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Review

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Features and management of poisoning with modern drugs used to treat epilepsy

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Introduction

Patients become poisoned with anticonvulsant drugs in a variety of ways (Table 1).[1] The prevalence of self poisoning and suicide amongst epileptics is many times higher than that of the non-epileptic population.[2] There are many possible reasons for this, including social stigma, employment and marital difficulties, frequent or poorly controlled seizures, frightening or affective auras, drug-induced cognitive changes, and the ready availability of drugs in large quantities. In addition, there is a higher prevalence of psychiatric diagnoses such as psychosis, personality disorders and endogenous depression in those with epilepsy.[2,3] Suicide attempts have also been postulated to result from post-ictal depression which may persist for several days after a seizure.

Anticonvulsant poisoning in children is a significant problem,[4] and not surprisingly, epileptics usually ingest their own anticonvulsants.[3,4] Thus the prevalence of acute, carbamazepine overdosage appears to be rising as its role as a therapeutic agent increases. Of 33 cases reported over a 4-year period to one Poisons Centre, 58% occurred in epileptics.[5] In contrast, the incidence of phenobarbitone poisoning has declined greatly in recent years as it has been replaced by newer anticonvulsants.[6]

Table 1 Causes of poisoning with anti-epileptic drugs

Type	Details
Iatrogenic	Excessive dose prescribed by a doctor
Inappropriate dose self-adjustment	By the patient or a carer without medical consultation
Suicide attempt	Deliberate ingestion
Accidental ingestion	Almost exclusively children
Drug interaction	Other therapy increases plasma concentration
Intercurrent illness	Elevations in serum concentration without change in dose during the course of an acute or chronic illness

Carbamazepine

Carbamazepine is used for the treatment of complex and simple partial seizures, tonic-clonic generalized (grand mal) seizures, and trigeminal neuralgia and some psychiatric conditions. It acts largely by reducing the permeability of neurones to sodium and potassium ions and blocking the re-uptake of noradrenaline. Peak serum concentrations are attained between 6 and 24 h after ingestion of therapeutic doses of carbamazepine.[7] This is because absorption from the gastrointestinal tract is slow, and the drug itself reduces gastrointestinal motility.[8] The half-life of carbamazepine is prolonged after massive overdose, and is typically 30 h.[9] Massive overdosage has been associated with the development of pharmacobezoars,[9] and maximum serum concentrations may then not be attained until as late as 72 h after

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ingestion.[10] It is metabolized to several metabolites, including carbamazepine 10,11-epoxide, which may contribute to toxicity after overdosage.[11]

Acute poisoning is dominated by neurological features.[12,13] Nystagmus, ataxia, intention tremor (usually gross), seizures and dysarthria[14] are frequent. Consciousness may be impaired and occasionally patients present with confusion or aggression.[13,15] Dizziness, mydriasis, divergent strabismus, complete external ophthalmoplegia or fixed dilated pupils have all been described. Abnormal reflexes and tone have been observed.[5,8] Dystonic posturing, myoclonus and athetoid movements may rarely occur.[16]

Cardiovascular effects such as sinus tachycardia, sino-atrial block, hypotension or hypertension are also common.[17,18] ECG abnormalities such as first-degree AV block, QRS prolongation and loss of P waves have been reported,[19,20] and existing heart block may be increased by carbamazepine poisoning.[21] Laboratory evidence of pancreatitis has been reported in a child of 5 years old[22] and in two adults.[23,24] Nausea and vomiting may occur.

More severe cases are characterized by central nervous system depression. Coma may be delayed for hours and may be cyclic as when coma lightens the gut 'wakes up' and more drug is absorbed.[8,11] In cases of very severe poisoning, sinus tachycardia or marked bradycardia may be seen.[25] Respiratory depression, irregular respiration or apnoea may occur within the first 24 h, and pulmonary oedema has been reported.[26] Seizures can occur following massive overdose[5] and death due to status epilepticus has been reported.[27] Survival in adults has been reported after ingesting as much as 640 mg/kg body weight, particularly in patients taking the drug regularly.[28] Death after carbamazepine overdosage is infrequent but may result from cardiac arrhythmias, aspiration pneumonitis, hepatitis or status epilepticus.[27] Previous cardiovascular disease and age do not appear to be important prognostic factors.[29]

