Use of Atypical Neuroleptics in a State Mental Institute
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Abstract
The authors sought to give a perspective of the local use of two atypical neuroleptics which may represent a new era in the treatment of schizophrenia. The findings from local drug trials and clinical reports are summarised. Both clozapine and risperidone are efficacious in reducing the psychotic symptomatology of schizophrenia as well as inducing less extrapyramidal side-effects. Differences in plasma clozapine levels were found in local Chinese patients when compared to American subjects. Combined use of clozapine and risperidone may give rise to adverse reactions. Both clozapine and risperidone are efficacious and safe in the treatment of schizophrenia.

Key words: Asian, Clozapine, Risperidone, Schizophrenia

Introduction
Schizophrenia is the most severe of all mental disorders and affects about 1% of the population. The main disturbances of schizophrenia comprise positive symptoms, negative symptoms and disorganisation.1,2 Positive symptoms represent active distortions of brain function like hallucinations, delusions, disorganised thinking and bizarre behaviour. Negative symptoms represent loss or decrease of normal function which are manifested as affective flattening (impoverished affect), avolition (lack of drive, ambition and spontaneity), anhedonia (diminished interests and pleasures), alogia (poverty of speech and reduced ability to relate to others), and poor attention. The modern era of pharmacotherapy of schizophrenia began when in 1951, a French anaesthetist named Henri Laborit noticed that his surgical patients went into a state of calmness when he gave them chlorpromazine. From this observation, he suggested that chlorpromazine could have a therapeutic role in psychiatric practice. This antipsychotic effect was demonstrated convincingly in subsequent studies.3 In the wake of chlorpromazine’s dramatic effect on psychotic patients, the pharmaceutical industry was galvanised and the results of the subsequent frenetic drug development were more than 30 antipsychotic analogues. However, none of these agents has proven to be substantially superior over another. What these agents have provided are differences in potency and the forms of administration i.e. oral versus injectable forms, as well as different side-effects profile.4 These drugs (also referred to as conventional or typical neuroleptics) also have a variety of side-effects which include sedation, cognitive impairment and extrapyramidal symptoms (EPS) like parkinsonism, dystonic reactions and tardive dyskinesia. They are not effective in about 30% of patients5 and are relatively ineffective for negative symptoms.6

Clozapine

Background
For the last 4 decades, no significant advances were made until the advent of clozapine which has been hailed as one of the most significant advances in antipsychotic pharmacotherapy since chlorpromazine. Clozapine is classified as an atypical antipsychotic because it does not cause EPS and tardive dyskinesia.

A definitive study in America in 19887 showed that clozapine was more effective than conventional neuroleptics in a group of patients with treatment-refractory schizophrenia which was defined as those with poor response to at least three different neuroleptics. Significant improvement in positive and negative symptoms was observed, with 30% of the patients meeting criteria for response at the end of six weeks. This landmark study led to the licensed use of clozapine in America, United Kingdom, and other countries including Singapore. Subsequently, clozapine has been reported to be clinically effective during long-term use in up to 60% of patients resistant to the conventional neuroleptics.8 It
has also been reported to have better efficacy in treating the negative symptoms. The optimal dose is still not established with doses ranging from 25 mg/day to 1600 mg/day. The risk of agranulocytosis remains the most serious and prohibiting adverse effect of clozapine. The cumulative incidence of agranulocytosis is 0.8% of patients treated with clozapine. It is not dose-related, and at present, there are no convincing data to suggest any particular mechanism responsible for this complication. The risk appears to be greatest during the first three months of treatment and greater among women and the elderly. As a consequence of this, mandatory blood monitoring is required through the course of treatment.

