More research needs to be devoted to prediction of who will develop toxic reactions. Studies such as those noting the association of valproate toxicity with young age (especially under two years) and polytherapy may reduce the number of patients with valproate liver failure by limiting the use of the drug in this higher risk group.[15] Caution in using phenytoin in patients undergoing radiotherapy may decrease some of the severe exfoliative dermatitis problems induced by phenytoin.[8] It is probable that some patients will continue to suffer severe adverse effects from anticonvulsants regardless of the number of contraindications that are proven. However, routine blood and urine screening does not appear at all likely to prevent these disasters.

Recommendations

1. Before starting an anticonvulsant patients should be informed, preferably in writing, of the possible severe adverse reactions and the early symptoms of the reaction. They should be warned to contact their physician immediately if these symptoms develop.
2. Prior to treatment, baseline liver function tests and a complete blood count and platelet count may be worthwhile to avoid exacerbating an unrecognized underlying problem or to help interpret abnormal tests at a later date.
3. Routine blood and urine screening for severe anticonvulsant reactions is of no proven value and is not recommended in asymptomatic patients receiving antiepileptic medications.
4. Patients receiving anticonvulsant medication should contact their physician if they have a rash or unexplained illness. At that time, blood and urine tests could be considered.
5. Further research is needed to identify patients at risk for serious anticonvulsant reactions.

Committee Members

Peter Camfield
Carol Camfield
Joseph Dooley
Kevin Farrell
Pierre Langevin
Peter Humphreys

References

1. DeVries SI. Haematological aspects during treatment with anticonvulsant drugs. Epilepsia 1965; 6: 1-15.
2. Compendium of Pharmaceuticals and Specialties, Canadian Pharmaceutical Association 1988, Southam Murray, Toronto.
3. Physicians' Desk Reference, Medical Economics Co., Oradell, N.J., 1988.
4. Schmidt D. Adverse effects of antiepileptic drugs. New York: Raven Press, 1982.
5. Spielberg S, Gordon G, Blake D, Goldstein D, Herlong A. Predisposition to phenytoin hepatotoxicity assessed in vitro. N Engl J Med 1981; 305: 722-8.
6. Gerson W, Fine S, Speilberg S, Sensenbrenner L. Anticonvulsant-induced aplastic anemia: increased susceptibility to toxic drug metabolites in vitro. Blood 1983; 61: 8, 889-893.
7. Fenichel GM. Valproate hepatotoxicity: two new cases, a summary of others and recommendations. Pediatric Neurology 1985; 1: 109-13.
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, Tibbles JAR. 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 and the VA Epilepsy Cooperative Study Group. Connective tissue changes, hypersensitivity rash and blood laboratory test changes associated with antiepileptic drug therapy. Annals of Neurology 1986; 20: 119-120 (Abstract).
11. Silverstein FS, Boxer L, Johnstone M. Hematological monitoring during therapy with carbamazepine in children. Annals of Neurology 1983; 13: 685 (letter).
12. Willmore LJ, Wilder BJ, Bruni J, Villareal HJ. Effect of valproic acid on hepatic function. Neurology 1978; 28: 961-4.
13. Physicians' Desk Reference, Medical Economics Co., Oradell, N.J., 1988, p. 989.
14. Ibid. p. 511.
15. Dreifus FE, Santilli N, Langer DH, Sweeney KP, Moline KA, Menander KB. Valproic acid fatalities: A retrospective review. Neurology 1987; 37: 379-385.

Screening of the Epileptic Patient - Is it worth the trouble?

Robert H.A. Haslam and Gideon Koren

From the Department of Pediatrics and the Division of Clincial Pharmacology & Toxicology, Hospital for Sick Children, Toronto, Ontario

Anyone who treats epileptic patients with anticonvulsants is wary of their potential side-effects which on rare occasion can cause death due to aplastic anemia, Stevens-Johnson syndrome or hepatotoxicity. Current dogma suggests that newly treated patients be followed with routine blood tests, including a complete blood count and liver function studies, particularly during the initial several months of treatment. It is the hope that an abnormal test will identify patients at risk for serious drug reactions and that promptly discontinuing the anticonvulsant will prevent the serious consequences. Unfortunately, such is not the case, as most deaths appear to be idiosyncratic and may occur in the face of relatively normal laboratory data. However, there are reports of patients who tolerate an anticonvulsant for months and then suddenly develop symptoms of toxicity. Some of these patients did not have routine blood screening nor symptoms of an idiosyncratic reaction prior to death.[1] Would screening have prevented fatal illness in such patients?