Plasma concentrations of carbamazepine and its 10,11-epoxide metabolite can be measured by high-performance liquid chromatography but how well they correlate with clinical toxicity is controversial.[30,31] Toxicity has been demonstrated when serum concentrations of carbamazepine exceed 20 mg/l (85 μmol/l).[20] Serum concentrations of 40 mg/l (170 μmol/l) or higher were associated with an increased risk of serious complications such as coma, seizures, respiratory failure and cardiac conduction defects.[32] However, falling serum concentrations are not reassuring when the patient remains hypotensive and comatose.[33] Free serum carbamazepine concentrations may correlate better with clinical toxicity,[34] but are not readily available and therefore have no practical role in the management of acute overdose.

Management consists of supportive measures. Gastric lavage may be indicated if a patient presents within one hour of a massive overdose of carbamazepine, provided the airway can be protected. Multiple-dose oral activated charcoal is indicated.[35–37] Although the half-life of carbamazepine decreases in a linear relationship with the amount of activated charcoal administered, the relationship with the time taken for clinical recovery is uncertain, because the studies did not have sufficient power to test the relationship between the dose of activated charcoal and time to recovery.[38,39]

Charcoal haemoperfusion enhances carbamazepine clearance, although the total quantity of drug eliminated is small[20] and multiple oral doses of activated charcoal are as effective[36] and less invasive. It has been claimed that a combination of haemodialysis and haemoperfusion not only reduced serum drug concentrations by 50%, but also produced rapid clinical improvement.[40] Haemodialysis and peritoneal dialysis are not effective because of the high degree of protein binding of the drug and its large volume of distribution.[41,42] Plasmapheresis was used to treat a young man who ingested an estimated 5.91 g of carbamazepine; only 335.3 mg of carbamazepine was removed and the procedure had little impact on the patients' clinical status.[43]

Ethosuximide

Succinimides have been used in the management of absence (petit mal) epilepsy for many years. Therapeutic doses of ethosuximide are rapidly and completely absorbed from the gastrointestinal tract.[44] The elimination half-life after a therapeutic dose is 40–60 h in adults and 29 h in children,[45,46] and metabolism occurs mainly in the liver by microsomal enzymes. Only 10–20% of therapeutic doses are excreted unchanged in the urine.

Acute intoxication with ethosuximide has been reported only rarely.[47] Lethargy, headache, dizziness, ataxia and fatigue predominate and nausea, vomiting and euphoria may be features in the initial stages. Respiratory depression may also develop after massive overdosage.

Supportive measures are all that are usually required for treatment. Gastric lavage and activated charcoal should be considered if the patient presents within one hour of ingestion of a large overdose, although the value of either treatment is unproven. Forced diuresis would not be expected to be of value because of the limited urinary excretion of succinimides. The use of haemodialysis, peritoneal dialysis, and exchange transfusion has not been studied, but would not be expected to be effective for pharmacokinetic reasons.

Phenytoin (diphenylhydantoin)

Phenytoin is a first-line agent in the control of tonic-clonic and psychomotor seizures, and the prevention and treatment of seizures associated with neurosurgery. It also finds use as an anti-arrhythmic agent, especially in digitalis- and tricyclic-antidepressant-induced ventricular arrhythmias, including the torsades de pointes variety.[25,48] Phenytoin toxicity also results from its deliberate addition by addicts to crack cocaine in the USA[49] to enhance the 'buzz'.

Phenytoin's main site of action is the motor cortex where it stabilizes transmembrane flux of ions and reduces post-tetanic potentiation of synapses. Phenytoin also increases brain concentrations of gamma-aminobutyric acid (GABA) which has an inhibitory action in the cerebral cortex.[50]

In overdosage, absorption of phenytoin from the gastrointestinal tract may be delayed and continue for as long as 60 h,[51] due to slow dissolution of the tablets, poor solubility of the drug and reduced gastrointestinal motility. As a consequence, peak plasma concentrations may not be attained for as long as 24 to 48 h. However, there is marked inter-individual variation, and the half-life in poisoned adults has varied from 24 to 230 h.[52] The minimum half-life after overdose in children was 6.8 h.[53]

