PEDIATRIC PHARMACOTHERAPY

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Phenytoin for Seizure Prophylaxis after Traumatic Brain Injury in Children
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The development of seizures after traumatic brain injury (TBI) can have a variety of negative consequences, including increased intracranial pressure, increased metabolic demands, and secondary brain injury. The incidence of early posttraumatic seizures (PTS), those occurring in the first week after injury, varies in the literature, with estimates in children ranging from 20-39%. The likelihood of seizures increases with severity of injury. Infants and children less than 2 years of age also appear to be at greater risk than older children. Late PTS are less frequent, with an incidence in children of 7-12%.[1-4]

Anticonvulsants have traditionally been used in the management of TBI in an effort to prevent both early and late PTS. Phenytoin is used most frequently, but there have also been reports of using carbamazepine and phenobarbital.[1-4] Despite the frequency of this practice, there is little evidence in the medical literature to support the efficacy of anticonvulsants in preventing PTS, particularly in pediatric TBI patients.

Current Recommendations
Treatment guidelines for adults with TBI from the American Academy of Physical Medicine and Rehabilitation,[5] the Brain Trauma Foundation,[6] and the American Academy of Neurology[7] recommend the use of phenytoin for prophylaxis of early PTS. Therapy is recommended for a period of no more than one to two weeks following injury. Long-term prophylaxis with phenytoin is not recommended, as studies in adults have failed to show a significant benefit from therapy.

In 2003, the Society for Critical Care Medicine (SCCM) published guidelines for the acute management of severe TBI in pediatric patients.[4] The expert panel concluded that there was insufficient evidence to support a treatment standard in this area, but the guidelines state that prophylactic anticonvulsant therapy with phenytoin may be considered as an option to prevent early PTS in pediatric patients at high

risk. The use of prophylactic anticonvulsants for preventing late PTS is not recommended. The guidelines were based on data from studies in adults and the three studies conducted in children that were available at the time of publication.

Early Posttraumatic Seizures
Although several early studies of anticonvulsants in TBI patients included both children and adults, few papers have specifically focused on the pediatric population. In 1993, Lewis and coworkers conducted a retrospective cohort study of 194 children (3 months to 15 years of age) with head trauma, including 31 with severe TBI.[8] A subset of 13 patients who received prophylactic phenytoin was compared to a control group of 17 patients who received no anticonvulsants. Nine of the 17 control patients (53%) experienced early PTS compared to only two of the 13 treated patients (15%), with p=0.04 using a one-tailed Fisher's exact test and p=0.57 using a two-tailed test. The authors concluded that prophylactic phenytoin reduced the incidence of early PTS in children with severe TBI.

In 2001, Tilford and colleagues published another retrospective cohort study of anticonvulsants for early PTS in children.[9] Data from three pediatric intensive care units were analyzed, providing a total of 477 children, including 128 with severe TBI. Multivariate analysis showed that use of anticonvulsants was associated with improved survival (odds ratio =0.17, 95% confidence interval 0.04-0.7, p=0.014).

While these two initial retrospective studies showed positive treatment results, the results of a recent prospective study did not demonstrate a benefit.[10] In 2003, Young and colleagues reported the results of a randomized, double-blind, placebo-controlled trial of phenytoin for the prevention of early PTS in children. A total of 102 patients with moderate to severe TBI were enrolled in three trauma centers. All were

less than 17 years of age (median age 6.1 years). Patients in the phenytoin group received a loading dose of 18 mg/kg infused over 20 minutes, followed by a maintenance dose of 2 mg/kg every 8 hours for a total of 48 hours. The median serum phenytoin concentration in this group was 16.2 mcg/ml (range 3.3 to 61 mcg/ml).

There was no significant difference in the incidence of early PTS during the 48-hour observation period. Three of the 46 children (7%) who were given phenytoin experienced PTS, compared to 3 of the 56 children (5%) in the placebo group. There were also no significant differences in survival or neurologic outcome at 30 days. Based on these results, the authors concluded that phenytoin did not reduce the incidence of early PTS.

The investigators also found lower rates of early PTS than previously reported, which they theorized may be due to the increased use of benzodiazepines in the initial management of children with TBI or improvements in intracranial pressure monitoring and control.[10] This study was published after the SCCM guidelines became available, and it is not yet clear how practice will be influenced by these results.

Late Posttraumatic Seizures
The results of several studies conducted in adults have not shown a significant reduction in late PTS with the use of anticonvulsants.[7] In 1983, Young and colleagues evaluated the efficacy of phenytoin in preventing late seizures in 244 children and adults with TBI.[11] Data for the 41 pediatric patients (median age 9.4 years) were evaluated separately. Patients were randomized to receive either placebo or phenytoin, using a total loading dose of 24 mg/kg intravenously (IV), followed by a maintenance dose of 8.8 mg/kg/day, titrated to maintain serum concentrations between 10 and 20 mcg/ml.

