4. GUIDELINES FOR THE USE OF ANTI-EPILEPTICS IN PALLIATIVE CARE

4.1 GENERAL PRINCIPLES

- Anti-epileptic drugs should be considered in all patients with primary or secondary brain tumours who have a history of one or more seizures.\(^1,2\)
- The acute management of seizures includes maintaining the airway, emergency drug treatment and a reassessment of the anti-epileptic drugs prescribed.\(^3\)
- A prolonged seizure in a patient who is not in the terminal phase requires immediate emergency management, resuscitation and possible admission to hospital.\(^3\)
- A clear distinction should be made between anti-epileptic drugs for the control of seizures and corticosteroid medication for control of symptoms due to tumour oedema e.g. headaches / vomiting due to raised intracranial pressure or focal neurological signs.\(^4\)
- Increasing the dose of corticosteroid is not recommended for seizures in the absence of new neurological symptoms / signs or evidence of raised intracranial pressure. However, as seizures may increase cerebral oedema, patients who develop new seizures in spite of anti-epileptic drugs may need optimization of anti-oedema therapies before modifying anti-epileptic drugs.\(^4\)
- In the terminal phase, the aim is to prevent and control seizures with the minimum of disruption for the patient. Midazolam or clonazepam may be given without the need for transfer to hospital.\(^5,6\)
- Corticosteroids can be discontinued in the terminal phase unless they are required for control of raised intra-cranial pressure e.g. headaches/vomiting or seizures.\(^5,6,7\)

4.2 GUIDELINES

- Table 4.1 illustrates the World Health Organisation classification of seizures.\(^8\) [Level 4]

4.2.1 Antiepileptic medication

- The ideal drug for controlling seizures in palliative care patients is not easy to establish due to the variety of metabolic interactions and potential side effects.\(^4\) [Level 4]
- There are a variety of anti-epileptic drugs available and Table 4.2 gives further details.\(^6,9\) The choice of drug will depend on the type of seizure.\(^3,6\) [Level 4]
- Clinical assessment should be used to optimise the dose of the anti-epileptic drug with the minimum of side effects.\(^3,9,10\) Monotherapy should be used whenever possible.\(^3\) [Level 4]
- It has been considered appropriate to use only new anti-epileptic drugs when the older drugs (e.g. carbamazepine, sodium valproate) have been unsuccessful, or where they are unsuitable due to contraindications or drug interactions. However, lamotrigine or carbamazepine are now considered first line therapy for partial onset epilepsy, and lamotrigine has the advantage of being better tolerated with few drug interactions.\(^11\) [Level 4]
- Clobazam and clonazepam can be used for myoclonic or generalised tonic-clonic seizures.
- They will be effective for short-term use but patients may develop tolerance to the anti-epileptic effects of the benzodiazepines. In addition, any benefit may diminish over time although this may not always be relevant in the palliative care setting. Despite the possibility of tolerance with benzodiazepines many patients do get a sustained response to drugs such as Clobazam.\(^3\) [Level 4]
The metabolism of dexamethasone is accelerated by carbamazepine and phenytoin which reduce the steroid effect. The metabolism of phenytoin can be either increased or decreased by dexamethasone so altering the anti-epileptic effect. When using these drug combinations it may be necessary to increase the dose of anti-epileptic and / or corticosteroid. Drug levels are useful for patients on phenytoin. Levels can be used to guide dose titration if seizures are poorly controlled or side effects become apparent. [9, 10, 12, 13] [Level 3]

<table>
<thead>
<tr>
<th>Table 4.1</th>
<th>International Classification of Seizures [8] [Level 4]</th>
</tr>
</thead>
<tbody>
<tr>
<td>2. Partial/focal (involves a localised area of brain). Note: May spread to involve the whole cortex i.e. secondary generalisation.</td>
<td>Simple (no effect on conscious level). Complex (interrupt consciousness to varying degree). Secondary generalised tonic-clonic seizures.</td>
</tr>
</tbody>
</table>

### 4.2.2 Management of seizures

- An acute seizure may settle spontaneously. Intranasal, buccal or subcutaneous midazolam should be available for the control of prolonged or recurrent seizures. Alternatively, lorazepam 2mg-4mg can be given intravenously or subcutaneously. [6, 10] [Level 4] For more information on intranasal midazolam see Figure 4.1.