Nausea and vomiting occur within 1–2 h of ingestion of a large overdose of phenytoin.[54] The most significant toxic effects are seen in the nervous system,[55] particularly the cerebellum. As concentrations of the drug increase, spontaneous horizontal nystagmus is observed. It is an early and *sine qua non* sign of phenytoin toxicity.[55] Later, vertical nystagmus, dysarthria, increasing drowsiness, marked ataxia and coarse resting tremor or involuntary movements become apparent.[55] The pupils usually remain normal but ophthalmoplegia,[56] transient abduction paresis[57] and slow saccades[58] have been reported. The tendon reflexes may be increased[59] or decreased[60] and extensor rigidity, opisthotonus and seizures may be seen with high drug concentrations. Cerebellar signs usually resolve when serum concentrations cease to be toxic, but this may take 4–5 days.[61] The risk of permanent sequelae appears small, and the long-term cerebellar effects of acute phenytoin toxicity are controversial, but if present only occur after massive prolonged exposure to plasma phenytoin concentrations of above 40 mg/l.[62]

Less common neurological features include hyperkinesia, ballismus, dystonia, asterixis, orofacial dyskinesia, transient hemiparesis and choreoathetosis, the last occurring mainly in children with pre-existing neurological deficits.[55]

Coma and respiratory depression are so unusual with phenytoin intoxication that, if present, an additional explanation should be sought.[63] Phenytoin-induced cardiovascular toxicity is rare unless the overdose has been given parenterally.[64] Bradycardia, atrioventricular block, decreased cardiac output, hypotension, idioventricular rhythm, ventricular tachycardia[65] and asystole[50] have been seen with massive doses, but predominantly in patients with antecedent heart disease. Cardiotoxicity is probably the cause of the rare deaths from phenytoin overdose. Rarely, hepatocellular damage has been recorded after phenytoin overdose.

Hyperglycaemia with ketosis has been reported following acute overdosage in both diabetic and non-diabetic patients, and may progress to hyperosmolar non-ketotic coma.[66,67] Hypoglycaemia has also been reported[68] as has hypernatraemic coma.[69]

Phenytoin toxicity is not normally seen with plasma concentrations of less than 15 mg/l (60 mmol/l). The presence of nystagmus usually indicates concentrations of at least 20 mg/l (80 mmol/l) and ataxia, levels of 30–40 mg/l (120–160 mmol/l).[50] Deaths are usually associated with plasma concentrations exceeding 90 mg/l (360 mmol/l), although some have been recorded at levels of 50–70 mg/l (200–280 mmol/l).[70]

There is no specific antidote for phenytoin intoxication. Most patients require nothing more than supportive measures. Gastric lavage and the administration of multiple-dose activated charcoal[71] should be considered if a patient presents within one hour of an overdose of phenytoin, provided the airway can be protected, though the clinical benefit is unproven. Seizures should be treated with diazepam 0.1–0.3 mg/kg intravenously to a maximum of 20 mg in an adult. This may be repeated in 10–20 min, if required. Hyperglycaemic, non-ketotic coma should be managed conventionally. Complete heart block is treated initially with atropine 0.6 mg, then by insertion of a temporary pacing wire, if required.

Multiple-dose oral activated charcoal may increase the clearance of phenytoin in adults[72,73] and children,[74] but there is as yet insufficient evidence of associated clinical benefit. Phenytoin is highly protein-bound and it is not surprising therefore that forced diuresis, peritoneal dialysis, exchange transfusion and haemodialysis have been of little or no value in the management of acute intoxication.[75,76] Charcoal haemoperfusion has been used in severe poisoning but has produced variable results and is of questionable value.[77,78] Similarly, plasmapheresis removes some phenytoin but not sufficient to be of value,[79] except perhaps in young children with features of cardiotoxicity.[80]

Sodium valproate (valproic acid)

Valproate is used in the treatment of absence (petit mal) seizures, and is therefore mostly used in chil-

dren; it is also used as an adjunct in multiple seizure types. It is thought to act by increasing cerebral and cerebellar GABA, an inhibitor of synaptic transmission,[81] though its precise mechanism is unknown.