**Local Experience**

In an uncontrolled and open study on local patients in Woodbridge Hospital with treatment refractory schizophrenia, we found that 79% of the 19 patients met the study criteria for response i.e. at least 20% decrease in the Brief Psychiatric Rating Scale (BPRS) total score from baseline and a BPRS at end point of 34 or less, or a Clinical Global Impression score of 3 or less. This response rate was higher than that reported in other studies (30% to 60%). The mean dose of our patients was 357 mg/day which was between the mean doses in European trials (284 mg/day) and (444 mg/day) in American studies. The most common side-effects we found was hypersalivation followed by sedation. The mechanism by which clozapine causes hypersalivation remains unknown but we found benxhexol to be effective in alleviating this side-effect. The use of other muscarinic receptor antagonists have also been shown to be effective. One of our patients developed fits while on clozapine therapy and was treated by adding on phenobarbione. There was no blood dyscrasia in any of the patients. We also found a worsening of pre-existing obsessive-compulsive symptoms in 2 of the patients. The emergence of obsessive-compulsive symptoms during clozapine treatment has been reported by others. These obsessive-compulsive symptoms which could be in some way related to the serotonin antagonism, have been reported to respond to selective serotonin reuptake inhibitors (SSRIs). However, our experience indicated that caution should be exercised with this combination. In 2 of our patients with schizophrenia who had a SSRIs added to clozapine, there was a worsening of their psychoses. In these two patients, there was an increase in the plasma clozapine concentrations which corresponded to a worsening of their psychoses. The withdrawal of SSRIs which lowered the plasma clozapine concentrations resulted in an improvement of their psychoses. This observation led us to suggest that there exists a therapeutic window for clozapine which could have been exceeded in these 2 patients.

**TABLE I: LOCAL STUDIES OF CLOZAPINE AND RISPERIDONE**

<table>
<thead>
<tr>
<th>Study</th>
<th>Type of study and sample size</th>
<th>Finding</th>
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<tbody>
<tr>
<td><strong>Clozapine</strong></td>
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<tr>
<td>Wong et al</td>
<td>Prospective uncontrolled open-label n = 19 Women = 13 Men = 6</td>
<td>79% with ≥20% decrease in BPRS, or CGI ≤3 Common side-effects hypersalivation, sedation</td>
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<tr>
<td>Chong et al</td>
<td>Pharmacokinetic study n = 14 Chinese Women = 10 Men = 4</td>
<td>Clozapine mean daily dose (373 mg/day) was lower than American studies but mean plasma clozapine concentration (1078 ng/ml) was higher</td>
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<td><strong>Risperidone</strong></td>
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<tr>
<td>Chong et al</td>
<td>Prospective uncontrolled open-label n = 20 Women = 11 Men = 9</td>
<td>85% with ≥20% decrease in PANSS, with significant reduction in ESRS scores</td>
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<tr>
<td>Lee at al</td>
<td>Pharmacokinetic study n = 20 Women = 11 Men = 9</td>
<td>High interindividual variability of serum risperidone and its metabolite 9-hydroxyrisperidone</td>
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<tr>
<td><strong>Clozapine-Risperidone Combination</strong></td>
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<tr>
<td>Chong et al</td>
<td>Case report n = 1 woman</td>
<td>Exacerbation of hoarding behaviour</td>
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<tr>
<td>Chong et al</td>
<td>Case report n = 1 woman</td>
<td>Development of atrial ectopics</td>
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BPRS: Brief Psychiatric Rating Scale; CGI: Clinical Global Impression; PANSS: Positive and Negative Syndrome Scale; ESRS: Extrapyramidal Rating Scale
Attempts were made to develop a drug with both D2 and 5-HT antagonist properties. One such designer agent is risperidone. 30 Following this, attempts were made to develop a drug with both D2 and 5-HT antagonist properties. One such designer agent is risperidone.

In two large, multicentre, double-blind, controlled, comparative studies, risperidone (4 to 8 mg/day) was at least as effective as haloperidol (10 or 20 mg/day) against schizophrenia, and risperidone at 6 mg/day proved to be significantly better than haloperidol at 20 mg/day against the negative symptoms of schizophrenia. It has been reported that it produces less extrapyramidal side-effects than haloperidol but more than placebo, 23 which still makes risperidone useful for neuroleptic-intolerant patients. As the incidence of extrapyramidal side-effects is dose-related, higher doses would be associated with increased severity of extrapyramidal side-effects, and possibly diminished efficacy.

