Psychiatric Bulletin (1991), **15**, 336–338

Working with clozapine

CLIVE ADAMS, Honorary Research Registrar and M. ADIB ESSALI, Honorary Research Registrar, Department of Psychiatry, Charing Cross Hospital, Fulham Palace Road, London W6 8RF

Clozapine is an atypical antipsychotic drug with relatively weak D2 and D1 blocking properties and strong 5HT and cholinergic blockade. Its potency as an antipsychotic drug is surprising considering the ratio of receptor blockade and it represents a true advance in treatment of schizophrenia. The efficacy of clozapine calls for revision of the seemingly over simplistic dopamine theory of schizophrenia. Now clozapine is available in the UK to consultant psychiatrists who register with the Clozaril Patient Monitoring Service (CPMS).

We have cared for 32 treatment-resistant schizophrenic patients who were entered in an open trial of clozapine and recorded their psychiatric and physical progress over six months. Detailed results will be published once all these data are collected from the other centres and analysed. Here we only wish to present some personal views on using this drug in Britain based on our own experience and not to pre-empt the overall results of the trial.

Clozapine has a chequered history; it has been known since 1966, but not marketed because its lack of extrapyramidal side-effects was felt to indicate lack of antipsychotic potency. Once available, clozapine was withdrawn from clinical trials in the UK because of 16 cases of agranulocytosis in South Finland in 1975. More recently it has been remarketed because of a combination of research supporting its usefulness in people with intractable schizophrenic illness and the fact that with compliance to a tight blood monitoring service deaths from the agranulocytosis do not happen.

A recent review of studies of the course of schizophrenia (Westermyer & Harrow, 1990) estimates that 15–20% have a severe illness that is unremitting. Every general psychiatrist looks after people whose symptoms are intractable and who have proved resistant to multiple treatments. The claims made for clozapine are for significant improvement in both positive and negative symptoms in 30% of treatment-resistant people at six weeks (Kane *et al*, 1988) and up to 60% at six months follow-up (Meltzer, 1989). That clozapine should prove attractive to psychiatrists is not at all surprising.

The resistant groups

Those termed treatment-resistant are so varied and difficult a group that every aspect of a clinician's skill is tested in the attempt to use this drug for which compliance is vital.

In our study, the patients referred were often to be found in the corridors of the old mental hospital or on rehabilitation wards. The illness had made them withdrawn and suspicious but in addition they had often had long experience of doctors approaching them with new potions. Lack of insight in some made the necessity of such pills an anathema; the presence of insight resulted in mistrust of change and fear caused by the knowledge of how dreadful relapse can be. Many knew well the fine balance they held between relative sanity and outright terrible madness. The side-effects of antipsychotic drugs were well known to them and understandable further resistance occurred when the nature of granulocytopenia and the necessity for blood monitoring were explained.

Resistance was met from the staff caring for these people. Only once was this a result of a negative closed attitude, an embittered power struggle between staff, demoralised and institutionalised, and anything new. Much more commonly the resistance was from a positive and sensible protectiveness of this vulnerable population. It was remarkable how often staff working with minimal resources in demeaning conditions were helpful, supportive, and open to new approaches. The caution was founded in good sense and knowledge of the patient's illness, his/her potential for relapse and the dangers and difficulties this might cause. Staff often asked intelligent, probing questions and were hungry for knowledge of new treatment approaches.

By the end of the selection procedure many people originally referred had, for some reason or other, proved unsuitable. For every one person given clozapine four had been referred and assessed. The highly selected cohort was still very heterogeneous. They ranged from schizophrenic patients profoundly disturbed in affect, thought, perceptions, and totally unable to live independently to those whose encapsulated delusional system allowed reasonably

independent life styles. Further selection occurred when patients discontinued taking the drug because they found the side-effects intolerable or when compliance faltered for no good reason. Some were stopped because of significant drops in white cell counts and yet others discontinued when they attributed to the drug bizarre properties – once man knew how clozapine was a tool used by the secret service to spy on him.

The drug

To the clinician, clozapine presents a unique blend of benefits and difficulties. From our clinical experience with the use of clozapine we have little doubt that a proportion of truly treatment-resistant schizophrenic people do have relative improvements, some of which are clinically significant, when taking clozapine.

