

Phenytoin for the Prophylaxis of Posttraumatic and Postcraniotomy Seizures

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ABSTRACT

Patients with traumatic head injury and those who have undergone neurosurgery are considered at greater risk for seizures and are routinely given phenytoin for prophylaxis. The author conducted a literature review on the topic of seizure prophylaxis with phenytoin in posttraumatic and postcraniotomy patients. For posttraumatic seizures, phenytoin appears beneficial in preventing only early seizures (defined as occurring up to 1 week after injury). Phenytoin prophylaxis showed a beneficial effect after craniotomy in only one trial. On the basis of the literature review, prescribing guidelines were developed at the author's institution. Patients with traumatic head injuries and those who have undergone craniotomy receive phenytoin prophylaxis for 7 days after the injury or the craniotomy. Prophylaxis is not given for late seizures; however, anticonvulsant treatment is started if a seizure occurs.

Key words: phenytoin, posttraumatic, postcraniotomy, seizure prophylaxis

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RÉSUMÉ

Les patients victimes de traumatismes crâniens et ceux ayant subi une neurochirurgie auraient un risque plus élevé de crise d'épilepsie et reçoivent systématiquement de la phénytoïne en prophylaxie. L'auteur a passé en revue la littérature traitant de la prophylaxie à la phénytoïne des crises chez les patients ayant subi un traumatisme ou une craniotomie. Dans les cas de crises post-traumatiques, la phénytoïne semble être bénéfique pour prévenir les crises précoces (définies comme celles survenant moins d'une semaine après le traumatisme). Le traitement prophylactique post-craniotomique à la phénytoïne a montré un effet bénéfique dans seulement un essai. En se fondant sur la revue de la littérature, l'établissement auquel est rattachée l'auteur a élaboré un guide de prescription. Les patients ayant subi un traumatisme crânien ou une craniotomie reçoivent un traitement prophylactique à la phénytoïne de sept jours suite au traumatisme ou à la craniotomie. Le traitement prophylactique n'est pas prescrit dans les cas de crises tardives. Cependant, un traitement anticonvulsivant est amorcé si des crises surviennent.

Mots clés : phénytoïne, post-traumatique, post-craniotomique, prophylaxie anti-crise

INTRODUCTION

Patients who have sustained trauma to the head and neurosurgical patients are considered to be at increased risk for seizures and as such are often given phenytoin as prophylaxis.¹⁵ This article reviews the literature (on the basis of a MEDLINE search for the period 1980 to 1998) on the topic of seizure prophylaxis with phenytoin in posttraumatic and postcraniotomy patients and presents the recommendations that have been adopted by our institution.

PROPHYLAXIS OF POSTTRAUMATIC SEIZURES

The occurrence of posttraumatic seizures depends on the severity of injury. Early seizures, defined as occurring up to 1 week after injury, occur in 1% to 2% of patients with mild to moderate head injury and in 10% to 30% of those with severe head injury. Late seizures, defined as occurring more than 1 week after injury, occur in less than 5% of patients with mild to moderate head injury and in 10% to 50% of those with

severe head injury.^{2,4} Seizures have been associated with brain damage, increases in accidental injuries, and increased mortality rate.⁴ Because seizures have a negative impact on outcome, these patients are commonly given phenytoin to prevent seizures.

Early clinical trials that studied the use of phenytoin to prevent seizures after head injury showed a beneficial effect (Table 1). Wohns and Wyler⁶ published a retrospective, comparative study of 62 patients with severe head injury. The frequency of late seizures was higher in the untreated historical control group than in the group treated with phenytoin (50% and 10%, respectively). Servit and Musil⁷ prospectively studied 167 patients with head injury and compared phenytoin (combined with phenobarbital) prophylaxis with no treatment. Again, the frequency of seizure was higher in the control group than in the treatment group (24% and approximately 2%, respectively). These studies formed the basis for the clinical practice of initiating phenytoin prophylaxis after head injury and continuing such therapy for 3 months to 2 years.

The validity of these early trials has been questioned. The main areas of concern relate to study design: these studies were not randomized, double-blinded, or placebo-controlled.^{3,4}

Penry and colleagues⁸ conducted a randomized, double-blind trial with 125 patients to compare phenytoin (combined with phenobarbital) with placebo. No significant difference was observed between the treatment and control groups. The authors concluded that prophylactic treatment with phenytoin and phenobarbital does not reduce the frequency of posttraumatic seizures. No distinction was made between early and late seizures.

