Antipsychotic drugs (or neuroleptics) are a large class of drugs which can be divided into three groups: phenothiazine, miscellaneous and atypical (Box 1). They are used to tranquillise patients without impairing consciousness and without causing paradoxical excitement. They are often referred to as major tranquillisers but this is misleading since these drugs also relieve florid psychotic symptoms such as thought disorder, hallucinations and delusions, and prevent relapse.

Typical antipsychotic drugs work by blocking post-synaptic dopamine D2 receptors in the brain. They vary in potency, the greater the potency the greater the affinity for the D2 receptors. Low potency drugs, such as chlorpromazine which are given in higher doses, are generally less selective and thus are capable of producing more adverse effects at therapeutic doses because of interaction with other receptors. In contrast, high potency drugs, such as haloperidol, are more selective. Their adverse effects are generally due to dopamine blockade rather than...
Clinical antipsychotic drugs

### Box 1: Summary of types of antipsychotic drugs

<table>
<thead>
<tr>
<th>Phenothiazines</th>
<th>Miscellaneous</th>
<th>Atypical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subgroup 1: Butyrophenones:</td>
<td>Amisulpride</td>
<td>Clozapine</td>
</tr>
<tr>
<td>Chlorpromazine</td>
<td>Droperidol</td>
<td>Quetiapine</td>
</tr>
<tr>
<td>Promazine</td>
<td>Haloperidol</td>
<td>Olanzapine</td>
</tr>
<tr>
<td>Subgroup 2: Dihydropyridines:</td>
<td>Sertindole</td>
<td>Ziprasidone</td>
</tr>
<tr>
<td>Pericyazine</td>
<td>Pipamperone</td>
<td>Olanzapine</td>
</tr>
<tr>
<td>Thioridazine</td>
<td>Thioxanthenes:</td>
<td>Fluphenazine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Zuclopenthixol</td>
</tr>
<tr>
<td>Subgroup 3: Fluphenazine</td>
<td>Sulpiride</td>
<td>Perphenazine</td>
</tr>
<tr>
<td>Perphenazine</td>
<td>Chlorphenothiazine</td>
<td>Trifluoperazine</td>
</tr>
<tr>
<td>Prochlorperazine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tritilquapenazine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Others:</td>
<td>Oxypertine</td>
<td>Loxapine</td>
</tr>
</tbody>
</table>

### Extrapyramidal symptoms (EPS)

All antipsychotic drugs have the potential to cause extrapyramidal symptoms. In general, the older antipsychotic drugs cause these effects more frequently than the newer (atypical) ones. These effects result from blockade of dopamine receptors and are not dose related. They can, therefore, occur following therapeutic doses or in overdose. They may also be delayed for up to 24 hours post-ingestion. In some cases, a patient may only present in hospital a day after overdose of an antipsychotic drug because of onset of extrapyramidal effects. Extrapyramidal symptoms include dystonias, parkinsonism (including tremor) and akathisia. Dystonias are the most common extrapyramidal effects and can involve any part of the body and include opisthotonus (generalised contraction of the extensor muscles), torticollis (neck twisting), trismus (lock jaw), facial grimacing and oculogyric crisis (upward gaze). These symptoms are generally not life-threatening but may be very frightening and distressing to witness and experience. Extrapyramidal effects may last for 24-72 hours. Akathisia is a sense of restlessness and anxiety; it is a relatively rare extrapyramidal symptom. Treatment varies depending on the type of extrapyramidal symptoms the patient is experiencing (see Box 3). Patients who have developed parkinsonian side-effects may be prescribed an antimuscarinic drug, such as procyclidine or benztropine, with their antipsychotic medication.

### Neuroleptic malignant syndrome (NMS)

Neuroleptic malignant syndrome (NMS) is a rare and potentially life-threatening syndrome which is most commonly associated with chronic use of antipsychotic drugs. Combining one antipsychotic with another or with lithium increases the risk of developing the syndrome. Several risk factors exist for the development of NMS; these include previous brain injury, a state of exhaustion, increased agitation and dehydration. Although not associated with toxic drug concentrations, a relationship between NMS development and the loading dose or rate of increase of the antipsychotic exists (Kelner 1997a). The patient usually presents with rigidity, hypotonia, fluctuating consciousness and autonomic dysfunction including hyperthermia, sweating, tachycardia and tachypnoea. Rhabdomyolysis, disseminated intravascular...
Diagnosis of NMS is often difficult because the clinical picture may resemble other medical conditions (Velamoor 1998). Treatment is supportive with discontinuation of all antipsychotics, dopamine depleting or dopamine antagonistic drugs, rehydration, cooling measures if required and dantrolene (a skeletal muscle relaxant).

