Early detection and management of neurological serious adverse events in relation to the administration of anthelminthic medicines to people with asymptomatic neurocysticercosis

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1. Introduction

Preventive anthelminthic chemotherapy programmes involving the administration of praziquantel or albendazole are used to control various neglected parasitic diseases in endemic communities. To control taeniasis, the administration of a single dose of praziquantel or albendazole for 3 consecutive days to persons with neurocysticercosis is not without risk, although the reported incidence of serious adverse events seems to be low. In persons with neurocysticercosis, it is known that the time between infection and symptoms can be as long as 20 years; thus, administration of anthelmintics could occur in individuals who have viable cysticerci in the brain but no symptoms.

Although preventive chemotherapy with praziquantel (or 3 consecutive doses of albendazole) is contraindicated in individuals with prior neurological signs/symptoms, this will not prevent the occurrence of serious adverse events, as these can occur in a healthy individual after anthelmintic intake. Such events are uncommon, but their severity requires that all personnel involved in preventive chemotherapy be aware of them.

Preventive chemotherapy for taeniasis carries no risk of a neurological serious adverse event if the anthelminthic administered is niclosamide, as it is

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not absorbed through the intestinal tract and therefore does not reach the central nervous system.

Two main neurological serious adverse events can occur when providing anthelminthics to individuals with neurocysticercosis: (i) any epileptic seizure including status epilepticus and (ii) intracranial hypertension. Both are related to the development of an inflammatory reaction around the cysts, following the administration of anthelminthics. They are infrequent, but their potential severity deserves attention.

Status epilepticus and intracranial hypertension are neurological emergencies requiring immediate evaluation and management to avoid significant morbidity or mortality. The person should be taken to a hospital as soon as possible. Neuroimaging (i.e., a computed tomography scan of the brain) should also be performed as soon as possible; neurosurgery may be required in cases of intracranial hypertension not responsive to steroid administration.

As preventive anthelminthic chemotherapy programmes are usually conducted in rural areas where health infrastructure is precarious and usually far from hospitals, this document focuses on the emergency management of these complications in these areas, which generally lack the infrastructure to manage respiratory distress. We also include a previously published flowchart for the emergency management of epilepsy in settings where management of respiratory distress is possible (1). Therefore, phenobarbital and lorazepam are found only in the mhGAP flowchart.

2. Management of status epilepticus 

Definition of status epilepticus

• When an individual has a generalized tonic-clonic seizure lasting more than 5 minutes.
• When an individual has three or more recurrent generalized tonic-clonic seizures with no return to baseline consciousness between them.
• When an individual has a focal seizure or absence seizure lasting more than 10 minutes.

At the health centre

First general measures (in the case of any epileptic seizures):

• Check AIRWAY, BREATHING, CIRCULATION (“ABCs”). Ensure the person has nothing in their airway, is breathing well and has a stable pulse.
• Check BLOOD PRESSURE, TEMPERATURE and RESPIRATORY RATE.
• Start timing the duration of the convulsions, if possible.
• Make sure the person is in a safe place (i.e., clear the area around the person of any hard or sharp objects to prevent injury).
• Put the person down on their side to help keep their airway clear.
• Loosen any clothing around the neck, take off eyeglasses, and place something soft under the head (if available).
• DO NOT PUT ANYTHING INTO THE MOUTH AS THIS CAN INJURE THE TEETH OR THE JAW AND CAN OBSTRUCT THE OUTFLOW OF VOMIT OR SALIVA.

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2 Source: reference (1).
3 Adapted from reference (2).
• DO NOT LEAVE THE PERSON ALONE.

If the crisis continues, and status epilepticus occurs:

• Give medication to stop convulsions (emergency medication):
  - diazepam rectally (adult 10 mg, child 1 mg/year of age), OR
  - midazolam buccally/intranasally (5–10 mg adult, child 0.2 mg/kg).

• If the above are not possible, slow intravenous administration (same products, same doses over 3–5 minutes, or lorazepam (adult 4 mg, child 0.1 mg/kg)) should be used, taking care of the risk of respiratory depression.

• If the crisis persists after 10 minutes, repeat the same emergency medication.

• If the crisis persists, if the hospital is far away, and if an intravenous route can be established at the health centre, give glucose intravenously (adult: 25–50 mL of 50%; child: 2–5 mL/kg of 10%), and administer:
  - phenoxyin: 15–20 mg/kg intravenously up to a maximum dose of 1 g, over 60 minutes (risk of significant damage (cellulitis, necrosis) if extravasates. A good intravenous line is mandatory),

  OR

  - valproic acid: 20 mg/kg intravenously once up to a maximum dose of 1 g, over 30 minutes,
  WITH

  - an anti-inflammatory: dexamethasone 0.4 mg/kg/day in divided doses every 8 hours (intravenously or intramuscularly).

Take the person as soon as possible to the hospital to continue the management and for a precise diagnosis of the causes (neuroimaging, in particular).

3. Management of intracranial hypertension

Intracranial hypertension should be suspected in a person who develops progressive headaches, a few hours to a few days after anthelminthic administration, who does not respond to common pain medication (acetaminophen, nonsteroidal anti-inflammatory medicines) and may be progressively associated with nausea, vomiting, focal neurological deficits, impaired vision (decreased visual acuity and/or diplopia) and consciousness.

