*Clinical Neuropharmacology*
Vol. 20, No. 5, pp. 438–441


# Use of Antiepileptic Drugs in Nontraumatic Neurosurgical Procedures

## Is There Any Best Route and Time of Administration?

Adrian L. Rabinowicz, Jorge M. Salvat, Ramon C. Leiguarda, Federico Demonty, Fernando Salvat, Andres Cervio, Facundo Manes, and Alberto Lazarowski

*Departments of Neurology and Neurosurgery, Instituto de Investigaciones Neurologicas "Raul Carrea"—Fleni, Buenos Aires, Argentina*

We assessed in 15 consecutive patients the best route and time of administration for phenytoin (PHT) prophylaxis in neurosurgical procedures. We also correlated PHT levels in serum and cerebrospinal fluid after oral and parenteral loading doses. The mean PHT level was 13.9 μg/ml in serum and 2.03 μg/ml in cerebrospinal fluid (CSF), with a significant correlation between levels in both compartments ($r = 0.73$, $p < 0.01$). Mean PHT levels among the different groups were not statistically significant. We conclude that therapeutic levels of PHT in CSF can be achieved independently of the route of administration, as long as accepted loading doses are used. **Key Words:** Prophylaxis—Neurosurgery—Antiepileptic drugs—Phenytoin.

Epilepsy is a common disorder that affects 1% of the population (1). Seizures in the neurosurgical setting are commonly seen, and several studies address the impact of seizures in relation to the preoperative, intraoperative, and postoperative period (2–5). Regarding the latter, several authors also have analyzed the chances for developing epilepsy, thus making recommendations to avoid this situation (6). Furthermore, it is typical for neurosurgeons to deal with patients who, after surgery, go into status epilepticus—a life-threatening condition with a 10% to 15% mortality rate (7). In this scenario, prophylaxis with antiepileptic drugs (AEDs) has been reported in relation to a wide variety of neurosurgical conditions (3–6,8–10). Unfortunately, most of these studies are either retrospective or have multiple confounding variables that influence the interpretation of the results. Therefore, it is still debatable which patients need to be on AED prophylaxis. Temkin and others demonstrated that prophylaxis with phenytoin (PHT) decreased the risk of early seizures after head trauma and identified a subset of patients that should be on AEDs, also emphasizing the lack of efficacy of this drug to avoid late-onset epilepsy (5).

Address correspondence to Dr. A.L. Rabinowicz at Instituto de Investigaciones Neurologicas "Raul Carrea"—Fleni, Montaneses 2325, 1428—Buenos Aires, Argentina.

PHT is commonly prescribed by neurosurgeons after most of the surgical procedures. Some reasons related to this practice are PHT's relatively long half-life; its availability in oral and parental formulations, which allows its use in patients with altered mental status; and the possibility to obtain rapid levels within the therapeutic range after an initial loading dose (11). Nevertheless, there is no clear standard of practice for its use, and it remains unclear if one route of administration is faster or better than the other to obtain such blood levels.

The objectives of this study are twofold: 1) to correlate PHT levels in serum and cerebrospinal fluid (CSF) after loading doses using different routes; and 2) to define the best time and route of administration for prophylaxis in nontraumatic supratentorial neurosurgical procedures.

## MATERIALS AND METHODS

We enrolled 15 consecutive patients who underwent neurosurgical procedures secondary to supratentorial nontraumatic lesions (Table 1). All of the surgeries were performed by the same surgeon (J.M.S.). None of the patients had an antecedent of a seizure disorder or were previously exposed to AEDs for other neurologic conditions. After obtaining informed consent, all of the patients received prophylaxis with PHT at a loading dose of 15 mg/kg, independent of the route of administration. Patients were randomly and consecutively assigned to one of the following three groups:

*Group A:* n = 5, loading dose administered orally, in two divided doses 4 hours apart, given 24 hours before the surgery

*Group B:* n = 5, loading dose administered intravenously, given 24 hours before surgery, at an infusion rate of 50 mg/minute or less

*Group C:* n = 5, loading dose administered intravenously, at the same infusion rate as group B, given 2 hours before surgery.

