From the Canadian Association for Child Neurology

Routine screening of blood and urine for severe reactions to anticonvulsant drugs in asymptomatic patients is of doubtful value

Peter Camfield, MD, FRCPC
Carol Camfield, MD, FRCPC
Joseph Dooley, MB, FRCPC
Kevin Farrell, MB, FRCPC
Peter Humphreys, MD, FRCPC
Pierre Langevin, MD, FRCPC

Severe or fatal reactions to anticonvulsant agents are fortunately rare. We examined the value of routine screening of blood and urine to detect early signs of such reactions in asymptomatic patients. The basic assumptions of this type of screening program have been faulty or unproven, and the results of studies, although not definitive, have not supported the value of such programs. Our recommendations, approved by the Canadian Association for Child Neurology, suggest that asymptomatic patients not undergo routine screening of blood and urine but, rather, be informed of the early symptoms of severe toxic reactions and be asked to report them immediately to a physician.

Il est heureusement rare qu'on observe des réactions mortelles, voire graves, aux anticonvulsivants. On discute ici de la question de savoir si les analyses systématiques du sang et de l'urine permettent de les déceler chez le sujet qui ne présente pas de symptômes d'intoxication. Ce genre de dépistage repose sur des suppositions erronées ou du moins non prouvées. Bien que les essais dans ce sens ne soient pas terminés, les résultats obtenus jusqu'ici ne justifient pas ces analyses systématiques. Avec l'aval de l'Association canadienne de neurologie pédiatrique, nous recommandons plutôt d'expliquer aux patients ne présentant pas de symptômes d'intoxication comment être à l'affût de ceux-ci dès leur début et, le cas échéant, les signaler tout de suite au médecin.

From the Izaak Walton Killam Hospital for Children, Halifax, British Columbia's Children's Hospital, Vancouver, the Children's Hospital of Eastern Ontario, Ottawa, and Centre hospitalier de l'université Laval, Ste-Foy, PQ

Approved by the Canadian Association for Child Neurology at its annual meeting, held in Quebec June 16, 1988

Reprint requests to: Dr. Peter Camfield, Department of Neurology, Izaak Walton Killam Hospital for Children, PO Box 3070, Halifax, NS B3J 3G9

In 1965 DeVries[1] recommended that patients receiving anticonvulsant drugs undergo regular screening of blood and urine to avoid rare severe or fatal reactions. This recommendation has not been critically appraised, and yet it appears in most of the descriptions of anticonvulsant drugs in the Canadian *Compendium of Pharmaceuticals and Specialties*[2] (*CPS*) and the US *Physicians' Desk Reference*[3] (*PDR*).

We were asked by the Canadian Association for Child Neurology to form an ad hoc committee to examine the value of routine screening. We hypothesized that such a program would not be helpful and might occasionally interfere with treatment.

Background information

Anticonvulsant drugs on rare occasions induce severe or fatal reactions, such as aplastic anemia, hepatitis, nephritis and Stevens–Johnson syn-

← For prescribing information see page 1327

drome.[4] The exact frequency of such reactions is uncertain but has been estimated to be about 1 per 50 000 patients.[4]

Screening to avoid such reactions is advocated on the basis of three assumptions. First, severe or fatal reactions are assumed to be idiosyncratic and unpredictable in an individual patient. Spielberg and associates[5] suggested that those at risk might eventually be identifiable before treatment. They found that some patients with severe adverse reactions to certain anticonvulsant drugs have a genetically determined abnormality in arene oxide metabolism. Such abnormalities have been demonstrated in the lymphocytes of patients with phenytoin-induced hepatitis and of those with aplastic anemia due to phenytoin and carbamazepine.[5,6] Despite these findings, there is still no readily available way to identify a patient at risk for an adverse reaction.