Young and colleagues published 2 trials evaluating the efficacy of phenytoin in preventing early and late posttraumatic seizures. Both studies were prospective, randomized, double-blinded, and placebo-controlled. The first study⁹ involved 244 patients who, on the basis of criteria in the literature, were anticipated to have a 10% or greater probability of experiencing seizures. The frequency of early seizure was similar in the treatment and placebo groups, which led the authors to conclude that phenytoin prophylaxis was not effective in preventing early posttraumatic seizures. However, the frequency of early seizures reported in the study was very low. In the study reported by Temkin and colleagues¹⁰ the frequency of early seizures in the placebo group was 14.2%, whereas in the study by Young and colleagues⁹ the frequency was only 3.7%. Because the frequency of early seizures in the phenytoin groups for both studies was similar, a higher rate of seizures in the placebo group of the study by Young and colleagues⁹ would likely have resulted in a significant treatment effect.

The second trial by Young and colleagues¹¹ studied the efficacy of phenytoin in preventing late posttraumatic seizures. One hundred and seventy-nine patients with an estimated 15% probability of experiencing late seizures were randomly assigned to receive placebo or phenytoin. After 18 months of treatment, the frequency of seizures was not significantly different between the 2 groups. It was concluded that phenytoin treatment does not decrease the frequency of late posttraumatic seizures. However, the authors noted that it is unknown whether doses providing higher therapeutic blood concentrations of phenytoin would have been more effective since, in this study, patients with phenytoin plasma concentrations of 12 µg/mL (48 µmol/L) or higher did not have seizures.

The most recent and most comprehensive study of this issue was reported by Temkin and colleagues¹⁰ in 1990. This prospective, randomized, double-blind, placebo-controlled trial involved 404 patients with an estimated 20% probability of posttraumatic seizures. The patients were treated for 12 months with placebo or phenytoin; the phenytoin doses were regularly adjusted to provide serum concentrations within the proposed therapeutic range (40 to 80 µmol/L). The follow-up period was 24 months. The frequency of early seizures was significantly lower in the phenytoin group; however, the frequency of late seizures was similar in the 2 groups. The authors concluded that phenytoin prophylaxis has a protective effect in the first week after injury and no significant effect from day 8 to the end of the second year after the trauma.

Summary of Effectiveness in Posttraumatic Seizures

Phenytoin appears to be beneficial only in preventing early posttraumatic seizures.¹⁰ As the cost and relative risk associated with a short course of antiepileptic drug therapy appears low, prophylactic use of phenytoin to prevent seizures in the first week after injury appears justified in patients with head injury in high-risk groups (those with contusion [visible on computed tomography], hematoma or hemorrhage [subdural, intracranial, or epidural], depressed skull fracture, penetrating head wound, seizure within 24 h of injury, Glasgow coma score of 10 or less, loss of consciousness for 6 h or more, or focal neurological deficits).¹²⁻¹⁵

Prophylactic phenytoin does not appear to change the frequency of late seizures.⁸ This finding has been consistently reported in several prospective, controlled clinical trials (Table 1). Thus, long-term prophylaxis should be avoided because of a lack of demonstrated positive effects and potential adverse effects.¹²

Although these recommendations focus on phenytoin, they are thought to be applicable to other anticonvulsants.¹⁶ Guidelines for the role of antiseizure