- If seizures continue despite above measures, consider transfer to hospital for emergency management. A secure airway should be established, oxygen should be administered, cardio-respiratory function should be assessed and intravenous access should be established. Administer diazepam 10mg-20mg rectally and repeat 15 min later if status continues to threaten. Alternatively, consider giving midazolam 10mg via the buccal route or intravenously. [3] [Level 4]

- Clusters of seizures (i.e. with recovery in between attacks) may respond to oral clobazam.

- Starting dose is 10mg per day and the usual maintenance dose is 10mg-20mg twice daily. The maximum dose is 30mg twice daily. This drug can be used for a short period if required e.g. a few days. [10] [Level 4]

### 4.2.3 Use of anti-epileptics in the terminal phase

- In the terminal phase convert oral anti-epileptics to a continuous subcutaneous infusion of midazolam 30mg-60mg/24 hours. Clonazepam is an alternative and will require less volume. [3, 5, 6, 9, 10] [Level 4]

- If seizures are not controlled with midazolam / clonazepam, consider a change to phenobarbital 200mg-600mg/24h via a continuous subcutaneous infusion. Phenobarbital can be mixed with sodium chloride 0.9% or water, although anecdotal evidence suggests that may get less site reactions with sodium chloride 0.9%. It is generally recommended that a separate syringe driver should be used because of the high pH of the drug. [6] [Level 4]

- Discontinue oral corticosteroids unless needed for control of symptoms due to raised intracranial pressure e.g. headaches, vomiting, seizures. Dexamethasone may be administered by subcutaneous bolus injection (for doses <8mg daily) or by a CSCI. [7, 10, 14] [Level 4]
<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Indication</th>
<th>Dose of drug</th>
<th>Additional comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepine</td>
<td>Partial onset</td>
<td>Starting dose 100mg-200mg od-bd. Increase by 100mg-200mg every two weeks. Usual dose is 800mg-1.2g daily in divided doses. Maximum dose is 2g daily.</td>
<td>Titrated slowly to avoid drowsiness and rash. Beware of drug interactions.</td>
</tr>
<tr>
<td>Clobazam</td>
<td>Partial onset</td>
<td>20mg-30mg daily orally. Maximum dose is 60mg daily.</td>
<td>Not licensed for monotherapy.</td>
</tr>
<tr>
<td>Clonazepam</td>
<td>Myoclonic / tonic-clonic</td>
<td>1mg-8mg daily in divided doses orally. 1mg-8mg via CSCL.</td>
<td>Can be given subcutaneously via a syringe driver. May be useful in the terminal phase.</td>
</tr>
<tr>
<td>Diazepam</td>
<td>Acute treatment of tonic-clonic</td>
<td>10mg stat. Orally/intravenously/rectally.</td>
<td>There are many drug interactions. Useful for emergency management of seizures.</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>Partial onset</td>
<td>Seek specialist advice.</td>
<td>Complicated titration regime. Do not use for myoclonus.</td>
</tr>
<tr>
<td>Midazolam</td>
<td>Tonic-clonic</td>
<td>10mg-60mg over 24 hours via a subcutaneous infusion.</td>
<td>Useful in the terminal phase. Can also be given intranasally.</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>Generalised / Partial</td>
<td>60mg-180mg nocte orally. For stat dose give 100mg via an intramuscular/intravenous injection. Give 200mg-600mg over 24 hours via a subcutaneous infusion.</td>
<td>Can get problems on withdrawal. Can be given orally, im, sc, iv. Anecdotal evidence suggests may get fewer side reactions if use sodium chloride 0.9% as diluent although water can also be used.</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>Partial</td>
<td>Starting dose is 150mg-300mg daily orally. Increase gradually in 50mg increments. Give either as single dose or twice daily. Usual maintenance dose is 200mg-500mg/day.</td>
<td>Can be used for rapid control of seizures. Can be given intravenously. Beware of drug interactions. Potent enzyme inducer.</td>
</tr>
<tr>
<td>Sodium Valproate</td>
<td>Generalised / Focal</td>
<td>Starting dose is 300mg bd. Increase by 200mg/day at 3 day intervals. Usual maintenance dose is 1g-2g/day. Maximum dose 2.5g/day.</td>
<td>Has a better side effect profile compared to some of the other anti-epileptics. Can be given intravenously.</td>
</tr>
<tr>
<td>Topiramate</td>
<td>Partial onset</td>
<td>Seek specialist advice.</td>
<td>Mainly used by neurologists only.</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>Partial onset</td>
<td>Starting dose is 250mg bd. Increase by 250mg bd every two weeks. Usual maintenance dose is 1000mg-3000mg daily.</td>
<td>Generally well tolerated but can cause mood disturbance.</td>
</tr>
<tr>
<td>Oxcarbazine</td>
<td>Partial onset seizures</td>
<td>Starting dose 150mg-300mg bd. Increase by 150mg-300mg every one to two weeks. Usual maintenance dose is 600mg-900mg bd.</td>
<td>May be better tolerated than carbamazepine. May cause hyponatraemia.</td>
</tr>
</tbody>
</table>
**Figure 4.1  Using intranasal midazolam**²,¹⁶,¹⁷ [Level 4]

