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.

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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 patients[5] 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 1988[7] 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

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has also been reported to have better efficacy in treating the negative symptoms.[9] The optimal dose is still not established with doses ranging from 25 mg / day to 1600 mg / day.[10] 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.[11] 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.[11] 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,[12] 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%).[8,9] 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.[10] The most common side-effects we found was hypersalivation followed by sedation. The mechanism by which clozapine causes hypersalivation remains unknown but we found benzhexol to be effective in alleviating this side-effect. The use of other muscarinic receptor antagonists have also been shown to be effective.[13] One of our patients developed fits while on clozapine therapy and was treated by adding on phenobarbitone. 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.[14] 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).[15,16] However, our experience indicated that caution should be exercised with this combination. In 2 of our patients with schizophrenia who had a SSRI added to clozapine, there was a worsening of their psychoses.[17] 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. Some American

TABLE I: LOCAL STUDIES OF CLOZAPINE AND RISPERIDONE

Study	Type of study and sample size	Finding
Clozapine		
Wong et al[12]	Prospective uncontrolled open-label n = 19 Women = 13 Men = 6	79% with ≥20% decrease in BPRS, or CGI ≤3 Common side-effects hypersalivation, sedation
Chong et al[21]	Pharmacokinetic study n = 14 Chinese Women = 10 Men = 4	Clozapine mean daily dose (373 mg/day) was lower than American studies but mean plasma clozapine concentration (1078 ng/ml) was higher
Risperidone		
Chong et al[34]	Prospective uncontrolled open-label n = 20 Women = 11 Men = 9	85% with ≥20% decrease in PANSS, with significant reduction in ESRS scores
Lee at al[39]	Pharmacokinetic study n = 20 Women = 11 Men = 9	High interindividual variability of serum risperidone and its metabolite 9-hydroxyrisperidone
Clozapine-Risperidone Combination		
Chong et al[41]	Case report n = 1 woman	Exacerbation of hoarding behaviour
Chong et al[42]	Case report n = 1 woman	Development of atrial ectopics

BPRS: Brief Psychiatric Rating Scale; CGI: Clinical Global Impression; PANSS: Positive and Negative Syndrome Scale; ESRS: Extrapyramidal Rating Scale

studies found a possible association between plasma concentrations of clozapine and clinical response[18-20] i.e. patients with plasma clozapine concentrations above 370 ng / mL or 350 ng / mL were more likely to show a positive response. In a pharmacokinetic study on 14 local Chinese schizophrenic patients in Woodbridge Hospital,[21] we found that while the mean daily dose of our patients was lower than that reported in American studies, the plasma clozapine concentration attained was much higher. A possible reason for this higher levels could be that our patients were hospitalised and had no access to alcohol or tobacco. Alcohol consumption and cigarette smoking have been demonstrated to increase the activity of cytochrome P4501A2 (CYP1A2)[22] which is the major enzyme involved in the metabolism of clozapine.[23] Another possible reason could be due to pharmacokinetic and pharmacodynamic ethnic differences of our patient sample as differences in CYP1A2 activities between Orientals and Caucasians have been reported in another study.[24]

In a follow-up study of the responders from our initial study, we compared the number of days of hospitalisation over the next 2 years with the number of hospital days in the preceding 2-year period, when they were receiving conventional neuroleptics. The mean number of hospital days was reduced from 298 days to 224 days—a 25% reduction after the initiation of clozapine. This reduction of inpatient admissions and length of hospitalisation has been noted in other studies.[25-27]

Agranulocytosis has not been reported in any of our patients to date. The mandatory blood monitoring has been an obstacle in persuading some of our patients to a trial of clozapine.[28] Similar difficulty was encountered by Potter et al[29] who reported that the doctors in China had to make "considerable effort to overcome many patients' concerns and superstitions about blood drawn". This fear of loss of blood may be due to the culture bound notion of blood being a precious commodity as summed up by the Chinese saying that "a hundred grains of rice make a drop of blood".

Risperidone

Background

The pharmacology of clozapine is quite complex, because it is an antagonist at many types of receptor (dopaminergic, serotonergic, histaminergic, anticholinergic, and adrenergeric). The leading hypothesis is that some unique combination of dopamine D_2 and serotonin (5-HT) in particular the 5-HT_2 subtype antagonism accounts for its novel clinical actions.[30] Following this, attempts were made to develop a drug with both D_2 and 5-HT antagonist properties. One such designer agent is risperidone.