Table 1. Anticonvulsants for Prophylaxis of Posttraumatic Seizures

Reference	Study Type	Patient Characteristics	Methods of Prophylaxis	Results
Wohns and Wyler ⁶	Retrospective with historical control	<i>n</i> = 62 <i>Inclusion criteria</i> : severe head injury: depressed skull fracture, dural laceration, cortical laceration, changes in EEG results, clinical signs of focal cortical damage, posttraumatic amnesia > 24 h	<i>Control</i> : 12 patients <i>Phenytoin</i> : 50 patients <i>Treatment</i> : 1 year <i>Loading doses</i> : usually given <i>Dose</i> : adjusted to therapeutic range <i>Levels</i> : done	Frequency of late seizures (starting day 15 after injury) 50% (6/12) for control group, 10% (5/50) for treatment group
Servit and Musil ⁷	Prospective with untreated control	<i>n</i> = 167 <i>Injuries</i> : closed head injury with brain contusion (75%), penetrating brain injury (10%), basal skull fracture (12.5%), epidural hematoma (2.5%)	<i>Control</i> : 24 patients <i>Phenytoin and phenobarbital</i> : 143 patients <i>Treatment</i> : 1 year <i>Loading doses</i> : not specified <i>Doses</i> : phenytoin 160 to 240 mg/day oral; phenobarbital 30 to 60 mg/day oral <i>Levels</i> : not done <i>Follow-up</i> : at 8 to 13 years	Frequency of seizures 24% for control group, 2.1% for treatment group (<i>p</i> < 0.001) Adverse effects: none reported
Penry et al ⁸	Prospective, randomized, double-blind, placebo-controlled	<i>n</i> = 125 <i>Risk classes</i> : unconsciousness for more than 30 min; skull fracture; focal neurologic signs; dural penetration	<i>Treatment duration</i> : 18 months <i>Loading doses</i> : not specified <i>Doses</i> : phenytoin 200 mg/day oral and phenobarbital 60 mg/day oral, started within 12 h of injury <i>Levels</i> : done <i>Follow-up</i> : at 18 months	36-month cumulative probability of seizures: 13% for placebo group, 21% for treatment group (no statistical difference between placebo and treatment groups nor among the 4 risk classes)
Young et al ⁹	Prospective, randomized, double-blind, placebo-controlled	<i>n</i> = 244 <i>Inclusion criteria</i> : probability of seizures > 10% (penetrating missile wound; intracranial hematoma; frontal, temporal, or parietal depressed skull fracture; closed head injury causing loss of consciousness for 6 h or focal neurologic deficits)	<i>Placebo</i> : 108 patients <i>Phenytoin</i> : 136 patients (comparable groups) <i>Treatment duration</i> : 1 week <i>Loading dose</i> : 11 mg/kg IV started within 24 h <i>Dose</i> : adjusted to therapeutic range, according to levels <i>Route</i> : IM followed by oral <i>Levels</i> : done every 24 h	Frequency of seizures 3.7% (4/108) for placebo group, 3.7% (5/136) for treatment group (<i>p</i> = 0.75) More than 78% of patients had therapeutic plasma levels of phenytoin
Young et al ¹¹	Prospective, randomized, double-blind, placebo-controlled	<i>n</i> = 179 <i>Inclusion criteria</i> : probability of seizures ≥ 15% (penetrating missile wound, intracranial skull fracture, closed head injury causing loss of consciousness for 6 h or focal neurologic deficits)	<i>Placebo</i> : 74 patients <i>Phenytoin</i> : 105 patients (comparable groups) <i>Treatment duration</i> : 18 months <i>Loading dose</i> : 11 mg/kg IV, started within 24 h <i>Dose</i> : adjusted to therapeutic range, according to levels <i>Levels</i> : done every 24 h for first week, then every 2 or 3 days for inpatients and at 1, 3, 6, 8, 12, 15, and 18 months for outpatients	Frequency of seizures 10.8% (8/74) for placebo group, 12.4% (13/105) for treatment group (<i>p</i> = 0.75) 20 patients switched from phenytoin to phenobarbital (of whom 2 patients [10%] had a seizure) 2 of 11 patients who had seizures while on phenytoin had therapeutic levels of the drug
Temkin et al ¹⁰	Prospective, randomized, double-blind, placebo-controlled	<i>n</i> = 404 patients <i>Inclusion criteria</i> : probability of seizures 20% (cortical contusion visible on computed tomography; subdural, epidural, or intracerebral hematoma; depressed skull fracture; penetrating head wound; seizure within 24 h of injury; Glasgow coma score ≤ 10)	<i>Placebo</i> : 196 patients <i>Phenytoin</i> : 208 patients (comparable groups) <i>Treatment duration</i> : 12 months <i>Loading dose</i> : 20 mg/kg IV, within 24 h <i>Dose</i> : adjusted to therapeutic range according to levels (IV or oral doses, 200 to 1200 mg/day; nasogastric doses, up to 2600 mg/day) <i>Levels</i> : total and free phenytoin (in ICU, 3 times/week; in ward, weekly; for outpatients, at 1, 3, 6, 9, and 12 months) <i>Follow-up</i> : at 24 months	Frequency of early seizures (with drug loading, to day 7) 14.2% (± 2.6%)* for placebo group, 3.6% (± 1.3%) for treatment group (<i>p</i> < 0.001) Decrease in risk of seizures with phenytoin: 73% (95% CI 38% to 88% decrease) Frequency of late seizures (day 8 to year 1) 15.7% (± 3.2%) for placebo group, 21.5% (± 3.6%) for treatment group (<i>p</i> > 0.2) Frequency of late seizures (day 8 to year 2) 21.1% (± 3.7%) for placebo group, 27.5% (± 4.0%) for treatment group (<i>p</i> > 0.2) Morality rate similar for the 2 groups. Levels were therapeutic in 70% to 75% of patients treated with phenytoin. Adverse reactions: rash in 17/196 patients in placebo group and 25/208 patients in the treatment group (<i>p</i> < 0.010); leukopenia and increased liver function tests in 8/196 patients in placebo group and 12/208 patients in treatment group (not statistically significant)

EEG = electroencephalography, ICU = intensive care unit, CI = confidence interval.

