Cloxazolam *(rINN)*

Cloxazolamum; CS-370; Kloksatsolaami; Kloxazolam. 10-Chloro-11b-(2-chlorophenyl)-2,3,7,11b-tetrahydro-oxazolo[3,2-*d*][1,4]benzodiazepin-6(5*H*)-one.

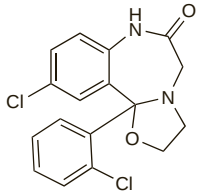
Клоксазолам

$C_{17}H_{14}Cl_2N_2O_2$ = 349.2.

CAS — 24166-13-0.

ATC — N05BA22.

ATC Vet — QN05BA22.



Pharmacopoeias. In *Jpn.*

Profile

Cloxazolam is a long-acting benzodiazepine with general properties similar to those of diazepam (p.986). It has been given in oral doses of up to 12 mg daily in divided doses for the short-term treatment of anxiety disorders (p.952). A dose of 100 micrograms/kg may be used for premedication (p.1780).

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Tolestan; ***Belg.:*** Akton; ***Braz.:*** Anoxolan; Clozal; Elum; Eutonis; Olcadil; ***Port.:*** Cloxam; Olcadil; ***Switz.:*** Lubalix†.

Clozapine *(BAN, USAN, rINN)*

Clozapina; Clozapinum; HF-1854; Klotsapiini; Klozapin; Klozapina; Klozapinas. 8-Chloro-11-(4-methylpiperazin-1-yl)-5*H*-dibenzo-[*b*,*e*][1,4]diazepine.

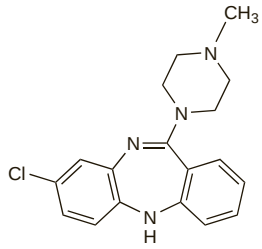
Клозапин

$C_{18}H_{19}ClN_4$ = 326.8.

CAS — 5786-21-0.

ATC — N05AH02.

ATC Vet — QN05AH02.



Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), and *US.*

Ph. Eur. 6.2 (Clozapine). A yellow crystalline powder. Practically insoluble in water; soluble in alcohol; freely soluble in dichloromethane. It dissolves in dilute acetic acid.

USP 31 (Clozapine). A yellow crystalline powder. Insoluble in water; soluble in alcohol, in acetone, and in chloroform; sparingly soluble in acetonitrile.

Stability. A suspension of clozapine 100 mg in 5 mL, made by crushing clozapine tablets and suspending the powder in a syrup-based mixture containing carboxymethylcellulose preserved with methyl hydroxybenzoate and propyl hydroxybenzoate (Guy's Hospital paediatric base formula), was considered to be stable for at least 18 days after preparation.[1]

1. Ramuth S, *et al.* A liquid clozapine preparation for oral administration in hospital. *Pharm J* 1996; **257:** 190–1.

Adverse Effects and Treatment

Although clozapine may share some of the adverse effects seen with the classical antipsychotics (see Chlorpromazine, p.969), the incidence and severity of such effects may vary; antimuscarinic effects with clozapine may be more pronounced. Sedation and weight gain may also be more prominent. Clozapine can cause reversible neutropenia which may progress to a potentially fatal agranulocytosis; strict monitoring of white blood cell counts is essential (see Precautions, below). Eosinophilia may also occur. Anaemia, thrombocytopenia, and thrombocythaemia have been reported rarely.

Extrapyramidal disorders, including tardive dyskinesia, appear to be rare with clozapine. Clozapine has little effect on prolactin secretion. Clozapine appears to have a greater epileptic potential than chlorpromazine but a comparable risk of cardiovascular effects such as tachycardia and orthostatic hypotension. In rare cases, circulatory collapse with cardiac and respiratory arrest has occurred, and hypertension has also been reported. Clozapine is also associated with an increased risk of developing myocarditis that may, in rare cases, be fatal; cardiomyopathy and pericarditis have also been reported.

Additional adverse effects of clozapine include dizziness, hypersalivation (particularly at night), headache, nausea, vomiting, constipation (which, in a few cases, has led to gastrointestinal obstruction, faecal impaction, and paralytic ileus), urinary incontinence and retention, fatigue, and transient fever which must be distinguished from the signs of impending agranulocytosis. There have also been rare reports of dysphagia, parotid gland enlargement, confusion, delirium, thromboembolism, acute pancreatitis, hepatitis and cholestatic jaundice, and very rarely fulminant hepatic necrosis. Isolated cases of acute interstitial nephritis have been reported. Abnormalities of glucose homoeostasis and the onset of diabetes mellitus occur uncommonly; severe hyperglycaemia, sometimes leading to ketoacidosis or hyperosmolar coma, has been reported very rarely. There have also been rare reports of hypercholesterolaemia and hypertriglyceridaemia. Many of the adverse effects of clozapine are most common at the start of therapy and may be minimised by gradual increase in dosage.