Overdose of antipsychotic drugs
Antipsychotic medications are frequently taken in overdose due to the nature of the conditions they are used to treat. Overdose of these agents can be potentially serious, and can involve various cardiac complications. However, in most cases overdose of antipsychotic drugs is associated with low morbidity and mortality. Death from overdose of an antipsychotic drug is relatively rare (Parsons and Buckley 1997), once in hospital even patients with severe toxicity usually make a full recovery with supportive care.

There is relatively little published information on overdose with this class of drugs (Parsons and Buckley 1997) even though some of them, such as the phenothiazines, have been prescribed for many years. Only a small number of large case series have been published. There are occasional reports of overdose with the newer, atypical antipsychotic drugs, but in general, information on antipsychotic drug overdose is limited, particularly with respect to toxic and fatal doses. These drugs are often taken in overdose with other drugs, particularly other antipsychotic medications, antimuscarinic drugs (such as procyclidine or benztrapine) or ethanol, which can complicate the clinical picture. A list of general symptoms to be expected following antipsychotic overdose is included in Box 2. All antipsychotic medications may cause these symptoms to varying degrees. CNS depression is the most common feature of overdose with this group of drugs. Children and elderly people are more susceptible to these sedative effects. Co-ingestion of other sedative drugs (including alcohol) will increase the CNS depression. Respiratory depression may require ventilation in some cases. Convulsions are relatively rare (except following loxapine or clozapine overdose). Tachycardia and hypotension are typical cardiovascular features of antipsychotic drug overdose. ECG changes including prolongation of the PR, QRS and QT intervals and arrhythmias may occur.

Antipsychotic drug overdose should always be considered when a known psychiatric patient presents to the emergency department with symptoms of unknown cause. The different groups will be discussed in turn followed by discussion of the treatment of antipsychotic drug overdose.

**Phenothiazine antipsychotics**
These drugs are commonly prescribed and can be divided further into three subgroups:
- Chlorpromazine, methotrimeprazine and promazine
- Pericyazine, pipethazine and thioridazine.
- Fluphenazine, perphenazine, prochlorperazine and trifluoperazine.

Symptoms common to overdose of all phenothiazines are drowsiness progressing to coma, hyporeflexia, hallucinations, slurred speech, agitation, antimuscarinic effects such as dry mouth, blurred vision and urinary retention. Also, tachycardia, hypothermia (rarely hyperthermia), convulsions, hypotension and ECG changes including widening of the QRS, QT prolongation, AV block, bundle branch block, ventricular tachycardia and ventricular fibrillation.

**Group 1** (Chlorpromazine, methotrimeprazine and promazine): Sedation tends to be the primary symptom in overdose of this group of drugs. The antimuscarinic symptoms may be marked with a possibility of impaired thermoregulation and urinary retention. Chlorpromazine is the most common drug in this group to be taken in overdose; it commonly causes...
clinical antipsychotic drug overdose

Box 3. Summary of EPS and NMS

<table>
<thead>
<tr>
<th>Clinical effects</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extrapyramidal symptoms:</td>
<td></td>
</tr>
<tr>
<td>Dystonias (can involve any part of the body, include opisthotonus, torticollis, trismus, oculogyric crisis)</td>
<td></td>
</tr>
<tr>
<td>Procyclidine, benztrapine or diazepam</td>
<td></td>
</tr>
<tr>
<td>Parkinsonism (including tremor)</td>
<td></td>
</tr>
<tr>
<td>Akathisia (a sense of restlessness and anxiety)</td>
<td></td>
</tr>
<tr>
<td>Procyclidine, benztrapine or diazepam</td>
<td></td>
</tr>
<tr>
<td>Neuroleptic malignant syndrome:</td>
<td></td>
</tr>
<tr>
<td>Rigidity, hypertonia, fluctuating consciousness, hyperthermia, autonomic dysfunction (hyperthermia, sweating, tachycardia and tachypnoea). Risk of rhabdomyolysis and renal failure</td>
<td></td>
</tr>
<tr>
<td>Diazepam (generally unresponsive to procyclidine or benztrapine)</td>
<td></td>
</tr>
<tr>
<td>Essentially supportive care with dantrolene (a skeletal muscle relaxant) if required</td>
<td></td>
</tr>
</tbody>
</table>