*Standard deviation.



prophylaxis after head injury were recently published by the Joint Committee of the Brain Trauma Foundation, the American Association of Neurological Surgeons, and the Joint Section on Neurotrauma and Critical Care.¹² This report classifies interventions as *standards*, accepted principles of patient management that reflect a high degree of clinical certainty; *guidelines*, management strategies that reflect moderate clinical certainty; and *options*, strategies for patient management for which there is unclear clinical certainty. Avoiding prophylactic use of anticonvulsants (phenytoin, carbamazepine, or phenobarbital) for the prevention of late posttraumatic seizures is a standard. Use of phenytoin or carbamazepine to prevent early posttraumatic seizures is an option. However, the authors of the guidelines noted that the available evidence does not indicate that early seizure prophylaxis improves outcome after head injury.

PROPHYLAXIS OF POSTCRANIOTOMY SEIZURES

The frequency of postcraniotomy seizures varies greatly depending on the type, location, and severity of injury. In patients who have undergone craniotomy for aneurysm, the risk of seizure ranges from 3% to 26%.⁵ The frequency of seizures in patients with cerebral neoplasm can range from 10% to 50%.¹ Like patients with head injury, many of these patients are given phenytoin for prophylaxis. However, trials evaluating the efficacy of anticonvulsants in preventing seizures after supratentorial operations for aneurysm, intracranial hemorrhage, arteriovenous malformation, and tumour have yielded conflicting results (Table 2).

North and colleagues¹⁷ conducted a prospective, randomized, double-blind, placebo-controlled trial of 281 patients who had undergone supratentorial operations. The duration of prophylaxis with placebo or phenytoin (dose adjusted to therapeutic range) was 12 months, with a further 12 months of off-treatment follow-up. The frequency of seizures was similar in the placebo and treatment groups at the end of 1 year; however, there was a statistically significant difference between the 2 groups in seizure frequency for days 7 to 72, with a maximal effect observed in the second postoperative week. It was speculated that a more pronounced effect would have been seen in the first postoperative week if a phenytoin loading dose had been part of the study protocol.

A prospective, randomized, double-blind, placebo-controlled study involving 374 patients who underwent supratentorial operations was undertaken by Lee and colleagues.¹⁸ In this trial, patients were given placebo or phenytoin for 3 days after surgery. The frequency of seizures over these 3 days was similar for the 2 groups, and the authors concluded that phenytoin prophylaxis

did not significantly reduce seizure frequency in the early postoperative period.

Franceschetti and colleagues¹⁹ conducted a prospective, randomized, placebo-controlled trial involving 63 patients with supratentorial neoplasms who were free of seizures before their surgery. They found that neither early nor late postoperative seizures were significantly reduced when patients received phenytoin or phenobarbital prophylactically. However, because the study was poorly designed (small treatment groups, indeterminate length of treatment, and variable length of follow-up) and an exceptionally high number of patients were lost to follow-up, the study results have been questioned.

Foy and colleagues²⁰ conducted a prospective, controlled, randomized trial with 276 patients who had an estimated 20% or greater probability of postoperative seizures. Patients were randomly assigned to phenytoin, carbamazepine, and control groups and received treatment for either 6 or 24 months. There was no significant difference in the frequency of seizures between the treatment and control groups at 6 and 24 months. The authors concluded that prolonged prophylaxis with anticonvulsant drugs after supratentorial craniotomy should be avoided.

Summary of Effectiveness in Postcraniotomy Seizures

Only one trial has reported a beneficial effect of phenytoin prophylaxis. Other trials have failed to find a significant decrease in the frequency of seizures with administration of anticonvulsants after craniotomy. A summary of these trials is presented in Table 2. Some authors continue to recommend short-term anticonvulsant therapy after surgery,^{19,21-23} while others recommend avoiding prophylactic therapy and commencing treatment only after the occurrence of the first seizure.²⁴

ADVERSE EFFECTS OF PHENYTOIN

When considering whether a patient should receive prophylactic therapy, the expected benefits must be compared with the risks of treatment. The trials described above give an indication of the benefits of prophylaxis. To make appropriate treatment decisions, the adverse effects of phenytoin should be addressed.