Twenty-five patients received phenytoin (five of these patients were unable to tolerate phenytoin were switched to phenobarbital) and 16 received placebo. There was a 9.8% incidence of late PTS in the study subjects. At 18 months, three patients in the treatment group (12%) and one control patient (6%) had experienced a late seizure. The difference between the groups was not statistically significant (p=0.25, Fisher's exact test). Two patients in each group expired prior to completion of the study. The authors commented that problems with compliance and dosage titration may have contributed to the lack of benefit observed with phenytoin.

McQueen and colleagues published an additional study of the effects of phenytoin in preventing late PTS in patients with TBI later that year.[12] Their randomized, placebo-controlled, double-blind study enrolled 164 patients between 5 and 65 years of age. As with the Young study, the authors found no significant differences in either the incidence of late seizures (adjusted relative risk –0.77%, 95% CI -9.59 to +8.04) or mortality (adjusted relative risk -3.45%, 95% CI -9.56 to +2.66).[12,13] Based on these results and the lack of benefit seen in studies conducted in adults, the use of anticonvulsants is no longer recommended for prophylaxis of late PTS.

Phenytoin Administration
In pediatric TBI patients for whom phenytoin may provide a benefit, the recommended method for administration is a loading dose of 10 to 20 mg/kg given IV followed by an initial maintenance dose of 5 mg/kg/day, divided into two or three doses, also typically given IV. The maintenance dose may be increased up to 10 mg/kg/day as needed to provide serum phenytoin concentrations between 10 and 20 mcg/ml.[4]

Altered Pharmacokinetics
Achieving and maintaining target phenytoin serum concentrations is difficult in pediatric patients due to the changes in pharmacokinetic parameters associated with normal growth and development. In children with TBI, changes in hemodynamics and the rate of metabolism, decreased protein binding, and drug-drug interactions further compound the difficulty in optimizing therapy.[14-16]

Several small studies have assessed the pharmacokinetics of phenytoin in pediatric TBI patients. In 1990, Griebel and coworkers found reduced phenytoin protein binding in 13 pediatric neurotrauma patients (1.5 to 16 years of age) compared to a group of 27 matched controls with epilepsy.[14] The TBI group received an initial loading dose of 10 to 20 mg/kg IV followed by a maintenance dose of 5.9 ± 0.4 mg/kg/day, also given IV. The controls were receiving an average oral phenytoin dose of 6.6 ± 0.4 mg/kg/day at the time of study enrollment. The phenytoin free (unbound) fraction increased significantly over the 10-day study period, despite a reduction in total phenytoin concentrations. The maximum free fraction at 10 days was also significantly higher in the TBI patients than in the controls (p<0.01). In addition, the authors found a significant linear relationship between the free fraction and serum albumin concentrations.

O'Mara and colleagues conducted a prospective study of phenytoin pharmacokinetics in 16 children (0.5 to 16 years of age) with acute neurotrauma.[15] The patients were given a 15 mg/kg IV loading dose followed by a maintenance dose of 5 mg/kg/day, also IV. In the 12 evaluable patients, the Michaelis-Menten constant was lower than the value predicted using a previously developed Bayesian model for phenytoin pharmacokinetics, while the maximum rate of metabolism was higher than predicted. Initial free phenytoin fractions were between 0.08 and 0.15, with wide interpatient variability. Unlike the study by Griebel, free fractions were not elevated. There was no correlation between pharmacokinetic parameters and Glasgow coma scores, serum albumin, or concomitant medications. Based on their assessment, the authors concluded that patients between 0.5 and 9 years of age may require higher doses of 8 to 10 mg/kg/day, while older children may need lower doses of 6 to 8 mg/kg/day.

An additional pharmacokinetic study was conducted in 2000.[16] Ten pediatric patients (2 to 12 years of age) were treated with phenytoin following severe TBI, using a 15-20 mg/kg loading dose followed by a maintenance dose of 7 mg/kg/day initiated within 12 hours of the loading dose. An initial inhibition of metabolism (Vmax 2.82 ± 2.35 mg/kg/day) was followed by an induction of metabolism (Vmax 20.79 ± 13.71 mg/kg/day), approximately two-fold higher than that previously reported for children not acutely ill. Serum albumin declined during the study, resulting in an alteration in phenytoin protein binding.