**TABLE 1.** *Demographic data*

| Group | Patient | Age/sex | Diagnosis | Loading dose (mg) | Blood level (μg/mL) | CSF level (μg/mL) |
|---|---|---|---|---|---|---|
| A | 1 | 37/F | AVM | 1000 | 16.6 | 2.43 |
| | 2 | 64/F | Brain tumor | 1400 | 14.1 | 1.55 |
| | 3 | 67/M | Metastasis | 1400 | 18.7 | 2.62 |
| | 4 | 54/M | AVM | 1000 | 11.7 | 1.21 |
| | 5 | 42/M | Brain tumor | 2000 | 8.4 | 0.76 |
| B | 1 | 46/F | Metastasis | 900 | 14.2 | 0.74 |
| | 2 | 54/M | Hygroma | 1200 | 12.4 | 1.27 |
| | 3 | 37/M | Brain tumor | 1100 | 13.8 | 1.24 |
| | 4 | 39/M | Metastasis | 1100 | 12.2 | 1.53 |
| | 5 | 75/F | Metastasis | 700 | 20.5 | 4.31 |
| C | 1 | 52/F | Brain tumor | 900 | 17.8 | 3.41 |
| | 2 | 46/F | AVM | 800 | 14.7 | 4.51 |
| | 3 | 59/M | MCA aneurysm | 1500 | 13.2 | 3.03 |
| | 4 | 75/M | Brain tumor | 1200 | 7.7 | <0.5 |
| | 5 | 43/F | MCA aneurysm | 700 | 13.4 | 1.84 |

CSF, cerebrospinal fluid; AVM, arteriovenous malformations; MCA,

In groups A and B, blood levels were obtained 8 to 10 hours after completion of the loading dose. In all groups, both serum and CSF were simultaneously assessed during the surgery. Five milliliters of CSF were directly sampled from the cistern. PHT levels were determined by fluorescence polarization immunoassay technology (TDX-Abbott Laboratories, Illinois, U.S.A.). For this method, sensitivity was determined to be 0.5 μg/ml (95% confidence) with a coefficient of variation of less than 5%.

Spearman rank test was used for statistical analysis. Significance was defined as a $p < 0.05$.

## RESULTS

Cell count and biochemical analysis of CSF were normal for all patients studied. The mean PHT level, from the samples obtained during surgery, was 13.9 μg/ml (range 7.7–20.5) in serum and 2.03 μg/ml (range 0.26–4.5) in CSF (Table 1). A significant correlation between serum and CSF levels was found ($r = 0.73$, $p < 0.01$), independent of the route and time of administration (Fig. 1). Mean PHT levels among the three groups did not reach statistical significance.

## DISCUSSION

The primary finding of this study is that adequate blood levels can be achieved with PHT independent of the route and time of administration, as long as an appropriate loading dose of the drug is delivered. Furthermore, the good correlation between blood and CSF levels, which was obtained in all patients of the cohort, support the use of this medication

