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Clinical Efficacy of Clozapine in Treatment-Refractory Schizophrenia: An Overview

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The treatment of patients with schizophrenia who fail to respond to antipsychotic medications remains a challenge. Despite numerous attempts to establish effective somatic treatment approaches for this population, clozapine appears to be the only well established alternative. Depending upon trial duration and response criteria, between 30% and 60% of previously unresponsive patients appear to derive clinically significant benefit from clozapine. Clozapine also has important advantages in terms of its reduced propensity to produce extrapyramidal side-effects. Agranulocytosis remains an important risk, so strategies to improve the benefit-to-risk ratio should be explored. Issues such as trial duration, dosage, blood levels and predictors of response require additional study.

Despite the great efficacy of antipsychotic medications in the treatment of schizophrenia, a substantial proportion of patients continue to experience clinically significant psychopathology despite adequate courses of antipsychotic drugs. Estimates of the proportion of patients who are treatment-refractory vary considerably and are influenced by several factors including: phase of illness (first versus subsequent episodes); definition of refractoriness, and duration of treatment trial. Among patients experiencing their very first episode of schizophrenia, 14% did not respond adequately to antipsychotic drugs (Lieberman *et al*, 1991). Of those who had experienced many previous episodes, at least 25% failed to respond.

Criteria for treatment refractoriness

The definition of refractoriness varies and influences prevalence estimates. Some patients derive measurable benefit from antipsychotic medication, but continue to be severely psychotic and functionally impaired. Therefore, refractoriness should not necessarily imply total lack of response. However, there is a spectrum of response which includes those patients who derive clinically significant benefit, but continue to experience psychotic symptoms which interfere with functioning or are subjectively distressing. Although these patients are not typically labelled as refractory (the terms suboptimal responder or partial responder would be more applicable), they pose a challenge to clinicians who try to produce further systematic improvement. Obviously, as criteria for identifying refractory or non-responsive patients become less conservative, the proportion of patients meeting these criteria increases.

In addition, the time course of response is critical in establishing treatment responsiveness. In general, we view six weeks as an adequate trial of antipsychotic medication, but if ultimate maximum level of therapeutic response is the issue, six weeks may be inadequate. For example, in a cohort of first episode patients, Lieberman *et al* (1991) observed that the median time to achieve complete remission of psychotic symptoms is 11 weeks and the mean is 35 weeks. These patients demonstrated significant benefit during the first six weeks of treatment, but such data illustrate the difference between using initial rather than ultimate response to characterise residual levels of symptoms.

Alternative somatic treatments

Despite the frequency of persistent symptoms among schizophrenic patients, few alternative somatic treatments have emerged as consistently helpful. The most frequently employed strategies in refractory patients include: dosage increase; switching to an alternative antipsychotic drug; or the use of various adjunctive treatments such as lithium, benzodiazepines, propranolol, carbamazepine or electroconvulsive therapy. Christisen *et al* (1991) reviewed the literature on many of these treatments and were struck by the paucity of available data given the magnitude of the problem. Even as obvious a question as the value of switching antipsychotic medication has not been adequately addressed. Although clinical anecdotes abound, controlled trials are necessary to address issues such as relative change in dose or passage of additional time when assessing the efficacy of an alternative antipsychotic drug. Preliminary data from a study by our department (Kane *et al*, unpublished) suggest that for those patients failing to respond to an initial four-week course of a standard antipsychotic (fluphenazine, 20 mg/day), an additional four weeks

of therapy with the same treatment, a higher dose, or a different medication (haloperidol), does not produce substantial further improvement. Clearly, more research is needed to establish appropriate clinical criteria and methods for the study of alternative treatments for non-responsive patients.

Clozapine

Efficacy

Clozapine has emerged as the best-established alternative treatment for refractory patients. Several review articles have summarised aspects of clozapine's efficacy and adverse effects (Ereshefsky *et al*, 1989; Fitton & Heel, 1990; Baldessarini & Frankenburg, 1991; Safferman *et al*, 1991). (See other papers in this issue for further discussion of agranulocytosis and neurological side-effects.) Although clozapine has proven to be at least equal in efficacy and frequently superior to standard antipsychotic drugs, very few investigations have involved double-blind trials focusing specifically on carefully described, treatment-refractory patients.