There are several types of toxicity associated with phenytoin.²⁵ Acute toxic effects, such as drowsiness, nystagmus, ataxia, and seizures, are usually associated with high dosages or high serum drug concentrations.²⁶ Because phenytoin exhibits nonlinear pharmacokinetics, a small increase in dosage may result in a disproportionately larger increase in serum concentrations and the possibility of acute toxic effects. These acute adverse reactions can usually be alleviated by reducing the phenytoin dose.



Table 2. Prophylactic Phenytoin for Prevention of Postcraniotomy Seizures

Reference	Study Type	Patient Characteristics	Methods of Prophylaxis	Results
North and colleagues ¹⁷	Prospective, randomized, double-blind, placebo-controlled	<i>n</i> = 281 <i>Inclusion criteria:</i> supratentorial operation for aneurysm, head injury with or without clot, meningioma, metastasis, sellar tumour, glioma, ventriculoatrial shunt	<i>Placebo:</i> 141 patients <i>Phenytoin:</i> 140 patients <i>Treatment duration:</i> 12 months <i>Loading dose:</i> none <i>Doses:</i> 250 mg IV twice daily started in recovery room; then 200 mg oral 3 times daily (initially) once patient able to take oral medications; adjusted to therapeutic range according to levels <i>Levels:</i> done weekly for inpatients, every 2 months for outpatients <i>Follow-up:</i> at 12 months	Frequency of seizures (day 0 to 1 year): 18% (26/141) for placebo group, 12.8% (18/140) for treatment group (difference not significant) Difference between placebo and phenytoin in frequency of seizure related to postoperative time: day 0 to 6, <i>p</i> > 0.05 (not significant); day 7 to 72, <i>p</i> < 0.05 (for day 9 to 13, <i>p</i> < 0.02); day 82 to 343, <i>p</i> > 0.05 (not significant) 81% of patients had therapeutic levels; 18 patients had seizures while on phenytoin: generalized seizure in 9 patients (8 of whom had subtherapeutic levels), focal seizure in 9 patients (7 of whom had therapeutic levels) Adverse effects resulting in treatment withdrawal: 2.1% (3/141) for placebo group, 8.6% (12/140) for treatment group
Lee and colleagues ¹⁸	Prospective, randomized, double-blind, placebo-controlled	<i>n</i> = 374 patients <i>Inclusion criteria:</i> supratentorial operation for meningioma (50 patients), aneurysm (41), glioma (30), intracranial hemorrhage (18), arteriovenous malformation (12), metastatic tumour (5), head trauma (210), others (8)	<i>Placebo:</i> 185 patients <i>Phenytoin:</i> 189 patients (comparable groups) <i>Treatment duration:</i> 3 days <i>Loading dose:</i> 15 mg/kg IV intraoperatively <i>Doses:</i> 5-6 mg/kg daily in 3 divided doses for the first 3 postoperative days <i>Levels:</i> measured on the third day	Frequency of seizures within 24 h: 2.2% (4/185) for placebo group, 0.5% (1/189) for treatment group (<i>p</i> > 0.1) Frequency of seizures within 3 days: 4.9% (9/185) for placebo group, 1.1% (2/189) for treatment group (<i>p</i> > 0.05) Therapeutic levels achieved in 59.8% of patients receiving phenytoin
Franceschetti et al ¹⁹	Prospective, randomized (group B only), placebo-controlled (group B only)	<i>n</i> = 128 patients <i>Inclusion criteria:</i> supratentorial neoplasms (meningiomas in 42%, slow-growing glial tumours in 6%, malignant glial tumours in 37%, metastatic lesions in 15%)	GROUP A, PATIENTS WITH PREOPERATIVE SEIZURES <i>Phenobarbital:</i> 41 patients <i>Phenytoin:</i> 9 patients <i>Carbamazepine:</i> 4 patients <i>Polytherapy:</i> 11 patients GROUP B, PATIENTS WITHOUT PREOPERATIVE SEIZURES <i>Placebo:</i> 22 patients <i>Phenobarbital:</i> 25 patients <i>Phenytoin:</i> 16 patients <i>Treatment duration:</i> not reported <i>Initial dosing for group B:</i> phenobarbital 4 mg/kg daily oral for 5 days, phenytoin 10 mg/kg daily oral for 5 days <i>Subsequent dosing for group B:</i> phenobarbital 2 mg/kg daily oral, phenytoin 5 mg/kg daily oral (adjusted to therapeutic range) <i>Levels:</i> done preoperatively and postoperatively daily for 1 week, then every 6 months <i>Follow-up:</i> from less than 6 months to more than 1 year	Frequency of early postoperative seizures: 17% (11/65) for group A, 11% (7/63) for group B (within group B, 18% [4/22] for placebo group, 7% [3/41] for treatment group) (2 of the 3 patients with seizures had subtherapeutic plasma levels) (difference not significant) Frequency of late postoperative seizures (45 patients lost to follow-up): 34% (15/44) for group A, 15% (6/39) for group B (within group B, 21% [3/14] for placebo group, 13% [3/25] for treatment group) (difference not significant)
Foy et al ²⁰	Prospective, randomized, untreated control	<i>n</i> = 276 patients <i>Inclusion criteria:</i> conditions with > 20% incidence of postoperative seizures (aneurysm in 54.0%, arteriovenous malformation in 4.3%, hematoma in 2.5%, abscess in 2.2%, meningioma in 18.0%, benign tumours in 18.0%)	<i>Control:</i> 59 patients <i>Phenytoin:</i> 55 patients for 6 months and 56 patients for 24 months <i>Carbamazepine:</i> 50 patients for 6 months and 56 patients for 24 months <i>Treatment duration:</i> 6 or 24 months <i>Loading dose:</i> phenytoin 15 mg/kg IV starting 24 h before surgery, carbamazepine 200 mg oral every 6 h starting 24 h before surgery <i>Doses:</i> phenytoin 100 mg IV or oral q8h, carbamazepine 200 mg oral q8h <i>Levels:</i> after surgery, then at 1 week, 3, 6, and 9 months, 1 and 2 years <i>Follow-up:</i> 3 to 8 years	Frequency of seizures (day 0 to 4 years) :42.4% (25/59) for control group, 38.2% (21/55) for phenytoin 6 months, 28.6% (16/56) for phenytoin 24 months, 42.0% (21/50) for carbamazepine 6 months, 35.7% (20/56) for carbamazepine 24 months (<i>p</i> = 0.33) Levels: no significant difference in seizure frequency between patients whose levels were monitored and those whose levels were not monitored; no significant difference in seizure frequency between patients who had optimal levels and patients with suboptimal levels Occurrence of early seizures did not increase the likelihood of late seizures Adverse effects (for patients treated with anticonvulsants): rashes in 13%, other side effects in 1.4%



