-IV criteria for psychotic disorders, including dementia, schizophrenia and schizoaffective disorder, and showing inadequate response with previous antipsychotics, lack of tolerability or safety and/or other reasons to merit the switch to another antipsychotic medication. The diagnoses were confirmed by the experienced psychiatrists (J.-Y.C., T.-T.C., G.-H.M. and Y.-P. L.). Patients were excluded if reporting unstable medical condition, history of neuroleptic malignant syndrome or with a current use or known history (over the past 6 months) of substance dependence except for nicotine, caffeine, and betel nut according to the DSM-IV criteria. All selected patients from a chronic mental hospital had been treated with antipsychotics for many years. The eligible patients were treated with an initial dose of 50 mg/d amisulpride in the first week and flexible dose for twelve weeks. The previous antipsychotic agent was discontinued slowly within the first 4 weeks. The dose of amisulpride had been flexible (50 to 800 mg/day once daily) ever since the second week and based on or up to the investigator’s clinical judgments. Benzodiazepines were allowed as needed for insomnia or agitation, and anticholinergic agents, for extrapyramidal side effects. No other antipsychotic medication during trial was permitted.

Measures

Safety assessments involved adverse event reporting, physical examination, blood pressure, heart rate and ECG monitoring, and laboratory tests. Extrapyramidal symptoms were evaluated with Simpson-Angus Scale (SAS), Barnes Akathisia Scale (BAS) and Abnormal
Involuntary Movement Scale (AIMS). Efficacy parameters were based on changes in score on PANSS and CGI-S. The raters for PANSS were trained using videotapes of standardized PANSS interviews. Their performance was then tested by assessing 3 additional patient interviews. Each rater was required to achieve an intraclass correlation coefficient (ICC) of at least 0.80 to participate in this study. Raters were retested at the end of the study, and no rater’s ICC fell below 0.80.

**Data Analysis**

Changes of scores (PANSS total and subscale scores, CGI-S, AIMS, SAS, BAS and clinical laboratory data, as well as body weight and vital signs) from baseline to endpoint were analysed with paired t-test. The Statistical Package for Social Science (SPSS), version 13.0 (SPSS, Inc., Chicago, Illinois), was used for statistical analyses. All statistical tests were 2 tailed, and significance was determined at the 0.05 level.

**Results**

45 patients (mean age: 66.7 ± 5.7 years) were recruited, and 34 patients (75.6%) completed the 12-week study (Table 1). 43 patients (95.6%) were schizophrenia, one (2.2%) was delusional disorder, and one had combined psychotic disorder not otherwise specified and mental retardation. 11 patients (24.4%) discontinued and withdrew from the study due to the emergence of acute psychotic episode (n = 4), noncompliance (n = 1), non-specific somatic complaints and withdrawal of the informed consent (n= 6). The reasons for retracting the informed consent were non-clinically significant somatic complaints (n = 3) and his/her opinion (n = 3).

Of the 34 patients completing the study, mean equivalent dosage of antipsychotics in baseline was 340.4 ± 292.2 mg and mean dosage of amisulpride at end point was 365.2 ± 204.8 mg/day

<table>
<thead>
<tr>
<th>Table 1</th>
<th>The demographics of 34 elderly patients with chronic psychosis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± SD</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>67.3 ± 6.1</td>
</tr>
<tr>
<td>Age at diagnosis (yr)</td>
<td>28.2 ± 10.2</td>
</tr>
<tr>
<td>Equivalence dose of amisulpride in baseline (mg/day)</td>
<td>340.4 ± 292.2</td>
</tr>
<tr>
<td>Amisulpride dose in endpoint (mg/day)</td>
<td>365.2 ± 204.8</td>
</tr>
<tr>
<td>Gender: male / female; n (%)</td>
<td>19 (55.9) / 15 (44.1)</td>
</tr>
</tbody>
</table>
The PANSS total score (mean ± SD) was 76.1 ± 13.6 at baseline and 72.6 ± 12.3 at endpoint (12-week). Paired $t$-tests showed statistical significance ($t = 2.78, p < 0.01$). The PANSS negative symptoms subscale score also revealed statistical significance (from 24.6 ± 6.5 to 22.8 ± 6.1; $t = 3.44, p < 0.01$).