Second, it is assumed that a presymptomatic phase occurs before the reaction and that it can be detected by means of screening blood and urine. To our knowledge this assumption has not been proven for any anticonvulsant drug, and in most cases the onset of reactions is sudden; for example, a child died from valproate-induced liver failure 1 week after screening had revealed a normal serum aspartate aminotransferase level.[7]

Third, if a reaction is detected in the presymptomatic phase, then the severity of the reaction is assumed to be limited after the anticonvulsant therapy is stopped. Although possibly correct this assumption has not been tested. In some cases it appears that the reaction cannot be altered once it begins.[8]

For these reasons we believe that there is no clear medical rationale for the screening recommended in the *CPS* or the *PDR*.

Studies of screening for anticonvulsant reactions

Two studies have directly addressed the screening question. In the first,[9] 199 children with epilepsy underwent prospective screening of blood and urine with conventional tests to detect toxic effects on the liver, blood and kidneys. Screening was done before the start of anticonvulsant therapy, 1, 3 and 6 months afterward, and then every 6 months. The drugs included phenobarbital, phenytoin, carbamazepine and valproic acid. No serious clinical reactions were detected, and the number of abnormal test results was equally great before and during therapy. Six percent of the tests had to be repeated because of abnormal findings, yet the repeat tests showed results that were closer to normal even though there had been no change in the anticonvulsant doses. The authors noted that therapy had been unnecessarily stopped in two cases because of screening test abnormalities.

In the second prospective study,[10] 662 adults with newly diagnosed epilepsy were randomly assigned to receive carbamazepine, phenytoin, phenobarbital or primidone and were screened for at least 6 months. None of the patients stopped taking their medication because of drug-related changes in laboratory results. The authors concluded that routine screening is probably not cost-effective and has doubtful clinical value for asymptomatic patients taking one antiepileptic drug.

Because severe or fatal reactions did not occur in either study, the issue of the sensitivity of screening has not been settled. A definitive test of the value of screening is virtually impossible. The issue could only be completely settled through a randomized controlled trial of screening versus no screening, and a sample of about 1 million patients with epilepsy would be required.[9]

The distinction between abnormal test results and severe reactions is important. For example, in one study 27 of 200 children treated with carbamazepine had a leukocyte count of less than 4.0 $\times 10^9$/L at some point during treatment;[11] however, none had a clinical reaction, and the leukopenia was transient in nearly all. In three of the children therapy was stopped because neutropenia persisted (duration not stated), even though there were no symptoms. In a detailed study of liver function tests in 25 patients receiving valproic acid 4 patients were found to have increased levels of serum aspartate aminotransferase.[12] Three were asymptomatic; the dose was reduced, and the level returned to normal. The fourth patient had leg edema and malaise but recovered after the valproic acid therapy was stopped. Thus, the specificity of an abnormal screening test result is very low for a clinically significant toxic reaction.

Problems with screening

The frequency of screening recommended by the drug manufacturers is almost impossible to achieve in routine clinical practice, especially in the treatment of "needle-shy" children. For example, in the section on carbamazepine in the *PDR* it is recommended that screening of blood counts, reticulocyte counts and serum iron levels be done once before treatment, weekly for 3 months and monthly thereafter for 2 to 3 years and that baseline and periodic liver function tests also be done.[13] For valproic acid the recommendations are slightly less specific, but it is suggested that liver function tests be done "at frequent intervals", especially during the first 6 months of treatment.[14]

A basic premise in screening is that all abnormalities in test results, however slight, must be promptly rechecked and the patient re-examined immediately, since any abnormal finding may indicate the beginning of a severe reaction. In one study this meant repeating 6% of all the tests.[9] This is time consuming and causes anxiety for both the family and the physician.[14]

We suspect that in some cases successful antiepileptic treatment is interrupted unnecessarily when screening reveals abnormalities.

Lastly, the screening process is very expensive. If every patient with epilepsy in North America were tested three times each year for blood counts and the serum aspartate aminotransferase level the annual cost would exceed $400 million. This amount exceeds all annual funds in North America devoted to epilepsy research[9] and does not account for time spent by physicians or time lost from work by families.

Alternatives

If we assume that routine screening is ineffective, bothersome to patient care and expensive there must be another way to approach the very real but rare problem of severe reactions to anticonvulsant drugs.