Chronic toxic effects are usually attributed to duration of phenytoin treatment. For example, gingival hyperplasia can occur in up to 50% of patients and may become severe enough to require surgical removal of the hyperplastic tissue.²⁷ Negative cognitive or neurobehavioural effects (such as impaired memory, attention, or concentration) are other examples of long-term toxic effects.²⁸⁻³⁰ These effects are especially detrimental to patients with brain injuries, who may already have cognitive deficits. Dikmen and colleagues³¹ studied the neurobehavioural effects of phenytoin prophylaxis in patients with head injuries. They concluded that phenytoin had significant negative cognitive effects and questioned the benefits of long-term use.

Phenytoin is also associated with a number of idiosyncratic toxic effects. Blood dyscrasias, hepatotoxicity, and lymphadenopathy occur, albeit rarely. Skin rash occurs in 2% to 10% of patients receiving phenytoin and may progress to more severe or even life-threatening reactions, such as Stevens-Johnson syndrome or toxic epidermal necrolysis.^{32,33}

GUIDELINES

On the basis of the efficacy data presented here and the risks associated with phenytoin use, it would seem prudent to avoid long-term phenytoin prophylaxis in patients who have sustained head injury. However, because the risks associated with short-term therapy are often dose-related (and hence avoidable) and because patients may benefit from early seizure prophylaxis, short-term phenytoin therapy is reasonable.

Studies have failed to demonstrate the efficacy of late seizure prophylaxis in patients who have undergone craniotomy; thus, long-term prophylaxis should be avoided in these patients as well. Early seizure prophylaxis is more controversial in this group of patients. Although the studies were unable to show a significant benefit, there was a trend toward a beneficial effect in the early treatment group. At our institution, it was felt that short-term seizure prophylaxis (for 7 days) in this group of patients was unlikely to be harmful and had the possibility of benefitting the patient. To make the prescribing guidelines as concise as possible, it was decided that both posttraumatic and postcraniotomy patients would receive the same seizure prophylaxis.