Miscellaneous antipsychotics
The miscellaneous antipsychotic group of drugs can be divided into five distinct chemical subgroups:
- Butyrophenones: benperidol, droperidol and haloperidol
- Diphenylbutylpiperidines: pimozide.
- Thioxanthenes: flupentixol and zuclopenthixol
- Substituted benzamide: sulpiride

Others: oxypropine and loxapine. Although these drugs belong to different chemical groups they tend to resemble the subgroup three phenothiazines in their effects, both therapeutically and in overdose. Extrapyramidal symptoms frequently occur but marked sedation and antimuscarinic effects tend to be less common.

Butyrophenones
Haloperidol is the most commonly taken drug in this group; severe poisoning from overdose is uncommon. It causes a high incidence of extrapyramidal effects in therapy compared to other antipsychotic medications. In overdose it typically causes drowsiness progressing to coma, hypo- or hypertension, constricted pupils, tachycardia (occasionally bradycardia), tremor and hyperthermia. Prolonged ventricular repolarization has been reported with haloperidol and this can lead to ventricular arrhythmias such as torsade de pointes (Henderson et al 1991), which may be delayed.

Diphenylbutylpiperidines
There are only a few cases of overdose of pimozide reported. A dose of 800 mg has caused prolongation of the QT interval and torsade de points (Krähenbühl et al 1995). Two children (aged six and four years old) developed extrapyramidal effects after ingesting 100mg of pimozide between them. The older child also had convulsions and a prolonged QT interval on the ECG. Extrapyramidal symptoms lasted three days (Salness et al 1992).
There are few reported cases of overdose with flupenthixol and zuclopenthixol. They tend to be less sedating than chlorpromazine in both therapy and overdose.

**Thioxanthenes**

There are few reported cases of overdose with flupenthixol and zuclopenthixol. They tend to be less sedating than chlorpromazine in both therapy and overdose.

**Substituted Benzamides**

The toxicity of sulpiride is considered to be relatively low. Coma has followed ingestion of various amounts of sulpiride, but patients have survived doses of up to 20 g (Dollery 1999). ECG changes may occur.

**Others**

Loxapine causes relatively little sedation in therapeutic doses, however, in overdose it has a high potential for serious neurological and cardiac toxicity. Convulsions are relatively common following overdose withloxapine and have been reported following doses of 450-2750 mg (Petterson 1981). Loxapine is the di-methyl metabolite of amoxapine, a tricyclic antidepressant which frequently causes convulsions in overdose (Parsons and Buckley 1997).

**Atypical antipsychotics**

This group includes amisulpride, clozapine, olanzapine, quetiapine, risperidone, sertindole and zotepine. They have recently been developed because of the high incidence of side effects with the older antipsychotics. As a group, they appear to be better tolerated in therapy causing fewer problems, especially extrapyramidal symptoms. Clozapine has proved useful in the treatment of patients with resistant disease. These drugs are not licensed for epileptic psychosis (in which they may be dangerous due to EEG effects) or confusional states (Kerpren 1999).

**Amisulpride**

There are very few cases of amisulpride overdose reported. Cardiotoxicity is a prominent feature of overdose. A dose of 3 g (with an unknown quantity of dothiepin) caused convulsions and prolongation of QT interval. Another patient was found dead and was subsequently found to have a toxic blood concentration of amisulpride (Tracqui et al 1995).

**Clozapine**

There is a risk of collapse due to hypotension on initiation of clozapine therapy and in overdose, many of the symptoms are an exaggeration of the side effects. Therefore even small doses can be problematic in patients not normally on clozapine. CNS depression and tachycardia are common features of overdose. In severe cases there may be ECG changes, hypotension, renal failure and convulsions. In a review of 150 cases most fatalities occurred after ingestion of more than 2 g, but higher doses have been survived (Le Blaye et al 1992). The most frequent cause of mortality was aspiration pneumonia. Serious toxicity may occur in an individual not on clozapine with doses above 400 mg (Le Blaye et al 1992). Children appear to be particularly susceptible to clozapine-induced toxicity. A single 100 mg tablet in a 4 year old caused confusion, ataxia, muscle rigidity, torticollis and myasthenia (Mady et al 1996). All patients on clozapine must be registered with the Clozaril Patient Monitoring Service (CPMS). This is because clozapine can produce a reversible neutropenia, which may progress to a fatal agranulocytosis. Fatalities are typically related to overwhelming infection (Keltner, 1997b). Thus, leucocyte counts must be monitored in these patients. However, neutropenia and agranulocytosis have not been associated with acute overdose of clozapine (Parsons and Buckley 1997).