The improvements range from the calming of bizarre behaviour without sedating or shifting other psychotic phenomena to the complete disappearance of chronic psychotic symptoms, leaving the person better than anyone could have hoped. Even if the psychotic phenomena remain unchanged despite clozapine, the new drug seemed well able to prevent deterioration despite the discontinuation of substantial doses of the usual antipsychotic treatments. Often patients would comment on how they felt more relaxed on clozapine and no longer suffered from the symptoms of parkinsonism.

Problems with some side effects were common. These included hypotension, drowsiness, constipation, weight gain, transient nausea, and troublesome hypersalivation. Less commonly, hyperpyrexia, hypertension and epileptic fits occurred, and still more rarely, granulocytopenia and agranulocytosis. Some worsening of symptoms and behaviour and difficulty in stabilisation of the mental state after clozapine was stopped occurred rarely. This may represent rebound phenomena.

Case 1. A 41-year-old single woman with a Dé Clerambault-type illness that resulted in her experiencing persistent auditory and somatic hallucinations, passivity phenomena, and delusions about an eminent medical person was referred. She had 12 years of treatment with several antipsychotic regimes. In the first three days of clozapine (50 mg) the somatic hallucinations disappeared followed by the auditory experiences a few days later (150 mg/day). The delusions remained. She was grief-stricken for her lost loved one and has since titrated the dose (100 mg/day) so she experiences some of his welcome interference. She is holding down a voluntary job for the first time in years.

To the clinician, side effects of drugs always cause difficulties and some of clozapine's are particularly troublesome. It is a sedating drug and does have the anticholinergic effects we are used to seeing. Hypersalivation is common with pillows soaked in the morning and the patient drooling unpleasantly in public. Dose reduction helps and sometimes the addition of procyclidine can decrease the flow.

Case 2. A 29-year-old man of low IQ with a very disabling hebephrenic-type illness from his teenage years settled somewhat on 600 mg of clozapine per day. From the start of treatment puddles of saliva were to be seen around where he sat, the bed was soaked in the morning, and his speech was even more difficult to understand than usual. Procyclidine, low-dose imipramine, and clonidine helped little but the flow and the distress it caused seemed to reduce with time.

In some patients the appetite is stimulated, presumably from a central 5HT effect, and weight gain can threaten to offset any benefit from alleviation of psychotic symptoms.

Case 3. A 22-year-old woman was experiencing very clear offensive auditory hallucinations continually for years despite much antipsychotic medication. At week 8 of treatment with 600 mg of clozapine, alone, they receded and all but disappeared. On the new drug, overeating was marked and she gained 15 kg in as many weeks. Decrease of the dose decreased her appetite but increased the intensity of the voices. Both the patient and her parents remain most upset by her appearance.

A transient severe hyperpyrexia can mimic infection, necessitate extra blood sampling and thus decrease compliance.

Case 4. A 57-year-old man with a resistant illness was started on clozapine. Other drugs had not been tailed off. Within three days his temperature had risen to 39°C with no signs of infection. He was most uncomfortable. In other cases the benign hyperpyrexia had settled in five days but his did not and it only disappeared immediately on stopping the drug.

Clozapine lowers the convulsion threshold to the same degree as other antipsychotic agents up to a dose of 600 mg/day (1%). Above this dose the occurrence of seizures increases to 14%.

Once a person is withdrawn from clozapine for whatever reason, there seems, in some cases, to be a period where restabilisation on more usual medications can prove difficult. Chouinard *et al* (1978) implicate clozapine in the causation of a rebound psychosis and this may be a rare complication of the use of this and other neuroleptic drugs.

Case 5. A 37-year-old man stopped 500 mg of clozapine after 11 weeks because of lack of response. In the next few days he described clearly the racing of his thoughts to a distressing degree. This settled in two weeks.

Case 6. A 34-year-old chronically withdrawn schizophrenic man completed 26 weeks of an average of 450 mg of clozapine daily. He was gently reduced as little improvement had occurred and indeed the drug was implicated in the appearance of epileptic phenomena. Still, three months after clozapine was stopped, he remains bizarrely psychotic with

disturbing hallucinations that result in high arousal and non-social speech. So far efforts to stabilise him on other medications have not been successful and he remains difficult to nurse.