On the basis of these conclusions, guidelines for the prophylactic use of phenytoin to prevent posttraumatic and postcraniotomy seizures were developed at our institution. The guidelines apply to posttraumatic patients with head injury considered to be at high risk for seizures. These patients have one or more of the following injuries or deficits: contusion (visible on computed tomography), hematoma or hemorrhage (subdural, intracranial, or epidural), depressed skull fracture, penetrating head wound, seizure within 24 h of

injury, Glasgow coma score of 10 or less, loss of consciousness for 6 h or more, and focal neurological deficits. The guidelines also apply to postcraniotomy patients with the following injuries: aneurysm or subarachnoid hemorrhage, cerebral arteriovenous malformation, and hematoma or hemorrhage (subdural, intracranial, or epidural). Patients with brain tumours, such as meningiomas, gliomas, and metastatic tumours, were perceived by the neurosurgery staff to be at higher risk and therefore were excluded from these guidelines. The literature is controversial, and thus cannot be used to support or refute the surgeons' perceptions.¹ Decisions on prophylactic anticonvulsant therapy for these patients are made on an individual basis by the physician.

The guidelines for early seizure prophylaxis (≤ 1 week after injury) are to give a phenytoin loading dose of 20 mg/kg intravenously perioperatively or within 24 h of injury. A phenytoin maintenance dose of 5 mg/kg is administered intravenously or orally each day for 7 days after the loading dose.³⁴ Nasogastric administration of phenytoin in patients receiving enteral feeding is avoided because of substantially reduced phenytoin serum concentrations in these patients.³⁵⁻³⁸ Seizure activity and signs and symptoms resulting from phenytoin toxicity are monitored. The guidelines for late seizure prophylaxis (> 1 week after injury) are to commence treatment with phenytoin only if a seizure occurs.

Ideally, phenytoin serum concentrations should be monitored during the prophylaxis period to ensure therapeutic levels.¹⁰ Our guidelines do not address the monitoring of phenytoin serum concentrations. At our institution, it was felt that a loading dose and a maintenance dose based on weight would suffice to achieve therapeutic levels (40 to 80 $\mu\text{mol/L}$) for almost all patients.³⁷ Phenytoin serum concentrations are to be determined if deemed necessary by the physician.

IMPLEMENTATION OF GUIDELINES

The guidelines and supporting data were presented to the staff neurosurgeons. The guidelines were amended with input from the neurosurgeons and then accepted. On entry to our program, all new neurosurgery residents receive a copy of the guidelines (and, if requested, an in-service training session). The physicians are encouraged to follow the recommendations; however, therapy can be altered on the basis of clinical judgement.

References

- 1 Agbi C, Bernstein M. Seizure prophylaxis for brain tumor patients. *Can Fam Physician* 1993;39:1153-64.



