GUIDELINE

Title: Chronic Seizure Guideline for Pharmacological Management in Palliative Care Patients

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Approved By: Clinical Practice Committee

A. PURPOSE:

To provide a general and pharmacological management strategy for recurrent seizures

B. ETIOLOGY:

Seizures are often encountered in palliative care practice. The major etiologies of seizures are: primary/metastatic intracranial lesions, AIDS, or toxic metabolic encephalopathy potentially secondary to high-dose opioids or phenothiazines. Seizures occur in about half of palliative persons with brain tumors during the course of the illness (1).

C. GENERAL PROCEDURE:

1) Palliative persons and their families often are bothered by and fearful of the symptoms of seizure and should be counseled about what to expect and do should a seizure occur. Families should be counseled that seizures usually are brief and self-limited and rarely the direct cause of a patients' death (2).
2) If prepared with immediate first-aid skills (e.g. prevention from self-injury, turning on his/her side, oxygen if applicable) and prepared with anticonvulsants that can be administered conveniently, palliative persons and families may be reassured and unnecessary emergency room visits avoided (see clinical practice guideline for "Acute Pharmacological Management of Acute Seizures").
3) Palliative persons who present with seizures should be cared for according to the available nursing procedures on sites.
4) Hypoglycemia is the most common metabolic cause of seizure activity. The only treatment required for the patient may be IV glucose. Importantly, prolonged seizure activity may also cause hypoglycemia, so that the cause-and-effect relationship may sometimes be reversed and further therapy will be required.

D. LACK OF EVIDENCE FOR PROPHYLACTIC USE OF ANTICONVULSANTS

1) In palliative persons with newly diagnosed brain tumors, anticonvulsants are not effective in preventing first seizure. Because of their lack of efficacy and their potential side effects, **prophylactic anticonvulsants should not be used routinely** in palliative persons with newly diagnosed brain tumors (1).

2) In palliative persons with brain tumors who have not had a seizure but have already been commenced on anticonvulsants, tapering and discontinuing anticonvulsants after the first postoperative week is appropriate, particularly in those palliative persons who are medically stable and who are experiencing anticonvulsant-related side effects (1).

3) Subgroup of palliative persons with brain tumors (e.g. those with melanoma, hemorrhagic lesions, multiple metastases, tumors located near the Rolandic fissure, slow-growing primary brain tumors) have a higher risk of developing seizures. There is **no evidence that prophylactic anticonvulsants are more effective** in this group (1).

E. USE OF ANTICONVULSANTS

1) Phenytoin and phenobarbital are the most widely used anticonvulsants for seizure control, and valproic acid is the second most widely used anticonvulsant. These three anticonvulsants operate through different molecular mechanisms to prevent seizures, and together represent three primary mechanisms (i.e. sodium channels, potassium channels and inhibitory transmission) (3)
2) The response to therapy is individualized and highly variable so, the dose should be titrated to clinical response rather than to a specific serum level (3).
   Recommended doses are shown in Table 2. Adjustment dosage should also take into consideration due to risk of dose-related toxicities.
3) The response to anticonvulsant therapy is highly variable. If the palliative person has side effects before reaching the target dose then a lower dose should be used, regardless of the serum concentration. Conversely, if the patient continues to have seizures but is free of side effects, a higher dose should be used even if the patient's serum drug concentration is high. Serum levels may be more useful to guide increases in dosing of phenytoin than other anticonvulsants owing to its nonlinear pharmacokinetics (4).
4) If the palliative person continues to have seizures, (a) higher dose of current anticonvulsant, if the person is free of side effects; (b) alternative anticonvulsant; (c) adding an adjunctive anticonvulsant; may be considered (4). Clinical assessment and consider possible contributing etiology (e.g. abnormal electrolytes, drug-drug interactions) is necessary.
5) There are no prospective randomized studies to evaluate the efficacy of the newer anticonvulsants as compared to classical anticonvulsants (3).

Table 1. Efficacy of anticonvulsants for common seizure types (adapted from ref 3)

Drug	Partial	Tonic-clonic	Absence	Myoclonic	Atonic/tonic
Phenytoin	+	+	−	−	0
Carbamazepine	+	+	−	−	0
Sodium valproate	+	+	+	+	+
Phenobarbital	+	+	0	?+	?
Benzodiazepines	+	+	?	+	+
Gabapentin	+	+	−	−	0

+ = efficacy; ?+ = probable efficacy; 0 = ineffective; − = worsens seizures; ? = unknown.