Although the results of these studies differ in some areas, it is apparent that phenytoin pharmacokinetics are altered in the presence of acute TBI. The clinical significance of these differences has not yet been established. In fact, data from the study by Young and colleagues did not show a correlation between therapeutic serum phenytoin concentrations and prevention of seizures, calling into question the utility of routine serum concentration monitoring.[10]

Adverse Effects

Short-term phenytoin administration for early PTS prophylaxis is generally well tolerated. However, intravenous site reactions leading to severe necrosis have been reported with the use of phenytoin in TBI patients, as well as hypersensitivity and dermatologic reactions ranging from a mild rash to Stevens Johnson Syndrome, hematologic abnormalities, ataxia, and transient hemiparesis.[4,7,16]

Summary
The use of anticonvulsants has become an accepted part of the medical management of patients with TBI. However, there is little evidence in the medical literature to support their use, especially in children. Although phenytoin is currently recommended during the first week after injury for the prevention of early PTS in children, a recent prospective controlled study failed to show a reduction in the incidence of seizures with treatment. Additional trials, including larger multi-center studies, are needed to clarify the utility of this therapy.

References
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Pharmacology Literature Review

Accidental Atomoxetine Ingestions
This paper reviews 40 cases of accidental ingestion of atomoxetine, a non-stimulant for the treatment of attention deficit/hyperactivity disorder. Sixty-three percent of the patients were boys, with an average age of 6.1 ± 4.9 years. Twenty-five patients were managed at home, 14 in hospital emergency departments, and one at a physician's office. Symptoms included tachycardia, drowsiness, nausea, hypertension, and vomiting. One child had a seizure. The patients were divided into three categories by severity of symptoms and their doses were compared. The average dose in patients with no symptoms was 40 ± 32 mg. In those with minor effects, the average dose was 167 ± 221 mg; and in those with moderate effects, the average dose was 249 ± 326 mg. None of the patients had severe or fatal adverse effects. The authors concluded that activated charcoal and/or observation appeared to be sufficient for accidental atomoxetine ingestion. Spiller HA, Lintner CP, Winter ML. Atomoxetine ingestions in children: a report from poison centers. **Ann Pharmacother 2005;39:1045-8.**

Oral Sucrose for Analgesia during Eye Exams
The efficacy of 24% oral sucrose, administered in conjunction with topical anesthetics, in reducing pain during eye exams was evaluated in a placebo-controlled, double-blind, cross-over study of 23 premature infants. Pain was measured with the Premature Infant Pain Profile (PIPP). When receiving both sucrose and the topical anesthetic, patients experienced significantly less pain at speculum insertion than when given anesthetic alone. Measurements after examination were no different with the addition of sucrose. Based on the relative safety and low cost of sucrose solutions, the authors suggest that this therapy be considered in neonates requiring eye exams. Gal P, Kissling GE, Young WO, et al. Efficacy of sucrose to reduce pain in premature infants during eye examinations for retinopathy of prematurity. **Ann Pharmacother 2005;39:1029-33.**

Formulary Update
The following actions were taken by the Pharmacy and Therapeutics Committee at their meeting on 5/27/05:

1. Meningococcal conjugate vaccine (Menactra®) was added to the Formulary for the routine immunization of patients 11 to 12 years of age. Information on this vaccine was presented in the May issue of *Pediatric Pharmacotherapy*.
2. Tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine, adsorbed (Boostrix®) was added to the Formulary for booster immunization of patients 10 to 18 years of age, pending approval by the Vaccines for Children (VFC) program.
3. Amphotericin B liposomal (AmBisome®) was added to the Inpatient Formulary. Amphotericin lipid complex (Abelcet®) was removed.
4. The restriction on ezetimibe (Zetia®) allowing prescribing only in patients unresponsive or intolerant of HMG CoA reductase inhibitors was removed.
5. Fluorouracil 0.5% cream (Carac®) was added to the Outpatient Formulary for the treatment of multiple actinic or solar keratoses of the face and anterior scalp. Fluorouracil cream (Efudex®) was deleted.
6. The Fortovase® formulation of saquinavir was replaced with Invirase®.
7. For the Outpatient Formulary, the use of tacrolimus 0.03% and 0.1% ointment (Protopic®) was restricted to second-line therapy.
8. The following products were removed from the Inpatient Formulary: ciclopirox cream, econazole cream, hexachlorophene liquid, flurandrenolide tape, fluorouracil solution and cream, podofilox solution, tacrolimus ointment, nedocromil inhaler, risedronate 5 mg tablets, zileuton tablets, mexiletine capsules, diazoxide injection, felodipine tablets, acebutolol capsules, oxtriphylline, therapeutic multivitamin (without minerals), vitamin A 50,000 units capsules, and vitamin A drops.
9. The following products were removed from the Outpatient Formulary: ciclopirox cream, mafenide cream, risedronate 5 mg tablets, and felodipine tablets.
10. Results from the intravenous immune globulin and aprotinin medication utilization evaluations were presented. The quarterly report of the Adverse Drug Reaction (ADR) monitoring program was also provided. For more information about the ADR report, please contact Drug Information Services at 4-8034.