

Therapeutics Bulletin

Management of drug-induced seizures

Contributors: Dr Veshni Pillay-Fuentes Lorente[1], Dr Roland van Rensburg[1], Prof. Eric Decloedt[1] and Prof. Jonathan Carr[2]

[1]Division of Clinical Pharmacology, Department of Medicine
[2]Division of Neurology, Department of Medicine

PO Box 241, Cape Town, 8000, South Africa
Tel: +27 21 938 9045/9335, Fax: +27 21 938 9860

Many drugs in overdose can induce seizures. Drugs known to cause seizures in overdose include sympathomimetics (e.g. amphetamines, cocaine, methylphenidate), antidepressants (e.g. amitriptyline, citalopram, fluoxetine), anticholinergics (e.g. atropine, hyoscine), antihistamines (chlorpheniramine, diphenhydramine), and antimicrobials (e.g. imipenem/cilastatin, isoniazid).[1,2] Seizures occur as a result of an imbalance between inhibitory and excitatory neurotransmitters. This may be due to either an increase of excitatory neurotransmitters and/or decrease of inhibitory neurotransmitters.[3] Drug-induced seizures are distinct in that they result from diffuse neuronal excitability and not from a single epileptic focus in the brain.[3] A suitable treatment approach would therefore be to increase the inhibitory neurotransmitter effects of gamma-aminobutyric acid (GABA) to overcome the drug-induced diffuse excitatory effects. For this reason benzodiazepines are the first-line antiseizure drugs of choice for drug-induced seizures, similar to the management of status epilepticus.

However, phenytoin should not be used for further treatment of drug-induced seizures. Phenobarbital should preferably be used.

Why is phenobarbital the preferred second-line agent?

Phenobarbital (also known as phenobarbitone) is recommended as further treatment for drug-induced seizures since it potentiates the effect of GABA, similar to the benzodiazepines. Phenobarbital binds to a different site on the GABA receptor than benzodiazepines, prolonging the duration of the chloride channel opening with chloride influx, and ultimately increasing the inhibitory neurotransmitter effects. Benzodiazepines increase the frequency of chloride channel opening, and the addition of phenobarbital to benzodiazepines can act synergistically to potentiate the inhibitory effects of GABA.[3]

Why should phenytoin not be used in drug-induced seizures?

Phenytoin inhibits voltage-gated sodium channels increasing the threshold of depolarization and subsequently the propagation of electrical potentials from a single epileptic focus.[4] Phenytoin is considered to be less effective in reducing diffuse neuronal excitability or increasing the seizure threshold in patients presenting with drug-induced seizures.[3] In addition, phenytoin is associated with adverse cardiovascular effects such as dysrhythmias and hypotension. Phenytoin could therefore potentially exacerbate the cardiovascular toxicity associated with many drugs when taken in overdose.[4]

Management of drug-induced seizures

1. Manage and secure airway, breathing, and circulation according to basic principles.
2. Exclude immediate, reversible causes of seizures, such as electrolyte abnormalities and hypoglycaemia.
3. 1st line treatment: **Benzodiazepines**

   Lorazepam

   Dose: 4 mg IV at a rate of 2 mg/minute.[5]

   Repeat dose if required. Maximum dose 8 mg over 12 hours.

   If lorazepam is not available, consider:

   Midazolam

   Dose: 10 mg, IM/IV, slow IV injection at a rate of approximately 1 mg over 30 seconds. Repeat once after 5–10 minutes if necessary.[6,7]

   OR

   Diazepam

   Dose: 10 mg, IV, not faster than 2 mg/minute, repeat once after 5–10 minutes if necessary.[6]

Note: Where isoniazid-induced seizures are suspected, administer pyridoxine (vitamin B6) immediately.

Pyridoxine

Dose: Estimate the isoniazid ingestion and give an equivalent pyridoxine dose up to a maximum of 5 g pyridoxine. If the ingested quantity of isoniazid is unknown, administer 5 g immediately. Repeat the pyridoxine dose if necessary.[8]

Pyridoxine is usually available as 25 mg tablets. The required dosage (e.g. 200 tablets = 5 g if unknown isoniazid amount) can be crushed, mixed with water, and administered via a nasogastric tube. Parenteral vitamin B preparations containing vitamin B6 may be available in the private sector and access should be discussed with the Clinical Pharmacologist on call.

4. 2nd line treatment: **Phenobarbital**

   Dose: 15 – 20 mg/kg IV at a rate no faster than 100 mg/min.[5]

   Maximum dose 1 000 mg – 1 500 mg.

5. Drug-induced seizures not responding to 1st and 2nd line treatments:

   Consider intubation and ventilation.

   Propofol

   Loading dose: 1 – 2 mg/kg IV.

   Maintenance dose: 1.2 mg/kg continuous IV infusion.

Contact the Clinical Pharmacologist on call as needed for assistance. All drug-induced seizures are serious adverse events and we encourage reporting via the Clinical Pharmacologist on call.



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