Effects on the blood. Clozapine can cause reversible neutropenia which, if the drug is not withdrawn immediately, may progress to a potentially fatal **agranulocytosis**. Particular concern over this adverse effect dates from 1975 when 17 cases of neutropenia or agranulocytosis, 8 of them fatal, were reported in Finland;[1] the calculated incidence[2] of agranulocytosis or severe granulocytopenia during this Finnish epidemic was 7.1 per 1000. These reports led to the withdrawal of clozapine in some countries or to restrictions in its use and intense haematological monitoring in others. After studies showing the efficacy of clozapine in severely ill schizophrenic patients unresponsive to adequate therapy with classical antipsychotics, the drug became available in the UK and USA in 1990 with strict procedures for monitoring of white blood cell counts. The UK CSM provided data on the reports it had received between July 1963 and January 1993 on agranulocytosis and neutropenia.[3] Clozapine was one of the individual drugs most frequently implicated, with 14 reports of agranulocytosis (1 fatal) and 119 of neutropenia (none fatal). Various estimates of the **incidence** of clozapine-associated agranulocytosis have been made; analysis of data from 11 555 patients given clozapine in the USA[4] showed a cumulative incidence of agranulocytosis of 8.0 per 1000 at 1 year and 9.1 per 1000 at 1⁄ years with the risk being increased in elderly patients. The majority of cases of agranulocytosis occurred within 3 months of the start of treatment with the risk peaking in the third month. The manufacturers report a lower incidence of agranulocytosis of 4.8 per 1000 patients for the first 6 months[5] and an annual rate of 0.8 per 1000 patients during the next 2⁄ years. These figures were based on data on 56 000 patients in the USA given clozapine up to the end of March 1993. Analysis of data[6] on 6316 patients registered in the UK and Ireland between January 1990 and July 1994 to receive (although not necessarily given) clozapine produced a cumulative incidence of agranulocytosis of 0.7% during the first year and 0.8% over the whole study period. Most cases of agranulocytosis and neutropenia occurred during the first 6 to 18 weeks of treatment. The incidence of agranulocytosis (0.07%) and neutropenia (0.7%) seen during the second year of therapy was of the same order of magnitude noted for some phenothiazine antipsychotics.

These data[6] and comparable data from the USA[7] were considered to indicate that mandatory haematological monitoring (see Precautions, below) helped to reduce the risks of clozapine-induced neutropenia and agranulocytosis and associated deaths.

The mechanism for clozapine-induced agranulocytosis is unclear and may be the result of direct toxicity or an immune response.[8,9] **Predisposing factors** for development of agranulocytosis have not been identified, apart from a possible excess of cases in female patients and an increased risk with increasing age. Furthermore, both agranulocytosis and neutropenia do not appear to be dose-related effects with clozapine. A postulated higher incidence of agranulocytosis in patients of Jewish background may be related to genetic factors.[10] Africans and Afro-Caribbeans appear to be at increased risk of developing neutropenia[6] and it has been noted[11] that many patients from these ethnic groups are currently already excluded from treatment with clozapine because their normal white blood cell and neutrophil counts are below the recommended range for treatment (see Precautions, below). However, UK licensed product information recommends that patients who have low white blood cell counts due to benign ethnic neutropenia may begin clozapine treatment with the agreement of a haematologist.

Evidence would suggest that development of clozapine-induced leucopenia or granulocytopenia precludes **retreatment** with clozapine at any future date; in a series of 9 re-treated patients, all developed leucopenia or agranulocytosis again.[12] In the USA, patients who have had clozapine withdrawn because of moderate leucopenia (judged to be when counts fall to 2000 to 3000 cells/mm^3) are considered eligible for a return to clozapine treatment when this count returns to normal; such patients are considered to have a five- or sixfold greater risk of agranulocytosis.[5]

