

HEPATIC ENZYME INDUCTION: IT DOES REALLY MATTER

P450 Enzyme Inducing and Nonenzyme Inducing Antiepileptics in Glioblastoma Patients Treated with Standard Chemotherapy

Oberndorfer S, Piribauer M, Marosi C, Lahrmann H, Hitzenberger P, Grisold W

J Neurooncol 2005;72(3):255–260.

The coadministration of antiepileptic drugs (AED) and chemotherapeutic agents in patients with glioblastoma multiforme (GBM) is common. Interactions of chemotherapeutic agents and AED have not been investigated sufficiently. The purpose of this study is to evaluate the effects of enzyme inducing (EI-AED) and non-EI-AED in patients with GBM treated with standard chemotherapeutic agents on survival and hematotoxicity. One hundred sixty-eight glioblastoma patients with standard treatment including surgery, radiotherapy, and chemotherapy were retrospectively analyzed. Patients were separated into three groups: *Group A* patients without AED ($n = 88$), *Group B* patients with EI-AED ($n = 43$), and *Group C* patients with non-EI-AED ($n = 37$). CCNU was the most frequently used first-line drug in all three groups (*Group A*: 77%; *Group B*: 81%; *Group C*: 78%). Second-line treatment, mainly temozolomide, was applied in 58 patients and third-

line treatment in 9. Carbamazepine was the most frequently administered AED in *Group B* (81%) and valproic acid in *Group C* (85%). For statistical analysis, only patients with CCNU first-line treatment were calculated. A significant difference regarding survival was detected between *Group B* (10.8 month) and *Group C* (13.9 month), as well as increased hematotoxicity for *Group C*. These results indicate that AED influence the pharmacokinetics of chemotherapeutic drugs in patients with GBM. Valproic acid might be responsible for increasing hematotoxicity. Whether the difference regarding survival between *Group B* and *Group C* is due to a decrease of efficacy of chemotherapeutic agents by EI-AED, or due to increased efficacy of chemotherapeutic agents caused by the enzyme-inhibiting properties of valproic acid, has to be evaluated in future studies.

COMMENTARY

This very interesting retrospective study appears to show differences in survival rates among patients with glioblastoma multiforme who required treatment with antiepileptic medications concurrently with chemotherapy. The presence of seizures in patients with glioblastoma is common. In this series, seizures requiring treatment occurred in 48% of the patients. The drug interaction of most concern was with CCNU (lomustine), a nitrosurea, which is known to be metabolized via cytochrome P-450. CCNU was used as the first-line treatment in the majority of the patients studied. It is not surprising that interactions, if present, would be clinically important, since chemotherapeutic agents are known to have a relatively narrow

therapeutic window. In other words, underdosing chemotherapeutic agents may lead to lack of effect, and overdosing may lead to serious toxicity.

The study was somewhat limited by its retrospective nature as well as by the absence of a sufficient number of patients who were on enzyme “neutral” antiepileptic drugs (i.e., neither inhibiting nor inducing), who could have served as an interesting control group. Without this group, it is unclear from the results whether there was reduced survival in patients receiving enzyme-inducing antiepileptic drugs as a consequence of increased clearance of chemotherapy or whether there was an enhanced survival in patients receiving valproic acid because of hepatic enzyme inhibition associated with that medication. On the surface, it might appear that enzyme induction had no impact, since patients who were on enzyme-inducing antiepileptic drugs had the same survival rate as patients taking no antiepileptic drug. However, this may not in fact be the case. Some studies

indicate that glioblastoma patients with concurrent seizures are diagnosed earlier and may have a longer survival for that reason (1). Therefore, the equal survival rate in these two populations may in fact be a sign that survival in the seizure group on enzyme inducers was lower than expected, whereas those on valproate and other nonenzyme inducers was appropriately increased.

