PROPHYLACTIC ANTIEPILEPTIC DRUGS IN PATIENTS WITH BRAIN TUMORS

Seizure Prophylaxis in Patients with Brain Tumors: A Meta-analysis

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PURPOSE: To assess whether antiepileptic drugs (AEDs) should be prescribed to patients with brain tumors who have no history of seizures.

METHODS: We performed a meta-analysis of randomized controlled trials (1966 to 2004) that evaluated the efficacy of AED prophylaxis versus no treatment or placebo to prevent seizures in patients with brain tumors who had no history of epilepsy. Summary odds ratios were calculated by using a random-effects model. Three subanalyses were performed to assess pooled odds ratios (ORs) of seizures in patients with primary glial tumors, cerebral metastases, and meningiomas.

RESULTS: Of 474 articles found in the initial search, 17 were identified as primary studies. Five trials met inclusion criteria: patients with a neoplasm (primary glial tumors, cerebral metastases, and meningiomas) but no history of epilepsy who were randomized to either an AED or placebo. The three AEDs studied were phenobarbital, phenytoin, and valproic acid. Of the five trials, four showed no statistical benefit of seizure prophylaxis with an AED. Meta-analysis confirmed the lack of AED benefit at 1 week (OR, 0.91; 95% confidence interval [CI], 0.45–1.83) and at 6 months (OR, 1.01; 95% CI, 0.51–1.98) of follow-up. The AEDs had no effect on seizure prevention for specific tumor pathology, including primary glial tumors (OR, 3.46; 95% CI, 0.32–37.47), cerebral metastases (OR, 2.50; 95% CI, 0.25–24.72), and meningiomas (OR, 0.62; 95% CI, 0.10–3.85).

CONCLUSIONS: No evidence supports AED prophylaxis with phenobarbital, phenytoin, or valproic acid in patients with brain tumors and no history of seizures, regardless of neoplastic type. Subspecialists who treat patients with brain tumors need more education on this issue. Future randomized controlled trials should address whether any of the newer AEDs are useful for seizure prophylaxis.

COMMENTARY

Prescribing prophylactic antiepileptic drugs (AEDs) for patients with cerebral tumors is not rooted in evidence-based decision making. Seizures may be associated with cerebral tumors in several ways. In many instances, seizures are the presenting symptom of the tumor. They are associated with 75% of oligodendrogliomas, 20% of cerebral metastases, and 27% of meningiomas (1,2). The occurrence of seizures after a diagnosis of cerebral tumor based on other symptoms also is common (15–45%) and may herald tumor progression (3,4). In addition, seizures are more common with supratentorial tumors than with infratentorial tumors, with tumors near the rolandic area, and with primary brain tumors (2). The incidence of seizures also varies with tumor histology, being higher with anaplastic astrocytomas, meningiomas, oligodendrogliomas, and metastatic melanomas and relatively lower with other cerebral metastases.

Seizures can be particularly destructive in the patient with an intracerebral neoplasm. Focal cerebral edema, due to ictal increases in cerebral blood flow and relaxation of the blood–brain barrier, may lead to increased intracranial pressure. Postictal paralysis may be unusually prolonged, or even permanent. It may not be surprising, then, that 33% of radiation oncologists, 53% of neurologists, and 81% of neurosurgeons in a 1996 study routinely used AEDs to prevent new-onset seizures in patients with cerebral tumors (5).

In 2000, however, the American Academy of Neurology published a practice parameter recommending that "prophylactic anticonvulsants should not be used routinely in patients with newly diagnosed brain tumors," and that such drugs be tapered within a week after surgery for such tumors (6). Four years later,

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relying on the additional evidence of a prospective, randomized trial that involved 100 patients with brain tumors, Sirven et al. summarized the convincing body of literature demonstrating lack of efficacy of prophylactic AED treatment in this context. Phenytoin (PHT), phenobarbital, and valproate are the only AEDs subjected to prospective, randomized, controlled trials of seizure prophylaxis in patients with cerebral tumors, and no benefit has been demonstrated.

AEDs not only are ineffective seizure prophylaxis in patients with cerebral tumors, but also may pose more risk of complications than in other patients. First, mutual interactions between enzyme-inducing AEDs and other drugs commonly used in these patients may be significant. Corticosteroids and the chemotherapeutic agents bischloroethylnitrosourea, cisplatin, carboplatin, and taxol can reduce AED serum concentrations by enzyme induction or reduction in bioavailability. Conversely, PHT levels are increased by concomitant use of 5-fluorouracil. Valproate can inhibit the metabolism of nitrosoureas and etoposide, causing clinical toxicity, and PHT may increase the dose requirement for corticosteroids and tamoxifen (2,7).

In addition, the risk of potentially serious allergic reactions to AEDs is increased in patients receiving treatment for brain tumors. Skin rashes with PHT or carbamazepine have been reported in 25% of patients with malignant gliomas (8). Severe erythema multiforme, Stevens–Johnson syndrome, and toxic epidermal necrolysis have been described with patients taking PHT, usually in association with tapering doses of corticosteroids. The observation that some of these rashes begin within the treatment field on the scalp suggests that the radiation may play a direct role in enhancing an allergic response, perhaps by depressing T-suppressor activity (9). However, no studies have examined the prophylactic effects of any of the newer generation of AEDs, and the risks of allergic reactions as well as complications related to drug interactions may be different with some of these drugs.

Because the purpose of treatment may be antiepileptogenic as much as antiepileptic, investigation of neuroprotective agents that may have an antiepileptogenic effect also may be valuable (10). Observations on the relative intractability of tumor-associated epilepsy, however, suggest that some of the failures to demonstrate benefit from prophylactic treatment from older AEDs may be related to epileptogenic processes that may already have occurred before diagnosis of the tumor.

Finally, the heterogeneous tumor types in various studies may have resulted in inadequate power to detect a prophylactic drug effect in some tumor types. The cumulative incidence of seizures in patients with metastatic melanoma, for example, is about 50%, and the risk/benefit ratio of AED use in these cases has not been independently investigated. A prospective, placebo-controlled trial seems ethically acceptable, given the current state of knowledge.

by Donna C. Bergen, MD

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