Gloucester Clozapine Clinic

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Twenty-four patients in the Gloucester rehabilitation service were considered suitable for clozapine treatment between January 1993 and May 1996. Five patients consistently refused to start clozapine and four patients (21%) discontinued clozapine, usually due to side-effects. Eight patients showed 'some positive response' and seven 'good positive response', of the 15 still taking clozapine. High rates of side-effects, but low readmission rates were found in this group. Putative reasons for the low discontinuation rates and apparent success of clozapine treatment in Gloucester include the wide experience engendered in the single consultant-led rehabilitation team, and the better coordinated, uniform approach to managing problems through the Clozapine Clinic.

Interest in treatment with clozapine was resurrected after the pivotal study carried out in the USA by Kane *et al* (1988). After six weeks 30% of patients with treatment resistant schizophrenia responded to clozapine, only 4% to haloperidol. A subsequent study has shown that six weeks is too early to define clinical change (Meltzer *et al*, 1990). King & Mills (1993) found that about one-third of patients taking clozapine improved dramatically (especially younger adults with early onset illness), about one-third derived significant benefit and about one-third did not respond. Over six months, clozapine produced an improvement in all four components of a quality of life scale, improved psychopathology on the Brief Psychiatric Rating Scale and significantly reduced rehospitalisation rate (Meltzer *et al*, 1990). Clozapine is a unique psychotropic, in having a system of blood test monitoring organised by the pharmaceutical company, due to the higher than usual risk of agranulocytosis.

Although considerable research evidence is available regarding the clinical outcome of clozapine treatment, there are less data concerning its value in real, natural clinical settings. This review of the working of the Gloucester Clozapine Clinic was an attempt to produce such information.

The study

The present study represents a naturalistic, retrospective audit of the clinical outcome of our use to date of clozapine in Gloucester. By contrast with previous studies, all patients considered suitable for treatment with clozapine since its first use in Gloucester in January 1993, until May 1996, were included. The case notes and medication charts of all subjects were examined and the clinical outcome was identified using a clinical global outcome scale, relating to both positive and negative symptoms. The scale, which was applied separately by three different raters, was devised as follows: worse (i.e. clinical deterioration); no change; some positive response (i.e. distinct improvement but major active problems remain); good positive response (i.e. major inroad on negative/positive symptoms); and, excellent positive response (effectively now in remission from being actively psychotic).

Interrater reliability was high (ratings identical for 13/15 patients), and where disagreement occurred the consensus view (two of three raters concurring) was used.

Findings

In total 24 patients were considered for and advised to take clozapine over the study period. Five patients consistently refused to take it, usually due to problems with blood tests (three patients), but also concerns about safety among a patient's family. Of the 19 patients who started taking clozapine, four (21%) had their treatment discontinued, for the reasons: no response (one case); non-fatal neuroleptic malignant syndrome (one case); recurrent chest infection plus non-response (one case); and fainting, hypotension, episodes of unconsciousness, seizures and failure to improve in the final case.

Of 15 patients still taking clozapine to May 1996, eight were rated as having shown 'some positive response' and seven 'good positive response' according to the clinical global outcome scale. Eleven of the patients were men and four women, with mean age 42.8 years (range 30 to 65). All patients were suffering from chronic, treatment-resistant schizophrenia with a mean duration of illness of 21 years (range 10 to 45 years). The mean number of antipsychotics

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taken before clozapine was 6.7 (range 3 to 10). Before starting on clozapine the patients had been admitted to hospital, mean 7.5 times (range 1 to 22). After starting on clozapine the mean number of hospital admissions was 0.2 (14 out of the 15 patients still taking clozapine having no admissions, one patient having three), over a mean period to date of 2.3 years' treatment.

The main side-effects reported were: drowsiness/sedation (11 cases); sialorrhoea (8); nausea/vomiting (3); sweating (3); hypotension/postural dizziness (3); weight gain (2); and seizures in one case.

The four patients whose treatment was discontinued had a mean age of 55 years (range 43 to 65 years), and mean duration of illness of 33 years (range 20 to 45 years).

Comment

This study shows the results of using clozapine in a standard clinical setting, rather than a clinical trial setting. Although advantages of reduced selection bias can be imputed, the inherent problems of a non-controlled clinical setting, with the lack of independent, blind rating, indicate that these results should be interpreted with caution, and cannot readily be compared with other studies of more rigorous design. However, it is interesting that Seabourne & Thomas (1994) described a similar audit of the use of clozapine in Manchester, which generated substantially different results. Eight consultants had treated 25 patients with clozapine, leading to mental state 'improvement' in 16 and 'no change' in nine. After two years, 15 of the 25 patients had discontinued clozapine treatment, due largely to side-effects. Although statistical comparison is not possible, it can be seen that in Gloucester there was a substantially lower drop-out rate, and apparently a better clinical outcome with clozapine than in Manchester. The authors postulate that the increased confidence and experience engendered in using this complicated treatment through the consultant/clinical medical officer led team may have influenced the results: it can be argued that success with clozapine treatment is often dependent on the ability to support and help patients with unpleasant side-effects such as sialorrhoea, which may continue for a considerable time before clinical benefits are evident. The apparent success may be attributed to better coordination of information and a more uniform approach to problems encountered.

Although treatment with clozapine has the disadvantage of needing repeated blood tests, which patients generally find unpleasant and aversive, the rate of refusal demonstrated in this audit was low (four patients out of 24). The discontinuation rate was also low (21%), the results creating an impression that older, more chronically ill patients found side-effects harder to tolerate and were more likely to discontinue treatment. The breakdown of side-effects suffered by patients taking clozapine reinforces the practical difficulties of establishing patients on a treatment which may in its own right confer substantial adverse clinical effects. The clinicians working in the clozapine clinic now have considerable experience in dealing with these problems, and have found a number of therapeutic approaches helpful. Patients are encouraged to persevere with treatment, and advised that side-effects such as sedation often settle given time. Sialorrhoea will generally respond to treatment with hyoscine hydrobromide, and indigestion/nausea to ranitidine. If weight gain is a serious problem, referral for specialist dietary advice and attempts to promote exercise have been useful.

The positive global clinical outcome (eight patients showing some improvement and seven patients good improvement) was reflected in the very low rate of hospitalisation post clozapine treatment, and underlines the potential economic benefits of its use. Davis & Drummond (1994) showed that 74% of the cost of treating schizophrenia is attributable to bed costs.

We have adopted a regular monitoring system to assess the clinical outcome of clozapine treatment, assessing patients before treatment and at three monthly intervals thereafter with the Brief Psychiatric Rating Scale (Overall & Gorham, 1962). The clozapine case load is steadily increasing, and the ability to demonstrate positive health outcome to purchasing authorities, which face rising drug budgets, is increasingly necessary. While the clinic is currently managed by a clinical medical officer supported by workers in the community rehabilitation team in one session weekly, it is likely that the clinic may need to be developed to run over two sessions, held in the community rehabilitation team base. Such issues emphasise the high cost implications of this complex but highly effective psychiatric treatment.

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