

sedation of children before diagnostic, dental, or medical procedures (but see under Carcinogenicity above).

Externally, cloral hydrate has a rubefacient action and has been used as a counter-irritant.

Cloral hydrate is given by mouth as an oral liquid or as gelatin capsules with cloral hydrate dissolved in a suitable vehicle. It has also been dissolved in a bland fixed oil and given by enema or as suppositories.

It should not be given as tablets because of the risk of damage to the mucous membrane of the alimentary tract.

The usual oral hypnotic dose in adults is 0.5 to 2 g given as a single dose at night; as a sedative 250 mg can be given three times daily to a maximum daily dose of 2 g. Oral dosage forms should be taken well diluted or with plenty of water or milk. The *BNFC* suggests that children aged 1 month to 12 years be given 30 to 50 mg/kg to a maximum single dose of 1 g by mouth as a hypnotic (but see above); those aged 12 to 18 years may be given 0.5 to 1 g. Although not licensed in the UK for sedation of children before a painless procedure, the *BNFC* suggests the following oral doses, given 45 to 60 minutes beforehand: 1 month to 12 years, 30 to 50 mg/kg (maximum of 1 g), although up to 100 mg/kg (maximum of 2 g) may be used with respiratory monitoring; 12 to 18 years, 1 to 2 g. The *BNFC* states that the doses above may be given rectally if the oral route is unavailable. In the USA, a suggested oral or rectal sedative dose for children is 8.3 mg/kg three times daily to a maximum daily dose of 1.5 g; a dose of 20 to 25 mg/kg has been given as a premedicant prior to EEG evaluation.

A reduction in dosage may be appropriate in frail elderly patients or in those with hepatic impairment.

Derivatives of cloral hydrate, such as cloral betaine (above), chloralose (p.2037), and dichloralphenazone (p.994), which break down in the body to yield cloral hydrate, have been used similarly.

#### References.

- McCarver-May DG, *et al.* Comparison of cloral hydrate and midazolam for sedation of neonates for neuroimaging studies. *J Pediatr* 1996; **128**: 573–6.
- Napoli KL, *et al.* Safety and efficacy of cloral hydrate sedation in children undergoing echocardiography. *J Pediatr* 1996; **129**: 287–91.

#### Preparations

**USP 31:** Chloral Hydrate Capsules; Chloral Hydrate Syrup.

**Proprietary Preparations** (details are given in Part 3)

**Ger.:** Chloralduurat; **Switz.:** Chloralduurat; Medianox; Nervifene; **UK:** Well-dorm; **USA:** Aquachloral; Somnote.

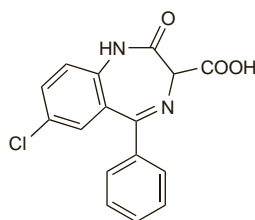
**Multi-ingredient:** **Belg.:** Dentophar; Sedemol; Sulfa-Sedemol; Synthol; **Fr.:** Bain de Bouche Liph; **Rus.:** Efcamon (Эфкамор); **Spain:** Dentol Topico; **Turk.:** Dılan.

#### Clorazepic Acid (BAN)

Clorazépico, ácido. 7-Chloro-2,3-dihydro-2,2-dihydroxy-5-phenyl-1H-1,4-benzodiazepine-3-carboxylic acid.

$C_{16}H_{11}ClN_2O_3 = 314.7$ .

CAS — 23887-31-2; 20432-69-3.



#### Clorazepate Monopotassium (USAN)

Abbott-39083; 4311-CB; Clorazepato monopotásico. Potassium 7-chloro-2,3-dihydro-2-oxo-5-phenyl-1H-1,4-benzodiazepine-3-carboxylate.

$C_{16}H_{10}ClKN_2O_3 = 352.8$ .

CAS — 5991-71-9.

#### Dipotassium Clorazepate (BANM, rINN)

Abbott-35616; AH-3232; 4306-CB; Clorazepate dipotassique; Clorazepate Dipotassium (USAN); Clorazepato de dipotasio; Dikalii clorazepas; Dikalio klorazepatas; Dikaliumkloratsepaatti; Dikaliumklorazepat; Dikalium-klorazepát; Kali Clorazepas; Kaliumkloratsepaatti; Kaliumklorazepat; Klorazepát didraselná sůl; Klorazepat Dipotasyum; Potassium Clorazepate. Compound of Potassium 7-chloro-2,3-dihydro-2-oxo-5-phenyl-1H-1,4-benzodiazepine-3-carboxylate with potassium hydroxide.