**Olanzapine**

Only a few cases of olanzapine overdose have been published, but it appears to be relatively well tolerated in overdose. In clinical trials 67 cases of overdose were reported to the manufacturer. The largest dose taken was 300 mg. Serious toxicity was not reported and no ECG changes occurred (personal communication, Eli Lilly & Company Ltd). However, large doses may cause CNS depression and ECG changes.

**Quetiapine**

A small number of overdose cases with quetiapine have been reported. An alleged overdose of 10 g caused only tachycardia and coma (Harmon et al 1998). These appear to be the most common effects in overdose. However, NPES (London) has had a case where convulsions were reported following an unknown quantity of quetiapine.

**Risperidone**

Several cases of overdose of risperidone have been reported, most patients recovered completely with supportive care. Drowsiness is common and ECG changes occur occasionally. Doses of less than 15 mg rarely cause life-threatening effects (Kuspis et
clinical antipsychotic drug overdose

al 1995). Up to 240 mg has been survived (Brown et al 1993). A 3.5 year old child developed only extrapyramidal effects after 4 mg (Cheslik and Erramouspe 1996).

SERTINDOLE: Sertindole has recently been suspended (Aston 1999) following reports of arrhythmias and sudden cardiac death. However, it remains available on a named-patient basis for patients already stabilised on the drug where other antipsychotic drugs are inappropriate. There are few cases of overdose reported. Clinical effects in overdose reported to the manufacturer include drowsiness, slurred speech, tachycardia, hypotension, and prolongation of the QT interval (Lundbeck, 1997).

ZOTYPINE: This is a relatively new drug and few overdose cases have been reported. Symptoms in overdose may include dry mouth, dilated pupils, hypotension, tachycardia, agitation, hypo- or hyperthermia, drowsiness, urinary retention, respiratory depression, convulsions, coma. ECG may show QT prolongation and therefore there is a possibility of arrhythmias.

Treatment of antipsychotic drug overdose

Gastric lavage and/or activated charcoal may be considered following overdose of an antipsychotic drug. Gastric decontamination is usually only worthwhile within one hour of ingestion. Asymptomatic patients should be observed. For most antipsychotic drugs six hours observation is recommended, the exceptions are pimozide, trifluoperazine and risperidone where a minimum 12 hours is suggested. The recommended observation time is the minimum time the patient should be observed in hospital, if they are symptomatic after this time then they should be kept in for as long as necessary, determined by their clinical condition.

There are no specific antidotes for any of the antipsychotic drugs, and treatment is essentially symptomatic and supportive. ECG monitoring is recommended because of the risk of ECG changes and cardiac arrhythmias. Ventilation may be required in patients with respiratory depression. Convulsions should be managed conventionally and hypotension usually responds to intravenous fluids. Determination of serum concentrations of antipsychotic drugs is not necessary following acute overdose. Routine biochemistry and blood gas analysis is recommended in patients with CNS depression. Acidosis increases the risk of cardiototoxicity and should be corrected. Treatment of choice for ventricular arrhythmias is isoprenaline infusion to raise the pulse to 120 beats per minute. If drug therapy fails overdrive pacing should be considered.

Conclusions

The antipsychotic drugs are a large diverse group. They are often taken in overdose because of the nature of the conditions they are used to treat, however, morbidity and mortality are low. CNS depression and cardiotoxicity are common features of overdose and most patients recover with supportive care.

References

Cheslik T, Erramouspe J (1996) Extrapyramidal symptoms in overdose may include dry mouth, dilated pupils, hypotension, tachycardia, agitation, hypo- or hyperthermia, drowsiness, urinary retention, respiratory depression, convulsions, coma. ECG may show QT prolongation and therefore there is a possibility of arrhythmias.