Patients must be informed of the risk of severe reactions despite their rarity. They should not be led into a false sense of security because of a screening program but, rather, be informed of the symptoms that occur early in a toxic reaction and be asked to report them immediately to their physician. A rash is usually the first sign of a severe reaction to phenobarbital, carbamazepine or phenytoin.[4] Liver failure due to valproic acid is almost always heralded by anorexia, lethargy and vomiting.[15] Aplastic anemia can be the result of any anticonvulsant drug and is accompanied by infection, bruising and symptoms of anemia.[4] We realize that the value of such a "clinical" screening program remains to be determined but believe that it is at least a more realistic way to attempt to identify patients with serious drug reactions as soon as possible.

More research is needed to predict who will have toxic reactions. Studies have revealed an association between toxic effects of valproate and low age (especially less than 2 years) and polytherapy.[15] This association may result in the decreased use of valproate in this high-risk group and thus a reduction in the number of patients with drug-related liver failure.[15] Caution in administering phenytoin to patients undergoing radiotherapy may decrease the number of severe cases of exfoliative dermatitis.[8]

Severe reactions to anticonvulsant drugs will probably continue to occur in some patients regardless of the contraindications that eventually might be discovered. However, routine screening will likely not prevent these disasters.

Recommendations

- Before anticonvulsant therapy is started patients should be informed, preferably in writing, of the possible severe reactions and the early symptoms. They should be warned to contact their physician immediately if any of the symptoms develop.
- Baseline liver function tests and a complete blood count and platelet count before treatment may be worth while to avoid exacerbation of an underlying problem or to help interpret abnormal test results later.
- Routine screening of blood and urine for severe reactions to anticonvulsant drugs has no proven value and is not recommended in asymptomatic patients.
- Blood and urine tests could be considered if a patient reports a rash or unexplained illness.
- Further research is needed to identify patients at risk for severe reactions to anticonvulsant drugs.

References

1. DeVries SI: Haematological aspects during treatment with anti-convulsant drugs. *Epilepsia* 1965; 6: 1-15
2. Krogh CME (ed): *Compendium of Pharmaceuticals and Specialties*, 23rd ed, Canadian Pharmaceutical Association, Ottawa, 1988
3. *Physicians' Desk Reference*, Med Economics, Oradell, NJ, 1988
4. Schmidt D: *Adverse Effects of Antiepileptic Drugs*, Raven, New York, 1982
5. Spielberg S, Gordon G, Blake D et al: Predisposition to phenytoin hepatotoxicity assessed in vitro. *N Engl J Med* 1981; 305: 722-728
6. Gerson W, Fine S, Spielberg S et al: Anticonvulsant-induced aplastic anemia: increased susceptibility to toxic drug metabolites in vitro. *Blood* 1983; 61: 889-893
7. Fenichel GM: Valproate hepatotoxicity: two new cases, a summary of others and recommendations. *Pediatr Neurol* 1985; 1: 109-113
8. Delattre JT, Safai B, Posner JB: Erythema multiforme and Stevens-Johnson syndrome in patients receiving cranial irradiation and phenytoin. *Neurology* 1988; 38: 194-197
9. Camfield C, Camfield P, Smith E et al: Asymptomatic children with epilepsy: little benefit from screening for anticonvulsant-induced liver, blood or renal damage. *Neurology* 1986; 36: 838-841
10. Mattson RH, Cramer JA, Collins JF et al: Connective tissue changes, hypersensitivity rash and blood laboratory test changes associated with antiepileptic drug therapy [abstr]. *Ann Neurol* 1986; 20: 119-120
11. Silverstein FS, Boxer L, Johnstone M: Hematological monitoring during therapy with carbamazepine in children [C]. *Ann Neurol* 1983; 13: 685
12. Willmore LJ, Wilder BJ, Bruni J et al: Effect of valproic acid on hepatic function. *Neurology* 1978; 28: 961-964
13. *Physicians' Desk Reference*, Med Economics, Oradell, NJ, 1988: 989
14. Ibid: 511
15. Dreifus FE, Santilli N, Langer DH et al: Valproic acid fatalities: a retrospective review. *Neurology* 1987; 37: 379-385