We reported a multicentre trial to assess clozapine's efficacy in the treatment of patients refractory to antipsychotic medication (Kane *et al*, 1988). Schizophrenic patients who had failed to respond to at least three different antipsychotics underwent a prospective, single-blind trial of haloperidol (mean daily dosage 61 (s.d. 14) mg) for six weeks. Those patients whose condition remained unimproved were then randomly assigned, under double-blind conditions, to clozapine (up to 900 mg/day) or chlorpromazine (up to 1800 mg/day) for six weeks. A total of 268 patients were entered into the double-blind trial; 88% of the clozapine-treated patients and 87% of the chlorpromazine-treated patients completed the six weeks. When *a priori* criteria were applied, 30% of the clozapine-treated patients and only 4% of the chlorpromazine-treated patients were classed as responders. Clozapine produced significantly greater improvement on the Brief Psychiatric Rating Scale (BPRS; Overall & Gorham, 1962), Clinical Global Impressions (CGI; Guy, 1976) scale and Nurses' Observation Scale for In-patient Evaluation (NOSIE-30; Honigfeld *et al*, 1966).

Although this is the only such study to date, there are several attempts in progress to confirm these results in patients who are less severely ill. Several open prospective and retrospective studies of clinical response to clozapine have been reported which generally support the conclusions from the controlled trial, that clozapine produces clinically meaningful improvement in 30–50% of patients judged to have been unresponsive to other treatment (Povlsen *et al*, 1985; Kuha & Miettinen 1986; Small *et al*, 1987*a*; Lindström, 1988; Mattes, 1989; Leppig *et al*, 1989; Naber *et al*, 1989; Meltzer *et al*, 1989; Owen *et al*, 1989). In addition, several of these studies have involved long-term follow-up (Povlsen *et al*, 1985; Kuha & Miettinen, 1986; Lindström, 1988; Leppig *et al*, 1989; Mattes, 1989; Meltzer *et al*, 1989) which demonstrated continued benefit from clozapine in terms of sustaining initial improvement and preventing relapse. In fact, some reports have suggested significant reductions in the number of readmissions to hospital and days of in-patient treatment after the initiation of clozapine compared with an equal period before clozapine treatment (Zapletálek *et al*, 1989; Naber & Hippius, 1990), or in contrast to a comparison group receiving conventional antipsychotic medication (Revicki *et al*, 1990).

Adequate trial duration

The appropriate duration for a trial of clozapine remains an important clinical question. In the Kane *et al* (1988) multicentre study, improvement appeared to continue throughout the six weeks on clozapine, but to level off (based on group means) after four weeks in the comparison group. As discussed previously, even with conventional antipsychotic drugs, six weeks is inadequate to achieve the full potential therapeutic benefit. Meltzer *et al* (1990) emphasised that a substantial proportion of patients do not achieve their full therapeutic response to clozapine after six weeks. Using a response criterion of 20% improvement from baseline on the BPRS total score, they found that among 38 patients followed for six months, only 14 (37%) met this criterion at six weeks, but 23 (61%) met this criterion by six months. Grace *et al* (unpublished), in a six-month open study of 31 clozapine-treated patients, reported that over 60% of the sample derived significant benefit, but that virtually all of the improvement occurred in the first 12 weeks. Although some patients may continue to improve for many months, the critical questions are when such improvement actually begins and what criteria should be used for deciding when to discontinue a treatment trial. Given the risk of agranulocytosis and the costs associated with clozapine use, this issue is very important. Percentage improvement measures are highly influenced by the baseline level of severity. Should we consider a patient whose total BPRS score declines from 70 to 55 to have responded equally to a patient who improves from 40 to 32? It may be most useful to focus on psychotic symptoms specifically, or negative symptoms specifically, to establish threshold response criteria.

We should not minimise the potential clinical importance of even slight improvement if it results in a meaningful change in subjective well-being, the level of care required, psychosocial functioning, or ability to participate in therapeutic efforts. It is impossible to make judgements regarding these potential gains based on scores on a rating scale for psychopathology. Certainly, the open studies reported by Meltzer *et al* (1990) and Lindström (1988) are particularly encouraging in their assessments of quality of life and/or vocational status.

Dosage

The most appropriate dose of clozapine (in terms of maximum benefit-to-risk ratio) is also unclear. Some investigators have had good results with relatively low doses of clozapine (Naber *et al*, 1989), whereas others used higher doses (Kane *et al*, 1988). Since some important adverse effects are dose-related (e.g. seizures) this is an important concern. It is hoped that further trials will be conducted using randomly assigned fixed-doses to help address this issue.

Blood levels

Given the large individual variability in plasma levels among patients receiving the same oral dose of clozapine (Cheng *et al*, 1988) an understanding of any relationship between plasma level and clinical response may be helpful in establishing minimum effective dosage requirements for clozapine. Relatively few data are available at present.