Дикалия Клоразепат

$C_{16}H_{11}ClK_2N_2O_4 = 408.9$ .

CAS — 57109-90-7.

ATC — N05BA05.

ATC Vet — QN05BA05.

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

**Ph. Eur. 6.2** (Dipotassium Clorazepate). A white or light yellow, crystalline powder. Solutions in water and in alcohol are unstable and should be used immediately. Freely soluble or very soluble in water; very slightly soluble in alcohol; practically insoluble in dichloromethane. Store in airtight containers. Protect from light.

**USP 31** (Clorazepate Dipotassium). A light yellow, crystalline powder which darkens on exposure to light. Soluble in water but, upon standing, may precipitate from the solution; slightly soluble in alcohol and in isopropyl alcohol; practically insoluble in acetone, in chloroform, in dichloromethane, in ether, and in benzene. Store under nitrogen in airtight containers. Protect from light.

#### Dependence and Withdrawal

As for Diazepam, p.987.

#### Adverse Effects, Treatment, and Precautions

As for Diazepam, p.987.

**Effects on the liver.** Jaundice and hepatic necrosis has been associated with clorazepate.<sup>1</sup>

- Parker JLW. Potassium clorazepate (Tranxene)-induced jaundice. *Postgrad Med J* 1979; **55**: 908–910.

**Effects on the nervous system.** For reference to extrapyramidal disorders associated with the use of benzodiazepines, including clorazepate, see Diazepam, p.988.

**Porphyria.** Clorazepate has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

#### Interactions

As for Diazepam, p.989.

#### Pharmacokinetics

Clorazepate is decarboxylated rapidly at the low pH in the stomach to form desmethyldiazepam (nordazepam, see p.1012), which is quickly absorbed.

#### References.

- Ochs HR, *et al.* Comparative single-dose kinetics of oxazolam, prazepam, and clorazepate: three precursors of desmethyldiazepam. *J Clin Pharmacol* 1984; **24**: 446–51.
- Bertler Á, *et al.* Intramuscular bioavailability of clorazepate as compared to diazepam. *Eur J Clin Pharmacol* 1985; **28**: 229–30.

#### Uses and Administration

Clorazepate is a long-acting benzodiazepine with general properties similar to those of diazepam (p.992). It is mainly used in the short-term treatment of anxiety disorders (p.952), as an adjunct in the management of epilepsy, and in the alcohol withdrawal syndrome (p.1626).

Dipotassium clorazepate is usually given orally but preparations for intravenous or intramuscular use are also available in some countries. Modified-release preparations given once daily are available in some countries for maintenance therapy.

In the UK, an oral dose of 7.5 mg of dipotassium clorazepate was given up to three times daily for the treatment of anxiety. In the USA rather higher doses have been recommended: 15 to 60 mg of dipotassium clorazepate may be given daily, in divided doses or as a single dose at night.

Up to 90 mg has been given daily in divided doses in the management of **epilepsy** or the **alcohol withdrawal syndrome**. Children aged between 9 and 12 years may be given a maximum of 60 mg daily in the management of epilepsy.

Reduced doses should be given to elderly or debilitated patients.

#### Preparations

**USP 31:** Clorazepate Dipotassium Tablets.

**Proprietary Preparations** (details are given in Part 3)

**Arg.:** Justum; Tencilan; Tranxilium; **Austria:** Tranxilium; **Belg.:** Tranxene; Uni-Tranxene; **Braz.:** Tranxilene; **Canad.:** Novo-Clopat; Tranxene†; **Chile:** Calner; Modival†; Tranxilium; **Cz.:** Tranxene†; **Fr.:** Tranxene; **Ger.:** Tranxil; **Ital.:** Tranxene; **Malaysia:** Sanor†; **Mex.:** Tranxene; **Neth.:** Tranxene; Tranxilium; **Philipp.:** Tranxene; **Pol.:** Cloraxene; Tranxene; **Port.:** Medipax; Tranxene; **S.Afr.:** Tranxene; **Singapore:** Tranxene; **Spain:** Tranxilium; **Switz.:** Tranxilium; **Thai.:** Anxielax; Cloramed; Cloraxene; Dipose†; Dipot; Flulium; Manotran; Polizep; Pomadom; Posene; Sanor†; Serene; Tranicap; Translor; Trancon; Tranxene; Zetran; **Turk.:** Anksen; Tranxilene; **UK:** Tranxene†; **USA:** Gen-Xene†; Tranxene; **Venez.:** Tranxene.