1. Idänpään-Heikkilä J, *et al.* Agranulocytosis during treatment with clozapine. *Eur J Clin Pharmacol* 1977; **11:** 193–8.
2. Anderman B, Griffith RW. Clozapine-induced agranulocytosis: a situation report up to August 1976. *Eur J Clin Pharmacol* 1977; **11:** 199–201.
3. CSM/MCA. Drug-induced neutropenia and agranulocytosis. *Current Problems* 1993; **19:** 10–11. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024456&RevisionSelectionMethod=LatestReleased (accessed 12/08/08)
4. Alvir JMJ, *et al.* Clozapine-induced agranulocytosis: incidence and risk factors in the United States. *N Engl J Med* 1993; **329:** 162–7.
5. Finkel MJ, Arellano F. White-blood-cell monitoring and clozapine. *Lancet* 1995; **346:** 849.
6. Atkin K, *et al.* Neutropenia and agranulocytosis in patients receiving clozapine in the UK and Ireland. *Br J Psychiatry* 1996; **169:** 483–8.
7. Honigfeld G, *et al.* Reducing clozapine-related morbidity and mortality: 5 years experience with the Clozaril National Registry. *J Clin Psychiatry* 1998; **59** (suppl 3): 3–7.
8. Gerson SL, *et al.* Polypharmacy in fatal clozapine-associated agranulocytosis. *Lancet* 1991; **338:** 262–3.
9. Hoffbrand AV, *et al.* Mechanisms of clozapine-induced agranulocytosis. *Drug Safety* 1992; **7** (suppl 1): 1–60.
10. Leiberman JA, *et al.* HLA-B38, DR4, DQw3 and clozapine-induced agranulocytosis in Jewish patients with schizophrenia. *Arch Gen Psychiatry* 1990; **47:** 945–8.
11. Fisher N, Baigent B. Treatment with clozapine: black patients' low white cell counts currently mean that they cannot be treated. *BMJ* 1996; **313:** 1262.
12. Safferman AZ, *et al.* Rechallenge in clozapine-induced agranulocytosis. *Lancet* 1992; **339:** 1296–7.

Effects on body-weight. Most antipsychotic drugs are associated with weight gain. A meta-analysis[1] found evidence of weight gain in patients receiving both classical (chlorpromazine, fluphenazine, haloperidol, loxapine, perphenazine, thioridazine, tiotixene, or trifluoperazine) and atypical (clozapine, olanzapine, quetiapine, risperidone, sertindole, and ziprasidone) antipsychotics. Two drugs, molindone and pimozide, appeared in contrast to be associated with weight loss, although in the case of pimozide this could not be confirmed statistically. Placebo treatment was also associated with weight loss. However, a later review considered that there was overwhelming evidence that atypical antipsychotics induced more weight gain than classical antipsychotics.[2]

A separate review[3] calculated the average monthly weight gain associated with atypical antipsychotics to be:

- olanzapine (2.28 kg)
- zotepine (2.28 kg)
- quetiapine (1.76 kg)
- clozapine (1.72 kg)
- risperidone (0.96 kg)
- ziprasidone (0.80 kg)

Weight gain occurred most frequently during the first 6 to 12 months of treatment. It was recommended that if weight gain was more than 2 kg during the first 2 weeks, a strict dietary regimen should be started immediately. However, more recent opinion is that a change of antipsychotic may be necessary. Anti-obesity drugs have been tried although their routine use is not generally recommended.[2,4]

1. Allison DB, *et al.* Antipsychotic-induced weight gain: a comprehensive research synthesis. *Am J Psychiatry* 1999; **156:** 1686–96.
2. Ananth J, *et al.* Atypical antipsychotic induced weight gain: pathophysiology and management. *Ann Clin Psychiatry* 2004; **16:** 75–85.
3. Wetterling T. Bodyweight gain with atypical antipsychotics: a comparative review. *Drug Safety* 2001; **24:** 59–73.
4. Allison DB, Casey DE. Antipsychotic-induced weight gain: a review of the literature. *J Clin Psychiatry* 2001; **62** (suppl 7): 22–31.

Effects on carbohydrate metabolism. Treatment with clozapine may be associated with an increased risk of glucose intolerance and diabetes mellitus; a similar association has also been noted for some other atypical antipsychotics.[1]

Data received by WHO indicated that up to December 2000, there had been 480 reports of glucose intolerance with clozapine, 253 with olanzapine, and 138 with risperidone.[2] In some cases weight gain was also reported, which may predispose to development of glucose intolerance. Other risk factors identified included an underlying diabetic condition, male gender, and use with some other medications including valproate, SSRIs, and buspirone. Regular monitoring of weight, blood glucose, and