Camfield et al suggest that routine screening of asymptomatic patients is unwarranted as the exercise will not likely identify patients at risk and furthermore the costs would be prohibitive. They recommend that education of the parents or patient as to the early warning symptoms of an idiosyncratic reaction fol-

https://doi.org/10.1017/S0317167100029267 Published online by Cambridge University Press

lowed by immediate withdrawal of the drug is likely to be much more effective. While we agree with the general principles advanced by Camfield and colleagues, we take exception to the theme that screening has no role to play in the identification of at risk patients.

Certain groups of patients are statistically more likely to have severe drug reactions to anticonvulsants. For example, epileptic children less than two years of age with an underlying neurological disorder, developmental delay or mental retardation who are treated with several anticonvulsants, including valproic acid have a 1/500 risk of developing fatal hepatotoxicity compared to the overall risk of 1/10,000.[2,3] A recently published follow-up study shows that the overall fatality rate has decreased significantly (1/49,000) possibly because more patients are receiving valproic acid as monotherapy and fewer high risk patients are prescribed the drug. Nonetheless, young patients remain at risk whether treated with monotherapy or polytherapy.[4] Although monotherapy is associated with less risk and routine screening may not identify the child who might succumb from valproic acid toxicity, it would be prudent to observe this group of children closely for clinical and laboratory evidence of an abnormality. Departure from the norm of any parameter should be cause for immediate removal of valproic acid in this cohort of patients.

Smith et al reported 6 deaths in children 3 to 10 years of age following an episode of status epilepticus.[5] Each had received multiple anticonvulsants (valproic acid in only one) for chronic and recalcitrant seizures. Examination of the liver indicated massive hepatic necrosis which was not pathognomonic of a specific cause such as anoxia or an idiosyncratic reaction. No one drug could be implicated. It was hypothesized that a metabolic event (such as accumulation of a neuropeptide in the brain) following a prolonged seizure may have produced increased vulnerability to the anticonvulsants. Apparently no patient was routinely monitored so that it is impossible to know whether the irreversible hepatic failure could have been prevented.

It is well known that some antiepileptics induce dose and concentration - dependant alterations in liver function.[6,7] Although these changes do not lead to severe idiosyncratic reactions and are reversible by decreasing or discontinuing the drug, the clinical consequences of prolonged elevation of liver enzymes in the asymptomatic patient is not known. Could these changes be the harbinger of chronic liver abnormalities or susceptibility to a more serious drug reaction?

Patients with an idiosyncratic reaction to either phenytoin, carbamazepine, or phenobarbital may or may not be sensitive to the other two drugs. Recent studies by Spielberg et al in our institution successfully predict such cross reactivity using a lymphocyte test.[8] It appears that such patients have a genetic absence of an epoxide-hydrolase enzyme necessary for metabolizing a toxic intermediate. This screening test, which has enormous potential in predicting rare but serious adverse effects, will soon be available for large scale screening.

We conclude that certain high risk groups (eg., children less than 2 years of age on polytherapy including valproic acid or patients with a prolonged history of poorly responsive seizures that require multiple anticonvulsants) should undergo routine screening tests. Future investigations and experience will likely uncover additional at risk populations of patients who might benefit from such testing. Furthermore, studies are required to determine the long-term sequelae of chronically elevated liver function enzymes in asymptomatic patients. Finally, the methodology will soon be available to identify those patients who have had a severe reaction to an anticonvulsant and who are potentially at risk from the other conventional antiepileptics. Until further investigations clarify the issues noted above, we advocate screening of at risk groups of patients as well as education programs aimed at identifying the early symptoms of a severe adverse reaction.

References

1. Zucker E, Daum-Cohen MI. Fatal carbamazepine hepatitis. J Pediatr 1977; 91: 667-668.
2. Dreifuss E, Santilli N, Langer DH, et al. Valproic acid hepatic fatalities: a retrospective review. Neurology 1987; 37: 379-385.
3. Scheffner D, Konig St, Rauterberg-Ruland I, et al. Fatal liver failure in 16 children with valproate therapy. Epilepsia 1988; 29: 530-542.
4. Dreifuss FE, Langer DH, Moline KA, Maxwell BA. Valproic acid hepatic fatalities II, US experience since 1984. Neurology 1989; 39: 201-207.
5. Smith DW, Cullity GJ, Silberstein EP. Fatal hepatic necrosis associated with multiple anticonvulsant therapy. Aust NZ J Med 1988; 18: 575-581.
6. Deutsch J, Fritsch G, Giolles J. Effects of anticonvulsive drugs on the activity of gammoglutamyl-transferase and aminotransferases in serum. J Pediatr Gastroenterol Nutr 1986; 5: 542-548.
7. Haidukewych D, Geetha J. Chronic valproic acid and coantiepileptic drug therapy and incidence of increases in serum liver enzymes. Ther Drug Monitor 1986; 8: 407-410.
8. Shear NH, Spielberg SP. Anticonvulsant hypersensitivity syndrome; in vitro assessment of risk. J Clin Invest 1988; 82: 1826-1832.