Valproate is rapidly absorbed from the gastrointestinal tract, and peak serum concentrations occur 1–4 h after a single therapeutic dose and the half-life is 7–15 h in healthy volunteers.[82] It localizes in structures with high activities of GABA degradative enzymes, and is thus distributed mainly to liver, lungs, spleen, skeletal muscle, kidney and gastrointestinal tract.[83] The pharmacokinetic disposition of valproate and its metabolites in the course of an acute overdose do not greatly differ from the therapeutic state.[84] It is thought that the 2-EN-valproate metabolite may play a role in neurotoxicity, as it has neurotoxic effects in animals,[69] and was found to be at highest serum concentration at the time of greatest neurological sequelae following overdose but this requires further evaluation. Valproate and its metabolites are excreted in urine.

Garnier *et al.*[85] reviewed 516 cases of acute valproate poisoning. Most patients experienced a benign course with mild drowsiness; patients may be apathetic, withdrawn, stuporous and confused. Coma only occurred if over 20 mg/kg body weight of valproate had been ingested and may relate to hyperammonaemia.[86,87] Cerebral oedema has been reported,[88] and its onset may be delayed.[84] It resolves with supportive management, and is unrelated to the dose of valproate ingested.[88] There are no reports of permanent neurological sequelae following overdose, except for one case of blindness due to optic nerve atrophy, but in this case cerebral hypoxia was a more likely cause.[89] Unlike other anticonvulsant drug toxicity, dysarthria, nystagmus and ataxia are not features of poisoning. Asterixis of hands and feet may occur, however, as may myoclonic movements and seizures.[90,91] Hypotension is common, and nausea, vomiting and diarrhoea have all been reported. Occasionally they are hyperactive.[92] Acute toxicity seems to be less severe in patients who are regularly taking valproate.[92]

Hypernatraemia, hypoglycaemia, hypocalcaemia, hypophosphataemia and metabolic acidosis have all been reported[91,93] and, if present, are prominent at an early stage and are correctable with supportive management.

Massive overdoses have been associated with bone-marrow suppression.[94] Leucopenia and thrombocytopenia have also occurred following valproic acid overdose: appearing rapidly and resolving within one week.[89,95] Pancreatitis has been reported and rarely hepatotoxicity occurs.[95–97] Few fatalities have been reported.[91,95,96,98]

There is little correlation between the depth of coma and seizures and free or total serum valproate concentrations. Valproate assays, therefore, are of little value in the management of severely poisoned patients except to confirm the drug ingested.

In the majority of cases of valproate overdose, supportive management is all that is necessary to ensure complete recovery. The drug is rapidly absorbed and methods to prevent further absorption are therefore of limited value. Maintenance of good (2–3 l/day in an adult) urine output and discontinuation of all anticonvulsive drugs and hepatic enzyme inducers is usually sufficient to ensure recovery within 24–72 h. The airway should be maintained, and if respiratory depression is present, the patient may require assisted mechanical ventilation after endotracheal intubation. If the patient is comatose, is convulsing or has lost the gag reflex, gastric lavage may be considered after endotracheal intubation if a substantial overdose has been taken up to one hour previously.

Activated charcoal may adsorb valproate remaining in the gut, but its efficacy has not been evaluated. Farrar *et al.*[99] however describe the use of continuous nasogastric administration of activated charcoal at 0.25 to 0.5 g/kg/h together with sorbitol in a 26-month-old boy who had ingested a minimum of 4.5 g of enteric coated valproic acid, with reduction in the composite elimination half-life from that expected, and improvement in clinical state. Seizures should be treated with intravenous diazepam (0.1–0.3 mg/kg) to a maximum of 20 mg in an adult. This may be repeated in 10–20 min if required.

Naloxone was used in a 19-month-old boy who was unconscious after ingesting 2.25 g of sodium valproate.[86] No opiates were found on drug screening of his urine. A less dramatic effect was produced by naloxone in a 22-year-old man,[100] and while Farrar *et al.*[99] report reduction in apnoeic episodes, there was no improvement in conscious level. Connacher *et al.*[95] and Mortensen *et al.*[101] also found naloxone to be of no benefit. In general, the patients who did not respond to naloxone had taken large overdoses and had higher serum valproate concentrations than those who responded, and the doses of naloxone administered to unresponsive patients were lower. The therapeutic role and dose-response relationship of naloxone in valproate intoxication require further evaluation.