Risperidone

Background

The pharmacology of clozapine is quite complex, because it is an antagonist at many types of receptor (dopaminergic, serotonergic, histaminergic, anticholinergic, and adrenergic). The leading hypothesis is that some unique combination of dopamine D2 and serotonin (5-HT) in particular the 5-HT2 subtype antagonism accounts for its novel clinical actions. 30 Following this, attempts were made to develop a drug with both D2 and 5-HT antagonist properties. One such designer agent is risperidone.

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Local Experience

A pilot study was done in Woodbridge Hospital on 20 patients with schizophrenia to evaluate the short-term efficacy and side-effect profile of risperidone. 34 In this open and uncontrolled study lasting 8 weeks, we found that 85% of patients responded which was defined as a 20% or more decrease in the Positive and Negative Syndrome Scale (PANSS). This response rate was higher than the response rate of 57% (at a fixed dose of 4 mg/day) of an American study 35 and the 72.7% (at a dose of 6 mg/day) of a Canadian study. 23 In these studies there was an agreement that the 4 to 8 mg/day range is optimal. The mean dosage of our responders (5.6 mg/day) falls within this range although it has been suggested that Asians require a comparatively lower dose of risperidone. 36 The demographic of our patients, with a mean duration of illness of 14 years and an average of 7 prior hospitalisations, indicated that many poor or partial responders to typical neuroleptics were included in the study. These more severely ill patients might have required a higher dose of risperidone. It is also possible that the 8 weeks was too short a time to finally titrate to the optimum dose. There was an overall reduction in extrapyramidal side-effects in our patients as indicated by a statistically significant reduction of the Extrapyramidal Symptom Rating Scale and a lower mean dose of benzhexol at the end point of the study compared to baseline. The adverse effects reported from other trials were agitation, anxiety, insomnia, headache, nausea, dizziness, weight gain, rhinitis, hypotension and sexual dysfunction. 36 We found that the most commonly reported side-effects by our patients were dizziness and sedation. As in other studies, we found no cases of blood dyscrasia. Like clozapine, risperidone has been reported to induce obsessive-compulsive symptoms. 37,38 One of our patients risperidone-induced obsessive rumination was successfully treated with clomipramine 25 mg/day.

Measurement of the serum concentrations of risperidone in these 20 patients were found to be highly variable. 39 This variability is likely to be due to the genetic polymorphism of the CYP2D6 which is the main enzyme involved in the metabolism of risperidone.
However, this is unlikely to have any effect on the overall antipsychotic effect of risperidone as the main metabolite (9-hydroxyrisperidone) is equipotent to the parent drug. We also found no linear relationship between the concentrations of either risperidone or its active moiety and reduction in PANSS scores. Higher serum concentrations did not seem to bring about greater reduction in PANSS scores which is in agreement that higher doses of risperidone did not produce further clinical improvement.

Augmentation of clozapine and risperidone has been reported to improve the efficacy of clozapine without any adverse effects. However, such a combination in one of our patients resulted in an exacerbation of her hoarding behaviour while in another there was an occurrence of atrial ectopics.

**Conclusion**

The higher response rates that we found in our two studies on clozapine and risperidone when compared to other overseas studies may in part be due to the small sample size and the inherent limitations of open design studies. Nonetheless, neuroleptics like clozapine and risperidone offer definite advantages over conventional neuroleptics. The combined use of these two atypical neuroleptics may be potentially problematic. Over the next decade, a number of new antipsychotic drugs are likely to be introduced into clinical practice. One of which is olanzapine which has just become available for clinical use and would need further evaluation in the local context. It is also expected that widespread use of newer types of antipsychotic drugs will lead to further developments in our knowledge and understanding of schizophrenia.

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**REFERENCES**