**Multi-ingredient:** **Arg.:** Euciton Complex; Maxitratobes; Tranxilium Di-gest; Vegestabil; **Fr.:** Noctran; **Spain:** Dorken.

#### Clotiapine (BAN, rINN)

Clothiapine (USAN); Clotiapina; Clotiapium; HF-2159. 2-Chloro-1-(4-methylpiperazin-1-yl)dibenzo[*b,f*][1,4]thiazepine.

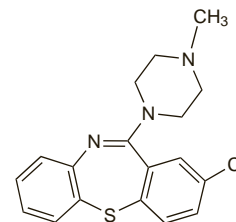
Клотиapiн

$C_{18}H_{18}ClN_2S = 343.9$ .

CAS — 2058-52-8.

ATC — N05AX09.

ATC Vet — QN05AX09.



#### Profile

Clotiapine is a dibenzothiazepine antipsychotic with general properties similar to those of the phenothiazines (see Chlorpromazine, p.969). It is used in a variety of psychiatric disorders including schizophrenia (p.955), mania (see Bipolar Disorder, p.372), and anxiety (p.952). It is given orally in doses ranging from 10 to 200 mg daily in divided doses; up to 360 mg daily has been given in severe or resistant psychoses. It may also be given by slow intravenous or deep intramuscular injection.

**Psychoses.** A systematic review<sup>1</sup> found that good evidence to support the use of clotiapine over other treatments in acute psychotic illness was lacking.

- Berk M, *et al.* Clotiapine for acute psychotic illnesses. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2004 (accessed 21/08/08).

#### Preparations

**Proprietary Preparations** (details are given in Part 3)

**Arg.:** Etumina; **Belg.:** Etumine; **Israel:** Entumine; **Ital.:** Entumine; **S.Afr.:** Etomine; **Spain:** Etumina; **Switz.:** Entumine.

#### Clotiazepam (rINN)

Clotiazépam; Clotiazepamum; Y-6047. 5-(2-Chlorophenyl)-7-ethyl-1,3-dihydro-1-methyl-2H-thieno[2,3-*e*]-1,4-diazepin-2-one.

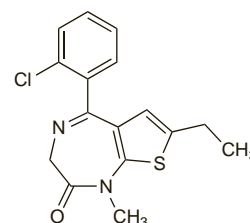
Клотиазепам

$C_{16}H_{15}ClN_2OS = 318.8$ .

CAS — 33671-46-4.

ATC — N05BA21.

ATC Vet — QN05BA21.



**Pharmacopoeias.** In *Jpn.*

#### Profile

Clotiazepam is a short-acting thienodiazepine with general properties similar to those of diazepam (p.986). A usual oral daily dose for the short-term management of anxiety disorders (p.952) is 5 to 15 mg given in divided doses but up to 60 mg daily has been used. For sleep disorders (p.957) 10 mg has been given as a single dose at night. An oral dose of 10 to 15 mg has been given for premedication (see Anaesthesia, p.1780). Reduced doses may be required in elderly or debilitated patients.

#### References.

- Jibiki I, *et al.* Beneficial effect of high-dose clotiazepam on intractable auditory hallucinations in chronic schizophrenic patients. *Eur J Clin Pharmacol* 1994; **46**: 367–9.

**Effects on the liver.** Development of hepatitis in a 65-year-old woman was attributed to clotiazepam begun 7 months earlier.<sup>1</sup> The patient took triazolam and lorazepam without any apparent effect on the liver, and it was speculated that the hepatotoxic effect of clotiazepam was related to the thiophene ring present in the chemical structure.

- Habersetzer F, *et al.* Clotiazepam-induced acute hepatitis. *J Hepatol* 1989; **9**: 256–9.

**Porphyria.** Clotiazepam is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in *in-vitro* systems.

#### Preparations

**Proprietary Preparations** (details are given in Part 3)

**Belg.:** Clozan; **Chile:** Rize; **Fr.:** Veratran; **Ital.:** Rizen; Tienor; **Jpn:** Rize; **Spain:** Distensan.

**Clozazepam** (rINN)

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

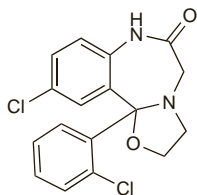
Клоксазолам

C<sub>17</sub>H<sub>14</sub>Cl<sub>2</sub>N<sub>2</sub>O<sub>2</sub> = 349.2.

CAS — 24166-13-0.

ATC — N05BA22.

ATC Vet — QN05BA22.