No studies are available to support the use of forced diuresis, haemodialysis, peritoneal dialysis, exchange transfusion or haemoperfusion in massive acute valproate overdosage.

However, when serum concentrations exceed those achieved by therapeutic doses of the drug, protein binding sites become saturated and the concentration of free valproate increases;[82,102] since it is of low molecular mass, it may be possible to remove it by haemodialysis. Four case reports have

been published describing the use of haemodialysis and/or haemoperfusion in the treatment of valproate overdose, but views on their efficacy are contradictory.[103] The use of haemodialysis and/or haemoperfusion is worthy of consideration in patients severely poisoned with valproate, but further assessment of their efficacy is required.

Lamotrigine

This is a relatively new drug which is used in addition to other anticonvulsants in the treatment of partial seizures and secondary generalized tonic-clonic seizures unresponsive to treatment with other anticonvulsants but its therapeutic role is continually evolving. Lamotrigine acts by stabilizing membranes and reducing the release of excitatory transmitters particularly glutamate and by blocking voltage-sensitive channels.[104]

It is metabolized in the liver largely by glucuronidation, and therefore is susceptible to enhanced metabolism by other enzyme inducers.[105] The half-life in therapeutic doses is 25–30 h and in overdose in one 26-year-old man was just under 10 h.[105]

A 26-year-old man ingested 1.35 g without developing serious toxicity, but patients with high concentrations develop symptoms of neurotoxicity including sedation, ataxia, diplopia, nausea and vomiting.[106] Hypertonia, nystagmus and widening of the QRS interval on the ECG have also been reported.

Gastric lavage is recommended if more than ten tablets have been ingested by an adult within 1–2 h. Activated charcoal should be given, although it is of unproven benefit. The cardiac rhythm should be monitored.

Vigabatrin

A relatively new anticonvulsant used for the treatment of complex partial seizures with or without secondary generalisation. It is often used as an adjunct when monotherapy has failed. It is an irreversible enzyme inhibitor of GABA aminotransferase.[107] Oral absorption of therapeutic doses is rapid and almost complete, and plasma concentrations peak at approximately 2 h after dosing. The elimination half-life is 5–7 h, but its duration of action is more than 24 h, because of irreversible binding to its target enzyme.[108] The drug is hydrophilic, distributed in total body water: penetration into CSF is dose-dependent.[109] Elimination occurs by urinary excretion.

There are very few reports of overdoses with vigabatrin.[110] Doses of 10 g per day have been ingested without serious effects. A concentration-effect relationship cannot be readily demonstrated.[111] Vertigo and tremor have been reported after ingestion of 14 g per day for 3 days,[112] and recovery was full. Drowsiness and coma have been reported after an overdose of 30 g with 250 mg of dipotassium chlorazepate. There was complete recovery from this overdose in 4 days, but either drug could have been responsible for the diminished conscious level. [112] Myoclonic jerks have been reported. One patient developed psychosis after taking an overdose of 8–10 g of vigabatrin which failed to resolve.[113] Chronic vigabatrin intoxication in animals causes intramyelinic oedema appearing as microvacuoles in brain white matter,[107] although there is no evidence for this in humans. Rodent studies show that vigabatrin can cause convulsions in high doses.

Gastric lavage should be performed if more than 12 g has been taken by an adult, or 2 g by a child, within 1–2 h. Activated charcoal should be given although it is of unproven efficacy. Measurement of serum drug concentration does not guide management, but confirms ingestion if this is in doubt.

Conclusions

Overdosage with anticonvulsant drugs is a serious problem and physicians should be particularly alert to its occurrence in the epileptic population. The majority of patients develop central nervous system or cardiovascular symptoms and signs of toxicity. Knowledge of overdosage with the newer anticonvulsant drugs such as lamotrigine and vigabatrin is limited, and clinicians should be encouraged to report any cases encountered in the literature.

Meticulous supportive care is required to achieve a good outcome in anticonvulsant drug poisoning; gastric lavage and activated charcoal should be given if the patient presents within 1–2 h of the overdose. Specific elimination methods such as haemodialysis or haemoperfusion are kinetically unfavourable and of doubtful clinical efficacy, as they tend to remove only a few therapeutic doses of tablets and fail to alter the clinical course of poisoning.

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