This is an emergency that should lead local health care providers to immediately refer the person to a hospital with radiological and surgical capabilities.

Before the person arrives at the hospital, it is recommended that the person’s head be held elevated at 30 degrees (but not more than 45 degrees). This can be a beneficial adjunct to reducing intracranial pressure.

If the hospital is remote, it is recommended that an intravenous line be established before leaving the health centre to administer the first dose of dexamethasone, an anti-inflammatory medicine (0.4mg/kg/day in divided doses every 8 hours by direct injection over 1–2 minutes or diluted in 0.9% sodium chloride; that is, a first administration of 0.13 mg/kg); or methylprednisolone, 160 mg once daily, by intravenous infusion (in 0.9% saline) over at least 30 minutes. If this is not possible, a first intramuscular injection of dexamethasone (0.13 mg/kg) should be given. If both options (intravenous (IV) and intramuscular (IM)) are not available, oral corticosteroids (8 mg of dexamethasone or 50 mg of prednisone) should be
administrated. It should be noted that if the person's clinical condition does not improve with this standard treatment, repeat administration (IV, IM or oral) may be required prior to hospital admission. At the hospital, fundus examination should be performed to confirm the diagnosis by showing optic disc swelling (papilledema), although its absence does not exclude intracranial hypertension.

Intracranial hypertension can have a variety of etiologies and a **computed tomography scan is urgently needed** to define the causes and best management (surgery may be required). If the event occurred in an area endemic for *Taenia solium*, within 2–5 days after preventive chemotherapy with praziquantel or albendazole, the most likely cause is the inflammation around the cysts. Two presentations may occur: intracranial hypertension due to inflammation of multiple parenchymal cysts that cause global brain oedema, or intracranial hypertension due to hydrocephalus, a consequence of inflammation of cysts located mainly in the ventricular system. In both cases, anti-inflammatory treatment should be the first therapeutic measure.

If not done before, an intravenous line should be placed, and treatment started (or followed) with **dexamethasone 0.4 mg/kg/day (in divided doses every 8 hours, intravenously or intramuscularly)** or methylprednisolone, 160 mg once daily, by intravenous infusion over at least 30 minutes.

### 4. Recommended medicines to be available at different health levels to deal with serious adverse events related to neurocysticercosis

**At all health centres**

- Diazepam (to be administered rectally) OR midazolam (to be used buccally/intranasally).
- Oral or IM corticosteroids (dexamethasone, prednisone)

**At health centres with intravenous capability**

- Valproic acid OR phenytoin (ideally both).
  - Valproic acid should not be used in pregnancy and in women and girls of childbearing potential.
- IV corticosteroids (dexamethasone, prednisolone, methylprednisolone)
5. Flow chart for emergency management of epilepsy in settings where management of respiratory distress is possible (from (1))
Have the convulsions stopped within 10 minutes of 1st dose of emergency medication?

NO ➔ Proceed to EPI 1 (Assessment)

YES ➔ GIVE 2nd DOSE OF EMERGENCY MEDICATION

Have the convulsions stopped?

NO ➔ Proceed to EPI 1 (Assessment)

YES ➔ REFER URGENTLY TO HEALTH FACILITY

DO NOT GIVE MORE THAN 2 DOES OF EMERGENCY MEDICATION

EPILEPSY

EPILEPSY ➔ Emergency

IS THE PERSON IN STATUS EPILEPTICUS?

➢ Convulsions continue after 2 doses of emergency medication, DB
➢ No recovery in between convulsions

NO ➔ Continue to check AIRWAY, BREATHING, and CIRCULATION (ABCs)
➢ Give oxygen
➢ Monitor need for intubation/ventilation continuously

YES ➔ STATUS EPILEPTICUS IS LIKELY

Management should occur in health facility

GIVE ONE OF THE FOLLOWING MEDICATIONS INTRAVENOUSLY

➢ VALPROIC ACID: 20 mg/kg i.v. once, up to maximum dose of 1 g, over 30 min
➢ PHENOBARBITAL: 15-20 mg/kg i.v. up to maximum dose of 1 g, over 150 mg/min
   *If no i.v. access, can give i.m. phenobarbital (same dose as i.v.)
➢ PHENYTOIN: 15-30 mg/kg i.v. up to max dose of 1 g, over 60 min
   ➢ give second i.v. line (DIFFERENT FROM DIAZEPAM)
   ➢ ADMINISTRATION CAUSES SIGNIFICANT DAMAGE IF EXTRAVASATES, MUST HAVE GOOD i.v. LINE
6. Simplified chart for remote primary health centres with limited resources

Management of neurological serious adverse events after mass drug administration in rural areas

**Headache**
- Paracetamol or ibuprofen
- Monitoring

**Seizures**
- Diazepam intrarectal (x2 if necessary)*
- Monitoring

**Improvement**
- Home recommendation
- EMERGENCY
  - Dexamethasone intravenously***
  - Transfer to hospital

**Worsening**
- Home recommendation
- EMERGENCY
  - Phenytoin or valproate acid intravenously**
  - Dexamethasone intravenously***
  - Transfer to hospital

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* If management of respiratory distress is possible, or intrarectal application is not feasible, intravenous administration of lorazepam or diazepam may be preferred
** If management of respiratory distress is possible, phenobarbital can also be an option
*** Dexamethasone or prednisolone or methylprednisolone
7. References and companion resources