**Pharmacopoeias.** In *Jpn*.**Profile**

Clozazepam 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.:** Tolstar; **Belg.:** Akton; **Braz.:** Anoxolan; Clozal; Elum; Eutonix; Olcadil; **Port.:** Cloxam; Olcadil; **Switz.:** Lubalix†.

**Clozapine** (BAN, USAN, rINN)

Clozapina; Clozapinum; HF-1854; Klotapiini; Klopazin; Klopazina; Klopazinas. 8-Chloro-11-(4-methylpiperazin-1-yl)-5H-dibenzo[b,e][1,4]diazepine.

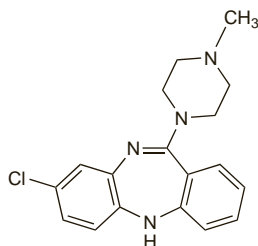
Клозапин

C<sub>18</sub>H<sub>19</sub>ClN<sub>4</sub> = 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.<sup>1</sup>

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.

The symbol † denotes a preparation no longer actively marketed

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 homeostasis 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;<sup>1</sup> the calculated incidence<sup>2</sup> 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.<sup>3</sup> 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<sup>4</sup> showed a cumulative incidence of agranulocytosis of 8.0 per 1000 at 1 year and 9.1 per 1000 at 1½ 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<sup>5</sup> and an annual rate of 0.8 per 1000 patients during the next 2½ 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<sup>6</sup> 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<sup>6</sup> and comparable data from the USA<sup>7</sup> 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.<sup>8,9</sup> **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.<sup>10</sup> Africans and Afro-Caribbeans appear to be at increased risk of developing neutropenia<sup>11</sup> and it has been noted<sup>11</sup> 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.<sup>12</sup> 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<sup>3</sup>) 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.<sup>5</sup>

- Idänpää-Heikkilä J, *et al.* Agranulocytosis during treatment with clozapine. *Eur J Clin Pharmacol* 1977; **11**: 193-8.
- Anderman B, Griffith RW. Clozapine-induced agranulocytosis: a situation report up to August 1976. *Eur J Clin Pharmacol* 1977; **11**: 199-201.
- CSM/MCA. Drug-induced neutropenia and agranulocytosis. *Current Problems* 1993; **19**: 10-11. Also available at: [http://www.mhra.gov.uk/home/ideplg?IdcService=GET\\_FILE&dDocName=CON2024456&RevisionSelectionMethod=LatestReleased](http://www.mhra.gov.uk/home/ideplg?IdcService=GET_FILE&dDocName=CON2024456&RevisionSelectionMethod=LatestReleased) (accessed 12/08/08).
- Alvir JMJ, *et al.* Clozapine-induced agranulocytosis: incidence and risk factors in the United States. *N Engl J Med* 1993; **329**: 162-7.
- Finkel MJ, Arellano F. White-blood-cell monitoring and clozapine. *Lancet* 1995; **346**: 849.
- Atkin K, *et al.* Neutropenia and agranulocytosis in patients receiving clozapine in the UK and Ireland. *Br J Psychiatry* 1996; **169**: 483-8.
- 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.
- Gerson SL, *et al.* Polypharmacy in fatal clozapine-associated agranulocytosis. *Lancet* 1991; **338**: 262-3.
- Hoffbrand AV, *et al.* Mechanisms of clozapine-induced agranulocytosis. *Drug Safety* 1992; **7** (suppl 1): 1-60.
- Leiberman JA, *et al.* HLA-B\*38, DR4, DQw3 and clozapine-induced agranulocytosis in Jewish patients with schizophrenia. *Arch Gen Psychiatry* 1990; **47**: 945-8.
- Fisher N, Baigent B. Treatment with clozapine: black patients' low white cell counts currently mean that they cannot be treated. *BMJ* 1996; **313**: 1262.
- 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<sup>1</sup> 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, molidone 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.<sup>2</sup> A separate review<sup>3</sup> 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.<sup>2,4</sup>

- Allison DB, *et al.* Antipsychotic-induced weight gain: a comprehensive research synthesis. *Am J Psychiatry* 1999; **156**: 1686-96.
- Ananth J, *et al.* Atypical antipsychotic induced weight gain: pathophysiology and management. *Ann Clin Psychiatry* 2004; **16**: 75-85.
- Wetterling T. Bodyweight gain with atypical antipsychotics: a comparative review. *Drug Safety* 2001; **24**: 59-73.
- 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.<sup>1</sup>

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.<sup>2</sup> 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