- Paediatrics has developed the use of intranasal midazolam for sedation and the management of seizures.
- Studies on seizure control in children demonstrate that it is as effective as intravenous diazepam. There is a shorter time to starting treatment and to control of seizures.
- The dose used in adults is determined by weight, i.e.
  - <50kg   5 mg intranasal midazolam.
  - >50kg   10 mg intranasal midazolam.
- Advantages of intranasal midazolam include:
  - The drug is lipid soluble and will cross the nasal mucosa and blood-brain barrier.
  - There is a rapid rise in blood and cerebrospinal fluid levels.
  - Peak plasma concentrations are reached in 5-12 minutes.
  - There is no need for intravenous access.
  - The drug can be administered by a trained carer.
  - It may be more acceptable than the rectal route.
- The buccal route can be used as an alternative to the intranasal route if there is excessive head movement due to seizures.
- The injection solution 10mg/2ml is used. The required dose is drawn up in a 2ml syringe and given via a Mucosal Atomization Device.
- Half of the dose is given in each nostril.
- For patients at home, the dose can be drawn up by the nurse and kept in the fridge for up to one month. It can then be given by a trained carer if the need arises.
- The Mucosal Atomization Device can be washed and reused but should only be used for a single patient.
- The intranasal route is an unlicensed route for administration of midazolam and the prescriber takes responsibility for its use.
- An information leaflet regarding intranasal midazolam for patients and carers is available on request from The Hospice of the Good Shepherd, Chester.

### 4.3 STANDARDS

1. For all patients with primary or secondary brain tumours, the following information should be documented in the case notes:¹⁴ [Grade D]
   - History of seizures including the frequency and type.
   - Anti-epileptic drug(s) used and the dose(s).
2. The dose of corticosteroids should not be increased if seizures occur in the absence of new neurological symptoms / signs or evidence of raised intracranial pressure, unless the patient is also taking phenytoin or carbamazepine.⁴,¹³,¹⁴,¹⁸,¹⁹ [Grade D]
3. All patients with a history of seizures should have access to medication that can be given in the event of an episode of prolonged seizures. 3,14 [Grade D]

4. If a patient is in the terminal phase, oral anti-epileptic drugs should be converted to midazolam / clonazepam via a continuous subcutaneous infusion. 3,5,6,9,10 [Grade D]

5. If a patient is in the terminal phase and unable to take oral medication, corticosteroids should be discontinued unless they are needed for control of symptoms related to raised intracranial pressure. If they are required, they can be given via the subcutaneous route. 6,14 [Grade D]

4.4 REFERENCES


### 4.5 CONTRIBUTORS

<table>
<thead>
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