The Oberndorfer et al. study is not the first to suggest that enzyme-inducing antiepileptic drugs may influence survival in patients with malignancies. In a chilling article by Relling and colleagues, in which children with acute lymphoblastic leukemia were studied retrospectively (2), those who had received enzyme-inducing antiepileptic drugs had a lower event-free survival and higher hematologic and CNS relapse rates. Since some of the children had been treated on a protocol, pharmacokinetic data were available on serum concentrations of their chemotherapeutic agents. Overall systemic exposure for two of the agents, methotrexate and teniposide, was significantly lower in the patients receiving enzyme-inducing antiepileptic drugs. The authors concluded that the poorer outcome in these children was directly related to treatment with enzyme-inducing antiepileptic drugs, and therefore, patients should be treated with non-enzyme-inducing agents, if at all possible. Enzyme-inducing antiepileptic drugs also have been found to influence the metabolism of other chemotherapeutic agents, such as cyclophosphamide, ifosfamide, busulfan, teniposide, etoposide, paclitaxel, and vinca alkaloids (3).

It may seem surprising to epileptologists, who are accustomed to monitoring serum concentrations and assessing drug interactions, that concentration monitoring is not routinely performed for older chemotherapeutic agents. Rather, patients are usually treated according to body weight and age. For agents developed more recently, clinical trials have usually separated patients into those receiving and not receiving enzyme-inducing antiepileptic drugs, and appropriately adjusted dosing schedules are provided, where indicated. However, use of the older chemotherapeutic agents is still prevalent (80% in the present study). Since the degree of enzyme induction from patient to patient is variable, it potentially would be dangerous to make a systematic increase in dosing these patients in the absence of clinical trial data, which currently do not exist. Therefore, patients receiving enzyme-inducing antiepileptic drugs continue to be underdosed.

This article highlights a potential untoward effect for patients with malignancy who concurrently must receive antiepileptic drugs. Although the consequences in this particular situation are dire, malignancies are not that common. However, chemotherapeutic agents may represent only the

tip of the iceberg for adverse consequences associated with enzyme-inducing drugs. Many commonly used medications are metabolized through the cytochrome P-450 system, including antidepressants, calcium channel blockers, some antibiotics, antifungal agents, antipsychotics, hydroxymethylglutaryl (HMG)-CoA reductase inhibitors, steroids, oral hypoglycemic, and of course, oral contraceptives (3). None of these medications are routinely monitored via serum drug concentrations. As is the case with CCNU, they are typically dosed according to FDA-approved labeling, with no accommodation for patients simultaneously receiving enzyme-inducing antiepileptic drugs. The clearance of these drugs may be increased by 50% or more by concomitant use of enzyme-inducing medications. In some cases, the results have been easy to identify, and corrective steps have been taken by the medical community. For example, the discovery of contraceptive failure in women taking enzyme-inducing antiepileptic medications has led to the common practice of recommending an increase in estrogen dose to 50 μg for these women (4). However, many of the consequences of increased clearance of concomitant medications may be more difficult to identify. If a patient receiving enzyme-inducing antiepileptic drugs is initiated on an antidepressant, for example, a failure to respond at typical drug dosages may be incorrectly interpreted as drug-resistant depression. Of greater concern, a lesser response may be overlooked altogether. Either of these effects would be very difficult to ascertain in a retrospective or even a prospective study.

In summary, this study brings attention to a drug interaction that may be common among patients with epilepsy. The clinical consequences of the interaction between enzyme-inducing antiepileptic drugs and other agents have been poorly studied and, certainly, further investigation is warranted.

by Jacqueline A. French, MD

References

1. Ozbek N, Cakir S, Gursel B, Meydan D. Prognostic significance of seizure in patients with glioblastoma multiforme. *Neurol India* 2004;52:76–78.
2. Relling MV, Pui CH, Sandlund JT, Rivera GK, Hancock ML, Boyett JM, Schuetz EG, Evans WE. Adverse effect of anticonvulsants on efficacy of chemotherapy for acute lymphoblastic leukaemia *Lancet* 2000;356:285–290.
3. Patsalos PN, Perucca E. Clinically important drug interactions in epilepsy: interactions between anti-epileptic drugs and other drugs. *Lancet Neurol* 2003;2:473–481.
4. Crawford P. Interactions between antiepileptic drugs and hormonal contraception. *CNS Drugs* 2002;16:263–272.