In two large, multicentre, double-blind, controlled, comparative studies,[31,32] 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,[33] 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.

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[31] and the 72.7% (at a dose of 6 mg / day) of a Canadian study.[32] 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.[35] 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.[40] However, such a combination in one of our patients resulted in an exacerbation of her hoarding behaviour[41] while in another there was an occurrence of atrial ectopics.[42]

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.

REFERENCES

1. Liddle P F, Barnes T R E. Syndromes of chronic schizophrenia. Br J Psychiatry 1980; 157:558-61.
2. Thompson P A, Meltzer H Y. Positive, negative and disorganisation factors from the Schedule of Affective Disorders and Schizophrenia and the Present State Examination. A three-factor solution. Br J Psychiatry 1993; 163:111-9.
3. Mitchell P. Chlorpromazine turns forty. Aust N Z J Psychiatry 1993; 27:370-3.
4. Lieberman J A. Understanding the mechanism of action of atypical antipsychotic drugs. Br J Psychiatry 1993; 163(22 suppl):7-18.
5. Kane J M. Treatment of schizophrenia. Schizophr Bull 1987; 13:133-56.
6. Meltzer H Y, Sommers A A, Luchins D J. The effect of neuroleptics and other psychotropic drugs on negative symptoms in schizophrenia. J Clin Psychopharmacol 1986; 6:329-38.
7. Kane J, Honigfeld G, Singer J, Meltzer H, and the Clozarid Collaborative Study Group. Clozapine for the treatment-resistant schizophrenic. Arch Gen Psychiatry 1988; 45:789-96.
8. Meltzer H Y, Bastini B, Kwon KY, Ramirez LF, Burnett S, Sharpe J. A prospective study of clozapine in treatment-resistant schizophrenic patients. Psychopharmacology 1989; 99:S68-S72.
9. Meltzer H Y. The effect of clozapine and other atypical antipsychotic drugs on negative symptoms. In: Marneros A, Andreasen N C, Tsuang M T, editors. Negative Versus Positive Schizophrenia. Berlin, Germany: Springer-Verlag, 1991:365-76.
10. Fleischhacker W W, Hummer M, Kurz M, Kurzthaler I, Lieberman J, Pollack S, et al. Clozapine dose in the United States and Europe: Implications for therapeutic and adverse effects. J Clin Psychiatry 1994; 55(suppl B):78-81.
11. Alvir J, Lieberman J A. Agranulocytosis: incidence and risk factors. J Clin Psychiatry 1994; 55(suppl B):137-8.
12. Wong K E, Chong S A, Ngui F, Winslow M, Devan G S, Leong O K, et al. Initial experiences with clozapine in Woodbridge Hospital. Singapore Med J 1997; 38:336-8.
13. Fritze J, Ellinger T. Pirenzepine for clozapine-induced hypersalivation. Lancet 1995; 346:1034.
14. Baker R W, Chengappa R, Baird J W, Steingard S, Christ A G, Schooler N R. Emergence of obsessive compulsive symptoms during treatment with clozapine. J Clin Psychiatry 1992; 53:439-42.
15. Allen L, Tejera C. Treatment of clozapine-induced obsessive-compulsive symptoms with sertraline. Am J Psychiatry 1994; 151:1069-7.
16. Cassady S L, Thaker G K. Addition of fluoxetine to clozapine. Am J Psychiatry 1992; 149:1274.
17. Chong S A, Tan C H, Lee H S. Worsening of psychosis with clozapine and SSRI combination: two case reports. J Clin Psychopharmacol 1997; 17:67-8.
18. Perry P J, Miller D D, Arndt S V, Cadoret R J. Clozapine and norclozapine plasma concentrations and clinical response of treatment-refractory schizophrenic patients. Am J Psychiatry 1991; 148:231-5.
19. Hagegawa M, Gutierrez-Esteinou R, Way I, Meltzer H. Relationship between clinical efficacy and clozapine concentrations in plasma in schizophrenia: effect of smoking. J Clin Psychopharmacol 1993; 13:383-90.
20. Miller D D, Fleming F, Holman T L, Perry P J. Plasma clozapine concentrations as a predictor of clinical response: A follow-up study. J Clin Psychiatry 1994; 55(suppl B):111-21.
21. Chong S A, Tan C H, Khoo Y M, Lee H S, Wong K E, Ngui F, et al. Clinical evaluation and plasma clozapine concentrations in Chinese patients with schizophrenia. Ther Drug Monit 1997; 19:219-23.
22. Kalow W, Tang B K. Use of caffeine metabolite ratios to explore CYP1A2 and xanthine oxidase activities. Clin Pharmacol Ther 1991; 50:508-19.
23. Bertilsson L, Carrillo J A, Dahl M L, Lierena A, Alm C, Bondessin U, et al. Clozapine disposition covaries with CY1A2 activity determined by a caffeine test. Br J Clin Pharmacol 1983; 38:471-3.
24. Grant D M, Tang B K, Kalow W. Variability in caffeine metabolism. Clin Pharmacol Ther 1983; 33:591-602.
25. Meltzer H Y, Cola P, Way L, Thompson P A, Bastani B, Davis MA, et al. Cost effectiveness of clozapine in neuroleptic-resistant schizophrenia. Am J Psychiatry 1993; 150:1630-8.
26. Revicki D A, Luce B R, Weschler J M, Brown R E, Adler M A. Cost-effectiveness of clozapine for treatment-resistant schizophrenia patients. Hosp Commun Psychiatry 1990; 41:850-4.
27. Reid W H, Mason M, Toprac M. Savings in hospital bed-days related to treatment with clozapine. Hosp Commun Psychiatry 1994; 45:261-4.
28. Chong S A, Chua L. Clozapine, Chinese and blood. Br J Psychiatry 1997; 171:89-90.
29. Potter W Z, Ko G N, Zhang L D, Yan W. Clozapine in China: a review and preview of US / PRC collaboration. Psychopharmacology 1989; 99:S87-S91.
30. Meltzer H Y, Matsubara S, Lee J C. Classification of typical and atypical antipsychotic drugs on the basis of D-1, D-2 and serotonin2 pk1 values. J Pharmacol Exp Ther 1989; 259:238-46.
31. Marder S R, Meibach R C. Risperidone in the treatment of schizophrenia. Am J Psychiatry 1994; 151:825-35.
32. Chouinard G, Jones B, Remington G, Bloom D, Addington D, MacEwan G N, et al. A Canadian multicenter placebo-controlled study of fixed doses of risperidone and haloperidol in the treatment of chronic schizophrenic patients. J Clin Psychopharmacol 1993; 13:25-52.