The risk of agranulocytopenia is 1–2%. Weekly blood sampling up to week 18 necessitates outpatient attendance twice a week, once to provide the sample and then a second time to see the clinician when the blood result returns from the CPMS.

Granulocytopenia is heralded by three successive gentle falls in the neutrophils before the fall becomes precipitous. Extra blood samples are needed during granulocytopenia and clozapine must be stopped if agranulocytosis occurs. Then daily blood samples monitor the normalisation of the white cell count over the next week. The patient must be in hospital and the help of haematologists sought early. Any infection needs aggressive treatment in a specialist unit. Other antipsychotic treatments are best avoided during this time.

Case 7. On day 70 of treatment with clozapine, a 30-year-old woman who had had three gentle falls in her white cells was found to have a white cell count (WCC) of 3.1×10^{-9}/L and a neutrophil count (NC) of 1.55×10^{-9}/L. Clozapine was stopped immediately. Five days later the WCC was 0.42×10^{-9}/L and the NC 0.01×10^{-9}/L. During this time she received 30 mg of Trifluoperazine. At this time she became symptomatic and a presumptive diagnosis of septicaemia was made. She was reverse-barrier nursed in a specialised unit and received intravenous antibiotic and antifungal therapy. In another six days, during which at least daily FBC monitoring was undertaken, the WCC and NC had returned to normal, but not before the haemoglobin and platelet count had also fallen somewhat. She made a swift recovery (Adams *et al*, 1990).

The blood analysis must be undertaken by the CPMS. Samples are posted and results returned by post. The postal service is surprisingly reliable and it is rare that a sample is destroyed in transit and another is requested. Postal holidays and strikes may be problematic but special transport systems are provided with the CPMS for such occurrences.

With clozapine causing an unusual ratio of central receptor blockade there is the implication that too high dosage would result in the therapeutic ratio being lost. There may be a therapeutic window. In addition the combination of clozapine and other receptor blocking drugs may be counter-productive. From the experience on the trial, there is the suggestion that those on moderate doses of clozapine alone do better (300–600 mg/day).

Finally, the implications for services if these people get significantly better are great. Cost of maintenance on 900 mg of clozapine per day is £6,544.95p per year. The need for skilled long-term input will be great as some emerge after years of illness in low-input environments.

Case 8. A 34-year-old man with a chronic illness improved markedly after a few weeks on clozapine (450 mg/day). Hallucinations decreased and insightful periods occurred. Always prone to depressive periods, on the 19th week of medication he killed himself. It is impossible to say now but it may be that a drug response with a return of insight endangered him.

Conclusion

Clozapine is a potent antipsychotic drug useful in a selection of people with treatment resistant schizophrenia, causing remission of chronic symptoms to a greater or lesser extent. It has significant and troublesome side-effects but does not cause severe movement disorders. Its use is demanding both for the clinician and patient but the risk:benefit ratio seems favourable to the sufferer of intractable symptoms. The benefit to the patient versus cost in medical/nursing time and pharmacy expenses may lead to contentious discussion as financial considerations become ever more important.

Acknowledgements

We wish to thank Professor Steven Hirsch and Dr Thomas Barnes for their help and support at all stages of this research and Dr Jeremy Speller for his advice in the preparation of this article.

References

ADAMS, C., RICCIO, M., MCCARTHY, D., BARNES, T. R. E. & HIRSCH, S. R. H. (1990) Agranulocytosis induced by clozapine with the early addition of trifluoperazine: a case report. *International Clinical Psychopharmacology*, **5**, 287–291.

CHOUINARD, G., JONES, B. D. & ANNABLE, L. (1978) Neuroleptic induced supersensitivity psychosis. *American Journal of Psychiatry*, **135**, 1409–1410.

KANE, J., HONGFELD, G., SINGER, J. & MELTZER, H. (1988) Clozapine for treatment-resistant schizophrenia: a double blind comparison with chloropromazine. *Archives of General Psychiatry*, **45**, 789–796.

MELTZER, H. Y. (1989) The follow up of clozapine treated treatment-resistant schizophrenics at six months. *Archives of General Psychiatry*, **46**, 672–675.

WESTERMYER, J. F. & HARROW, M. (1990) Prognosis and natural course of schizophrenia. *Current Opinion in Psychiatry*, **3**, 3–7.