This drug has been "archived" and will not be actively updated except for a compelling reason or request (August 2005).

CLOZAPINE
SUMMARY SHEET

TRADE NAME: Clozaril

Licensed Indication:

‘Clozapine is indicated in treatment resistant schizophrenia patients, i.e. patients who are non-responsive to, or intolerant of, conventional neuroleptics.

Non responsiveness is defined as the lack of a satisfactory clinical improvement despite the use of adequate doses of at least two marketed neuroleptics prescribed for a reasonable time.

Intolerance is defined as the impossibility of achieving adequate benefit with conventional neuroleptic drugs because of severe and untreatable neurological adverse reactions (extrapyramidal symptoms or tardive dyskinesia)

Other licence restrictions:

Clozapine can only be initiated in hospital in-patients who have normal leucocyte levels. The patient, consultant psychiatrist and hospital pharmacy must all be registered with the Clozaril Patient Monitoring Service (CPMS). Patients’ white blood cell (WBC) count and differential count must be monitored weekly for the first 18 weeks of treatment and then at two weekly intervals for the remainder of the first year. After this time if the neutrophil count is stable the frequency of monitoring may be changed to 4 weekly intervals. The drug will only be supplied on the receipt of a recent satisfactory WBC count.

Patients must always remain under the supervision of the specialist. However, patients who have received clozapine for 1 year or more and have had a stable haematological picture over this period such that they only require 4 weekly blood monitoring, can undergo shared care provided:

- a shared care arrangement has been agreed between the consultant psychiatrist and GP.
- the GP has registered with the CPMS.
- the patient has a stable mental profile and is community based.
- a community pharmacy has been nominated by the patient and registered with the CPMS

Background Information:

Schizophrenia is a complex and poorly understood disorder that affects approximately 200,000 people in the UK. It is difficult to predict which patients will have prolonged problems when they are first diagnosed since as many as 25-40% will only suffer a single attack.¹

The classic antipsychotic drugs such as chlorpromazine and haloperidol provide first line therapy for acute schizophrenia. They are effective in 75% of patients during an acute attack although 20-30% of initial responders become resistant to treatment with time. In addition approximately 15% of patients become intolerant of antipsychotic therapy due to profound side effects.²³ Clozapine provides one treatment option for the management of these patients.

Clinical Efficacy:
In resistant schizophrenia several retrospective and prospective controlled non-comparative trials have demonstrated a significant clinical improvement with clozapine treatment in 30-50% of resistant patients, and up to 80% of patients intolerant of typical antipsychotics.4

Kane et al entered 268 patients into a randomised double blind trial. These patients had failed to respond to at least 4 different neuroleptics including a 6 week trial of haloperidol. Patients were randomised to clozapine or chlorpromazine plus benztropine. After 6 weeks, 30% of clozapine treated patients and 4% of chlorpromazine treated patients were categorised as responders.5

A double blind randomised study has been conducted in 151 schizophrenic patients who had previously experienced either tardive dyskinesia or extrapyramidal side effects during therapy with at least 2 different standard antipsychotics. Patients were randomised to receive clozapine or chlorpromazine. After 8 weeks treatment clozapine use was associated with a wider spectrum of activity and a faster onset of action than chlorpromazine.6

Long term open studies have demonstrated continued efficacy with clozapine for periods of up to 12 years. Up to 45% of patients, however, are noted to discontinue treatment.7

Adverse Effects

Serious adverse effects necessitating withdrawal of clozapine have been reported in approximately 6% of patients, although at least one major side effect occurs in approximately 70% of patients.7

The most serious side effect of clozapine is neutropenia leading to agranulocytosis. This reaction is generally reversible but can prove fatal. The risk is greatest in the first 18 weeks of treatment and falls to 0.7% for developing neutropenia and 0.07% for developing agranulocytosis during the second year of treatment.8 The CPMS links the supply of drugs to the receipt of a recent satisfactory white blood count to reduce the risk of agranulocytosis. On registering with the CPMS GPs are given detailed information on the 4 weekly monitoring required. If neutropenia develops rapid withdrawal from clozapine may be advised. This can result in a serious relapse in the patient’s schizophrenic symptoms.

Other side effects include hypersalivation, drowsiness and sedation, dizziness, headaches, tachycardia and considerable weight gain. Clozapine use is associated with a very low incidence of extrapyramidal symptoms. Clozapine lowers the seizure threshold and can precipitate convulsions in patients who have an epileptogenic potential but no previous history of fits. Rare cases of myocarditis and fatal circulatory collapse have also been seen. The drug interactions are listed in the datasheet.

Health Economics

In 1987 the total cost for the health and social services for the treatment of schizophrenia in the UK was estimated at £310 million. Drug therapy only accounted for 3% of this cost. Studies of clozapine in the UK in institutionalised patients with moderate to severe schizophrenia and patients with resistant schizophrenia have shown clozapine treatment to be cost effective. Increased costs of the patients drug treatment is balanced by a reduction in the costs of in-patient treatment.

Conclusions

Clozapine is a useful treatment for schizophrenia in patients unresponsive to or intolerant of conventional antipsychotics. The need for 4 weekly blood monitoring linked to drug supply, to reduce the risk of agranulocytosis, prevents more widespread use. The dangers of serious relapse if treatment is stopped abruptly, and the difficulties of tracking down patients who do not attend for blood tests or collect their prescriptions, makes this drug unsuitable for use in general practice. Greater co-ordination than is currently available would be required.

Key References


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