33. Peuskens on behalf of the Risperidone Study Group. Risperidone in the treatment of patients with chronic schizophrenia: a multi-centre, double-blind, parallel-group study versus haloperidol. Br J Psychiatry 1995; 166:712-26.

34. Chong S A, Yap H L, Low B L, Choo C H, Chan A O M, Wong K E, et al. Clinical evaluation of risperidone in Asian patients with schizophrenia in Singapore. Singapore Med J (In press).

35. Jones B D. Clinical experience with risperidone. J Clin Psychiatry Monograph 1995; 13:21-5.

36. Borison R L, Diamond B I, Pathiraja A P, Meibach R C. Clinical overview of risperidone. In: Meltzer H Y, editor. Novel Antipsychotic Drugs. New York: Raven Press, 1992:233-9.

37. Kopala L, Honer W G. Risperidone, serotonergic mechanism, and obsessive-compulsive in schizophrenia. Am J Psychiatry 1994; 151:1714-5.

38. Remington G, Adamis M. Risperidone and obsessive-compulsive symptoms during treatment with clozapine. J Clin Psychopharmacol 1994; 14:358-9.

39. Lee H S, Tan C H, Khoo Y M, Chee K T, Wong K E, Chong S A, et al. Serum risperidone and 9-hydroxyrisperidone in Asian schizophrenics. Ther Drug Monit 1997; 19:579.

40. McCathy R H, Terkelsen K G. Risperidone augmentation of clozapine. Pharmacopsychiatry 1995; 28:61-3.

41. Chong S A, Tan C H, Lee H S. Hoarding and clozapine-risperidone combination. Can J Psychiatry 1996; 5:315-6.

42. Chong S A, Tan C H, Lee H S. Atrial ectopics with clozapine-risperidone combination. J Clin Psychopharmacol 1997; 17:130-1.