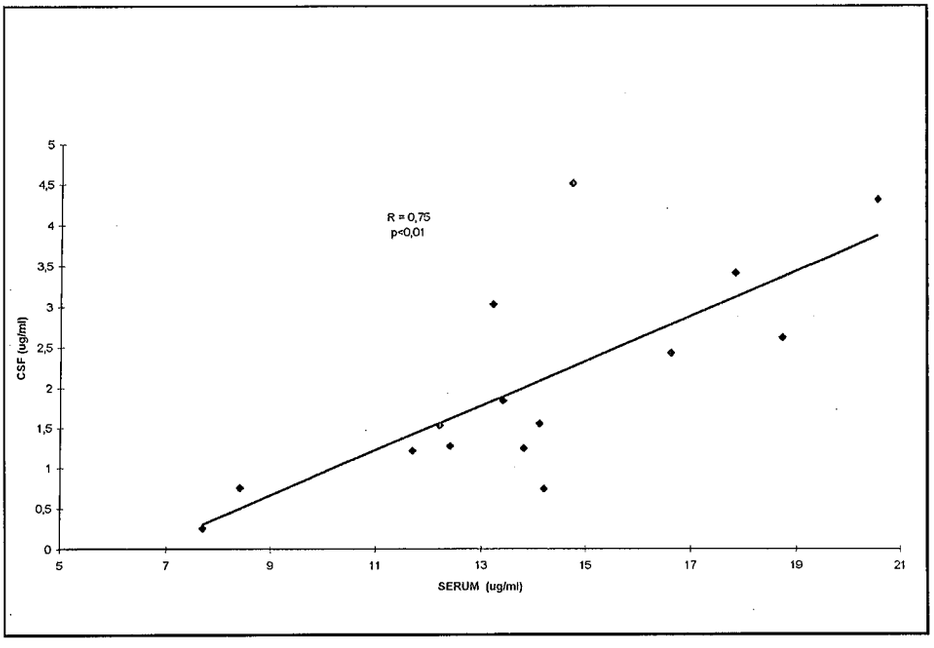


**Fig. 1.** Phenytoin levels in serum and CSF.

in the setting of acute and urgent neurosurgical procedures. Our results are in agreement with previous studies in animals that assessed the temporal pharmakocinetics in blood and CSF after acute and chronic administration of PHT (12,13). Because of its high solubility, PHT rapidly enters the brain, reaching a peak level in 15 minutes. This suggests ready penetration of the blood–brain barrier after intravenous or intraperitoneal administration, as has been documented in a rat model by Lolin and associates (12). Further, whereas PHT concentrations rose dose-dependently in serum, CSF concentrations did not, suggesting that the transport across the blood–brain barrier is rate-limiting (12). Based on these data in animals and on our own results in humans, it is critical to achieve high initial PHT blood concentrations if PHT entry into the brain is to be facilitated.

Previous studies addressed the issue of prophylactic AEDs in patients with head trauma, brain tumors, CNS infections, aneurysms, arteriovenous malformations, and craniotomy (6). Most of these studies analyzed, either retrospectively or prospectively, the incidence of seizures and the convenience of giving AED prophylaxis. Some of these reports shed light on the identification of populations at risk for developing seizures, thus providing recommendations for the management of seizures in neurosurgical practice. However, so far no absolute consensus guides either the initiation of prophylactic anticonvulsants or the duration of treatment.

We hope that this study provides useful insight related to the route and timing of administration of AEDs and allows neurosurgeons to perform a rational approach to the management of seizures.

## REFERENCES

1. Hauser WA, Hesdorferr DC. *Epilepsy: frequency, causes and consequences.* New York: Demos, 1990:1–51.
2. Annegers JF, Grabow JD, Groover RV, Laws E, Elveback L, Kurland L. Seizures after head trauma: a population study. *Neurology* 1980;30:683–9.
3. Foy PM, Copeland GP, Shaw MD. The incidence of postoperative seizures. *Acta Neurochir* 1981;55:253–6.
4. Sabo RA, Hanigan WC, Aldag JC. Chronic subdural hematomas and seizures: the role of prophylactic anticonvulsive medication. *Surg Neurol* 1995;43:579–82.
5. Temkin NR, Dikmen SS, Wilensky AJ. A randomized, double blind study of phenytoin for the prevention of posttraumatic seizures. *N Engl J Med* 1990;323:497–502.
6. DeGiorgio C, Rabinowicz AL. Seizures. In: Apuzzo M, ed. *Brain surgery: complication avoidance and management,* vol 1. New York: Churchill Livingstone, 1992:155–62.
7. Working Group on Status Epilepticus. Treatment of convulsive status epilepticus. *JAMA* 1993;270:854–9.
8. Rabinowicz AL, Ginsburg D, DeGiorgio CM, Gott P, Giannota S. Unruptured intracranial aneurysms: seizures and antiepileptic drug treatment following surgery. *J Neurosurg* 1991;75:371–3.
9. Wang EC, Geyer JR, Berger MS. Incidence of postoperative epilepsy in children following subfrontal craniotomy for tumor. *Pediatr Neurosurg* 1994;21:165–72.
10. Young B, Rapp RP, Norton JA. Failure of prophylactically administered phenytoin to prevent early post-traumatic seizures. *J Neurosurg* 1983;58:231–36.
11. Woodbury D. Phenytoin: absortion, distribution and excretion. In: Levy R, Dreifuss F, Mattson R, Meldrum B, Penry K, eds. New York: Raven Press, 1989:177–95.
12. Lolin Y, Ratnaraj N, Hjelm M, Patsalos P. Antiepileptic drug pharmacokinetics and neuropharmacokinetics in individual rats by repetitive withdrawal of blood and cerebrospinal fluid: phenytoin. *Epilepsy Res* 1994;19:99–110.
13. Woodbury DM. Phenytoin: proposed mechanisms of anticonvulsant action. *Adv Neurol* 1980;27:447–71.