Thorup & Fog (1977) studied 11 patients treated with clozapine and found no correlation between clinical response and drug plasma levels. Ackenheil *et al* (1976) and Brau *et al* (1978) also failed to find such a relationship. It appears that these latter reports did not involve a fixed-dose design. Perry *et al* (1991) evaluated 29 treatment-resistant in-patients meeting DSM–III–R criteria for schizophrenia (American Psychiatric Association, 1987). Of the patients with clozapine plasma levels greater than 350 ng/ml after four weeks of fixed-dose treatment, 73% were classified as responders in comparison with only 17% of those whose plasma level was below 350 ng/ml. Regression analysis suggested a linear relationship between clozapine plasma concentration and therapeutic response as measured by the BPRS. As these authors suggest, the next step to validate these findings would be to demonstrate the conversion of some non-responders to responders when blood levels are manipulated to the putative therapeutic range.

Haring *et al* (1990) reported on the influence of some patient variables on clozapine blood levels in 148 psychiatric in-patients. Dosages were kept constant for at least eight days and ranged from 12.5 to 700 mg/day. Dose, gender, smoking, weight, and age had significant influences on clozapine plasma levels, but together, only accounted for 37% of the variance. No attempt was made to correlate clozapine response with blood levels.

Although there are no data as yet to evaluate any upper limit to therapeutic plasma levels of clozapine, the apparent relationship between dose and seizure incidence (Lieberman *et al*, 1989) would suggest that serious adverse effects may limit the use of high blood levels. Simpson & Cooper (1978) reported plasma levels of 1313 and 2194 ng/ml in two patients who experienced *grand mal* seizures on clozapine.

Predictors of response

Honigfeld & Patin (1989) reported on 46 non-biological or pharmacodynamic predictor variables using data from Kane *et al* (1988). In general, no combination of variables accounted for more than 25% of the outcome variance under optimal conditions. It did appear, however, that clozapine's efficacy in treatment-resistant patients was greatest in the paranoid subtype. The only other variables which achieved any degree of statistical significance as predictors of more favourable response were lower ratings on grandiosity and higher numbers of previous hospital admissions. Fenton & Lee (unpublished) reported that in a cohort of 27 refractory patients, global ratings of improvement with clozapine treatment were positively correlated with independent living before hospital admission and negatively correlated with blunted/inappropriate affect ratings before clozapine treatment.

Small *et al* (1987*b*) found that clozapine responders have higher EEG alpha amplitude in frontal and temporal areas than non-responders. Friedman *et al* (1991) found that higher degrees of pre-frontal sulcal prominence ratings on computerised tomography scans were associated with poorer response to clozapine, but measures of ventricle : brain ratio were not.

Considerable efforts are underway to identify risk factors for the development of agranulocytosis. Current estimates of risk based on US data (Alvir *et al*, unpublished) suggest a cumulative incidence of 0.8% after one year of clozapine treatment. Although the mechanism of clozapine-induced agranulocytosis has yet to be elucidated fully, there is some evidence that genetic predisposition may be an important factor (Lieberman *et al*, 1990).

Diagnosis

Although the focus of clozapine research has generally been on schizophrenia, some investigators have contrasted response rates in treatment-refractory schizoaffective patients to those of patients with schizophrenia. Naber & Hippius (1990) reported the highest rate of improvement in the schizoaffective category with 54% experiencing marked improvement, and 11% experiencing nearly complete improvement, in contrast to 40% and 2.5% respectively for the other subtypes combined. Owen *et al* (1989) contrasted response to clozapine among 25 patients with schizophrenia with that of 12 patients diagnosed as schizoaffectives, and found significantly greater improvement on total BPRS score among the latter.

Cost, benefit and risk

Assessment of cost–benefit–risk issues in health care is always complex, and clozapine has highlighted this issue in the treatment of schizophrenia more than any new development in recent memory. The risk of agranulocytosis can be minimised if weekly WBC monitoring is assured. Given the nature of the patient population at risk and the health-care systems serving them, some have argued that failsafe systems must be in place to assure adequate monitoring. Others have argued that this should be treated as a routine aspect of health care. Concerns regarding physician, institutional and corporate liability also influence this argument to varying degrees in different settings and different countries. Cost issues are also complicated by the fact that the potential for long-term savings from a drug like clozapine, which may be substantial, are not easy to quantify. We must also ask ourselves whether cost would be as much of an issue if a cardiovascular disease rather than a mental illness were involved. An important result of clozapine is that current activity in antipsychotic drug development is very high, and considerable new research has been stimulated by clozapine's novel clinical effects.

Conclusions

Since the publication of the major multicentre study by Kane *et al* (1988) the international use of clozapine has increased considerably. Approximately 12 000 patients have now received treatment trials with clozapine in the USA and almost 1000 in the UK (Lader, unpublished). The clinical experience to date supports the important role that clozapine can play in producing clinically significant improvement among previously refractory or minimally responsive patients. A variety of important issues such as dosage, trial duration, the role of blood levels, predictors of response, and adverse reactions require additional study. Ultimately, such research should further improve the benefit-to-risk ratio of clozapine treatment and provide new directions for research to improve our understanding of treatment-resistant schizophrenia.

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