No change in CGI-S scores was observed. There was no significant difference in AIMS, SAS and BAS. Nevertheless, two patients were reported with EPS (one was tremor of hands and the other excess salivation). These symptoms subsided by titrating trihexyphenidyl 2 mg/day. Otherwise, no concomitant medication had been changed during the study. Mean changes in body weight at baseline and endpoint were 58.0 ± 9.4 kg and 56.1 ± 8.6 kg, respectively ($t = 3.69, p < 0.01$). Mean changes in prolactin levels at baseline and endpoint were 53.0 ± 32.1 ng/ml and 75.7 ± 45.7 ng/mL, respectively ($t = -2.91, p < 0.01$). No significant changes were observed in mean values for most biochemistry profiles, including fasting sugar, cholesterol and triglyceride (Table 2).

### Discussion

This 12-week and open-labeled study on elderly patients with chronic psychosis treated with amisulpride (50-800 mg/day) revealed well tolerance and efficacy in their psychotic symptoms. The results were consistent with those of several studies about the issues of safety and efficacy [6,7]. Although elderly early-onset patients with psychosis generally experienced sustained negative symptoms [8], our patients showed...
significant improvement in negative symptoms with amisulpride treatment. Previously, Danion et al. had reported improvement in schizophrenia patients with predominantly negative symptoms under low dose (100 to 300 mg/day) amisulpride treatment [7].

Regarding the safety issues, amisulpride in the present study appeared to be tolerated, and extrapyramidal symptoms were infrequent. A previous study mentioned that amisulpride was able to induce akathisia in the elderly [9], but there was no clinically significant finding in our patients. Risperidone has solicited more published studies involving geriatric patients than other SGAs. The most frequently reported side effects were somnolence, EPS and peripheral edema [10]. Clozapine and olanzapine were also associated with high risks of metabolic syndrome [2] and quetiapine in elderly patients reported somnolence, dizziness, postural hypotension and accidental injury [11]. In our study, there was no clinical finding in the above mentioned side effects except 2 amisulpride-associated EPS events. In addition, decreased weight and metabolic parameters supported the satisfactory safety profile of the amisulpride [12]. However, significantly increased prolactin levels were still shown in this study.

It was recognized that the relatively smaller number of patients and the 24.4% discontinuance rate were two major limitations of the study. Also to be noted that the open-label design of the study may lead to some bias and potentially bias in the interpretation of the results. Inclusion of the heterogeneous sample (elderly patients with psychosis) may be another limitation. Despite these limitations, the study supported the use of amisulpride in elderly patients with chronic psychosis, especially in the Chinese population. Further controlled trials with larger numbers of samples and double-blind mode are required to clarify the safety and benefit of amisulpride.

In conclusion, in our study, amisulpride appeared to demonstrate well tolerability and efficacy in treating elderly patients with chronic psychotic disorder.

Acknowledgments

This work was supported in part by the Yu-Li Veterans Hospital (YLVH-95-08-02A) and Sanofi-Aventis Taiwan Co., Ltd.

References


老年精神病患者使用 Amisulpride 之耐受性與療效之評估：十二週之開放性研究

陳姿婷 莫庚翰 劉彥平 許仕賢 王錦淵 陳美陵
龔伶芬 游亞歆 王世芳 官秋蕙 陳震宇*

摘要

前言：隨著老年精神病患者的盛行率及發生率增加，兼顧耐受性及療效的治療為目前關注的焦點。Amisulpride 之藥物顯示在治療精神分裂症患者的療效與傳統抗精神病藥物及新一代抗精神病藥物相當，且僅具較少的椎體外症候群及代謝症候群之副作用，故本研究探討老年慢性精神病患患者使用十二週 Amisulpride 後耐受性及療效評估。

方法：本研究為追蹤及開放性試驗，納入六十歲以上之符合 DSM-IV 診斷之老年精神病患。共 45 位進入研究，34 位完成研究，比較使用 amisulpride 50-800 mg/day 其前後活性與負性症狀評量表 (PANSS) 、抗精神病藥物相關之副作用量表及臨床血液生化學檢查等變化。

結果：PANSS 總分及負性症狀分數改善具統計上意義，對於抗精神病藥物相關之副作用量表方面無顯著改變，臨床生化值亦無變化，體重降低具統計意義，泌乳激素升高具統計意義，無其他臨床重大副作用。

結論：Amisulpride 在老年精神病患之治療具耐受性及相當療效。
（台灣老年醫學暨老年學雜誌 2009；4(3)：179-186）

關鍵詞：amisulpride、老年精神病患、耐受性

行政院國軍退除役官兵輔導委員會玉里榮民醫院精神部
通訊作者：陳震宇
通訊處：981 花蓮縣玉里鎮新興街 91 號
電話：(886)3-8883141 Ext. 436 傳真：(886)3-8880474
E-mail: sms0604@ms1.hinet.net