2. Dalmady-Israel C, Zasler N. Post-traumatic seizures: a critical review. *Brain Inj* 1993;7:263-73.
3. McQueen J, Blackwood D, Harris P, Kalbag R, Johnwon A. Low risk of late post-traumatic seizures following severe head injury: implications for clinical trials of prophylaxis. *J Neurol Neurosurg Psychiatry* 1983;46:899-904.
4. Pagni C. Posttraumatic epilepsy. Incidence and prophylaxis. *Acta Neurochir Suppl (Wien)* 1990;50:38-47.
5. Rabinowicz A, Ginsberg D, DeGiorgio C. Unruptured intracranial aneurysms: Seizures and antiepileptic drug treatment following surgery. *J Neurosurg* 1991;75:371-3.
6. Wohns R, Wyler A. Prophylactic phenytoin in severe head injuries. *J Neurosurg* 1979;51:507-9.
7. Servit Z, Musil F. Prophylactic treatment of posttraumatic epilepsy: results of a long-term follow-up in Czechoslovakia. *Epilepsia* 1981;22:315-20.
8. Penry J, White B, Brackett C. A controlled prospective study of the pharmacologic prophylaxis of posttraumatic epilepsy. *Neurology* 1979;29:600-1.
9. Young B, Rapp R, Norton J, Haack D, Tibbs P, Bean J. Failure of prophylactically administered phenytoin to prevent early posttraumatic seizures. *J Neurosurg* 1983;58:231-5.
10. Temkin N, Dikmen S, Wilensky A. A randomized, double-blind study of phenytoin for the prevention of post-traumatic seizures. *New Engl J Med* 1990;323:497-502.
11. Young B, Rapp R, Norton J, Haack D, Tibbs P, Bean J. Failure of prophylactically administered phenytoin to prevent late posttraumatic seizures. *J Neurosurg* 1983;58:236-41.
12. Bullock R, Chesnut R, Clifton G, Ghajar J, Marion D, Narayan R, et al. The role of antiseizure prophylaxis following head injury. *J Neurotrauma* 1996;13:731-4.
13. Temkin N, Dikmen S, Wilensky A, Keihm J, Chabal S, Winn H. Phenytoin for the prevention of post-traumatic seizures [letter]. *New Engl J Med* 1990;324:341.
14. Temkin N, Haglund M, Winn R. Causes, prevention, and treatment of post-traumatic epilepsy. *New Horiz* 1995;3:518-22.
15. Yablon S. Posttraumatic seizures. *Arch Phys Med Rehabil* 1993;74:983-1001.
16. Massagli T. Prophylaxis and treatment of posttraumatic epilepsy with phenytoin. *West J Med* 1992;157:663-4.
17. North J, Penhall R, Hanieh A, Frewin D, Taylor W. Postoperative epilepsy: a double-blind trial of phenytoin after craniotomy. *Lancet* 1980;1:384-6.
18. Lee S, Lui T, Chang C, Cheng W, Wang D, Heimburger R, et al. Prophylactic anticonvulsants for prevention of immediate and early postcraniotomy seizures. *Surg Neurol* 1989;31:361-4.
19. Franceschetti S, Binelli S, Casazza M, Lodrini S, Panzica F, Pluchino F, et al. Influence of surgery and antiepileptic drugs on seizures symptomatic of cerebral tumors. *Acta Neurochir* 1990;103:47-51.
20. Foy P, Chadwick D, Rajgopalan N, Johnson A, Shaw M. Do prophylactic anticonvulsant drugs alter the pattern of seizures after craniotomy? *J Neurol Neurosurg Psychiatry* 1992;55:753-7.
21. Baker C, Prestigiacomo C, Solomon R. Short-term perioperative anticonvulsant prophylaxis for the surgical treatment of low-risk patients with intracranial aneurysms. *Neurosurgery* 1995;37:863-71.
22. Deutschman C, Haines S. Anticonvulsant prophylaxis in neurological surgery. *Neurosurgery* 1985;3:510-7.
23. North J, Penhall R, Hanieh A, Frewin D, Taylor W. Phenytoin and postoperative epilepsy. *J Neurosurg* 1983;58:672-7.
24. O'Laoire S. Epilepsy following neurosurgical intervention. *Acta Neurochir Suppl (Wien)* 1990;50:52-4.
25. Wood A. Antiepileptic drugs. *New Engl J Med* 1996;334:168-75.
26. Stilman N, Masdeu J. Incidence of seizures with phenytoin toxicity. *Neurology* 1985;35:1769-72.
27. Perlik F, Kolinova M, Zvarova J, Patzelova V. Phenytoin as a risk factor in gingival hyperplasia. *Ther Drug Monit* 1995;17:445-8.
28. Bruni J. Phenytoin toxicity. In: Levy R, Mattson R, Meldrum B, editors. *Antiepileptic drugs*. 4th ed. New York: Raven Press; 1995. p. 345-50.
29. Massagli T. Neurobehavioural effects of phenytoin, carbamazepine, and valproic acid: implications for use in traumatic brain injury. *Arch Phys Med Rehabil* 1991;72:219-25.
30. Meador K, Loring D, Moore E, Thompson W, Nichols M, Oberzan R, et al. Comparative cognitive effects of phenobarbital, phenytoin and valproate in healthy adults. *Neurology* 1995;45:1494-9.
31. Dikmen S, Temkin N, Miller B, Machamer J, Winn R. Neurobehavioural effects of phenytoin prophylaxis of posttraumatic seizures. *JAMA* 1991;265:1271-7.
32. Bastuji-Garin S, Rzany B, Stern R, Shear N, Naldi L, Roujeau J. Clinical classification of cases of toxic epidermal necrolysis, Stevens-Johnson syndrome, and erythema multiforme. *Arch Dermatol* 1993;129:92-6.
33. Chan H, Stern R, Arndt K, Langlois J, Jick S, Jick H, et al. The incidence of erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis. *Arch Dermatol* 1990;126:43-7.
34. Willmore L. Post-traumatic seizures. *Neurol Clin* 1993;11:823-34.
35. Bader M. Case study of two methods for enteral phenytoin administration. *J Neurosci Nurs* 1993;25:233-42.
36. Bauer L. Interference of oral phenytoin absorption by continuous nasogastric feedings. *Neurology* 1982;32:570-2.
37. Levine M, Chang T. Therapeutic drug monitoring of phenytoin rationale and current status. *Clin Pharmacokinet* 1990;19:341-58.
38. Pugh C. Phenytoin and enteral feedings: a clinically significant interaction. *Hosp Pharm* 1989;24:562-9.

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