- Benzodiazepines may be used in the palliative person. Information is included in other guidelines. Refer to the use of benzodiazepines in the guidelines for "management of acute seizures" and "use of midazolam for palliative sedation".

Table 2. Dose of anticonvulsants (adapted form ref 4, 5, 6, 7,)

Drug Pharmacokinetics	Recommended indication	Starting dose	Maintenance	Interactions/Side effect	Incidence	Management
Phenytoin bioavailability 85-90%; half-life 10-34hr(dose dependent); time to steady state 9-40days	simple/complex partial, general tonic-clonic seizure	300 mg/d po	200 mg qd-300mg bid po	alter metabolism of anticoagulants, other anticonvulsants (dexamethasone reduce the level of phenytoin)	common	dosage adjustment
				rash	5-10%	discontinue if rash involves mucous membranes or is accompanied by fever or pain
				gingival hypertrophy	25%	transient dosage reduction or discontinue
				mild hirsutism	frequent	
Carbamazepine bioavailability 70-90%; half-life 18-54hr(initial dose), 19-20hr(repeated dose); time to steady state 21-28days	simple/complex partial, general tonic clonic seizure	200 mg bid po	800-1200 mg/d po	may stimulate the metabolism of own/other anticonvulsants	common	dosage adjustment
				vertigo, diplopia, drowsiness, confusion	dose-related	dosage adjustment or switch to other anticonvulsants
				dermatologic reaction (Steven-Johnson syndrome)	apprx 4% (very rare)	transient dose adjustment(discontinue)
				transient leucopenia	10-20%	monitor CBC/ switch to others if persistent
				aplastic anemia	occasional	discontinue

Valproic acid bioavailability 100%; half-life 5-20hr; time to steady state 1-3days	Broad spectrum	250-500 mg po bid	500 mg bid-1000 mg tid	gastrointestinal irritation		consider dosage reduction
				behavioral change, increase in appetite, weight gain	frequent	
				thrombocytopenia and platelet dysfunction	20-30%, may be transient	monitor, discontinue if significant
Phenobarbital bioavailability 95-100%; half-life 46-136hrs; time to steady state 14-21days	simple/complex partial, general tonic-clonic seizure	60-90 mg qhs sc	60-120 mg/d sc maximum recommended dose: 180-300 mg/d	may stimulate the metabolism of other drugs	common	dosage adjustment
				drowsiness, somnolence	common	tolerance usually develops with long-term administration
				dermatologic reaction	rare	transient dosage adjustment
				contraindication for porphyria		
Gabapentin bioavailability 60% or lower at higher doses; half-life 5-40hr; time to steady state 1-2days	Adjuvant therapy of partial seizure and tonic-clonic seizure	300 mg tid-qid po	900-3600 mg/d po	somnolence, dizziness, tremor, memory deficit, fatigue	occasional	dose adjustment

- Information on the pharmacokinetics of anticonvulsants in palliative persons is very limited. It is recommended to monitor for side effects closely, given that palliative persons are susceptible to dehydration, hypoalbuminemia, and drug-drug interactions due to polypharmacy for control of other symptoms.
- For information on other routes of administration, contact the site-specific pharmacy.

Suggested readings:

Glantz M., Cole B., Forsyth P. Practice parameter: Anticonvulsant prophylaxis in patients with newly diagnosed brain tumors. Report of the quality standards subcommittee of American Academy of Neurology. Neurology 54:1886-93, 2000.

Arnold S., Patchell R. Diagnosis and management of brain metastases. Hematology / Oncology Clinics of North America, 15: 1085-107, 2001.

Brodie M.J, Kwan P. Staged approach to epilepsy management. Neurology, 58: S2-8, 2002.

Holland K.D. Efficacy, pharmacology, and adverse effects of antiepileptic drugs. Neurologic Clinic 19:313-45, 2001.

Information for pharmacokinetics of anticonvulsants:

Drug Fact and Comparisons. Feb 2002.

diPiro J. et al. Pharmacotherapy; a pathophysiological approach. Section 6: Neurologic disorders 1999.

Herfindal E., et al. Textbook of Therapeutics; drug and disease management. 7th ed. Chapter 52 seizure disorders 2000.