Hematological Monitoring During Therapy with Carbamazepine in Children

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Carbamazepine (CBZ) is being prescribed more frequently for treatment of children and adults with generalized tonic-clonic and partial complex seizures. Early reports of aplastic anemia in elderly patients treated with this drug led to concern about its potential hematological toxicity. A variety of other hematological abnormalities have also been described in association with CBZ therapy, including agranulocytosis, thrombocytopenia, and transient leukopenia. The drug labeling recommends frequent blood tests and includes strict guidelines for discontinuation of therapy if relatively minor abnormalities occur, for example, total white blood cell count (WBC) less than 4,000 per cubic millimeter. Several authors have questioned the validity and practicality of these guidelines [1]. In fact, routine monitoring is not practiced at certain epilepsy centers. The major objection raised is that routine monitoring does not help predict which patients will develop severe idiosyncratic drug reactions.

It has been suggested that children are less likely than adults to develop hematological abnormalities while receiving CBZ therapy, but few large pediatric series have been reported. To determine the incidence and severity of hematological problems associated with CBZ, we reviewed the records of 200 children who attended the Pediatric Neurology Clinic at the University of Michigan Medical Center from 1978 to 1982 [4]. We compared two groups of patients. Group 1 consisted of 125 children in whom therapy was initiated before age 12 (39 were less than 6 years old); group 2 included 75 children who were between 12 and 17 years old at the start of therapy. Mean duration of treatment (18 months), mean CBZ level (6 μg/ml), and mean number of other anticonvulsants (1.5) were the same for the two groups. No patient developed any symptomatic hematological problem.

The Table summarizes the results of hematological surveillance in these children. Leukopenia (WBC less than 4,000 per cubic millimeter) was the most frequently noted abnormality and was almost twice as common in the younger age group. In most patients leukopenia resolved while CBZ therapy was continued, but 4 of the 200 had persistent or recurrent leukopenia while taking the drug. The drug was discontinued in 3 patients because of leukopenia. There was no detectable clinical difference between the patients in whom the drug was stopped and those for whom the decision was made to continue treatment.

Based on our experience and published series [3], it appears that CBZ is a relatively safe drug for children with seizures. However, although it is possible that leukopenia was sometimes unrelated to CBZ, its occurrence in a minority of patients merits further investigation and suggests that hematological surveillance is appropriate. Although reports in the literature are inconsistent about the value of routine blood counts in preventing or altering the outcome of idiosyncratic drug-related aplastic anemia, reputable authorities do recommend monitoring, especially for newer drugs [2]. The justifications for monitoring with CBZ therapy include early identification of patients developing potentially reversible symptomatic neutropenia or agranulocytosis, accumulation of more information about the natural history of drug-related leukopenia, and, possibly, early identification of patients developing aplastic anemia.

Hematological Abnormalities in Children Treated with Carbamazepine for Seizures

Abnormality	No. in Group 1 (n = 125)[a]	No. in Group 2 (n = 75)[b]
Hgb < 12 gm	0	0
WBC < 4,000/mm^3	21 (17%)	6 (8%)
WBC < 4,000/mm^3 3 mo or longer	4	0
Platelets < 200,000	2	2

[a]Age range, 1 to 11 years.
[b]Age range, 12 to 17 years.
Hgb = hemoglobin; WBC = white blood cell count.

The available data are insufficient to indicate the mechanism of neutropenia [5] or to support a particular schedule of laboratory testing. We suggest the following guidelines as a practical minimum:

1. Hemoglobin, hematocrit, WBC, and platelet estimate before therapy, monthly for six months, and then every three months.
2. If total WBC falls to less than 4,000 per cubic millimeter, neutrophil, platelet, and reticulocyte counts.
3. If neutrophil count falls to 1,000 to 1,500 per cubic millimeter and the patient is well, repeat in two weeks; if still in this range, consider discontinuing therapy unless strongly indicated. If neutrophil count drops below 1,000 per cubic millimeter, decrease dosage or discontinue drug and repeat count in two weeks.
4. If, in addition to neutropenia, there is a depression in platelet or reticulocyte count, hematological consultation is advisable.

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Familial Periodic Paralysis: Low Muscle Potassium Permeability or High Sodium Permeability?

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The recent article in the *Annals* on periodic paralysis and the sodium potassium pump by Robert B. Layzer [5] ends with a provocative attempt to postulate a single membrane abnormality that accounts for the attacks of inexcitability of skeletal muscle in familial periodic paralysis. It would be satisfying indeed to demonstrate that a single pinpoint lesion of the membrane could lead to such an impressive symptom.

Layzer's hypothesis is based on the assumption that attacks are induced by the low extracellular potassium ($[K]_o$) concentration that is either caused locally in affected muscles or generalized in the whole body by overactivity of the Na-K pump during periods of rest. Inexcitability results, according to this hypothesis, from depolarization of the membrane caused by a decrease in permeability to potassium (P_K). The P_K is lowered, supposedly, by the effect of the low $[K]_o$ on the potassium permeability of the membrane. By itself the decrease in P_K can increase the membrane potentials to values above -50 mV, enough to inactivate fast sodium transport. Layzer supposes that, as in cases of barium poisoning, membrane voltage can be temporarily maintained close to its normal level by the electrogenic part of the Na-K pump, its effect enhanced by the increased membrane resistance.

Apart from the fact that the hypothesis fails to explain why paresis develops before $[K]_o$ is lowered, it is not in keeping with pertinent observations made by a number of investigators. Most direct measurements of membrane voltage have revealed that during attacks the membrane is inexcitable but nevertheless not or only slightly depolarized [4, 6, 7, 8], and rarely depolarized far enough to fully inactivate fast sodium transport. Moreover, direct measurements of total membrane resistance are consistent with an increase in P_K rather than with a reduction. From the simplified Hodgkin and Katz equations [3] valid for steady-state conditions, it can be calculated that for P_{Na}/P_K ratios above 0.05, membrane potential is practically constant for all practical values of $[K]_o$ below 4.5 mmol/L. All this evidence supports the hypothesis that during attacks P_{Na} increases and not that P_K decreases. In this respect it is interesting that procaine, which selectively blocks sodium transport, partly restores excitability [4].

The assumption that P_{Na} is raised is in agreement with observations pointing to a cell-inward transport of water and Na and Cl ions early during attacks. The presence of Na ions at the inner surface of the membrane always strongly stimulates active Na-K transport, which can lower serum potassium levels rapidly. As Layzer states [5], it would not be difficult to construct another hypothetical scheme based on high P_{Na}. A high P_{Na} seems more in keeping with the experimental data than does a low P_K. A high P_{Na}, however, does not automatically explain the inactivation of fast Na transport.

Therefore, the scheme needs to be expanded. Poisoning of the muscle membrane by a venom extracted from the scorpion centruroides sculpturatus provides an interesting model for familial periodic paralysis. This venom not only blocks fast Na transport, as does tetrodotoxin, but simultaneously increases resting P_{Na} [1]. The resulting changes in membrane properties closely parallel the observed changes during attacks of periodic paralysis. Scorpion venom is a polypeptide, and one can easily complete the high P_{Na} scheme by postulating an inborn error of cellular protein metabolism that occasionally leads to the synthesis of a toxic polypeptide. The sensitivity for rest after strenuous exercise, and for glucose and insulin, points in the same direction. It also fits in with the fact that continuously active muscles (such as those used in respiration) are usually not affected, and that acidosis, which inhibits protein synthesis, prevents attacks.

The assumption that protein synthesis is deranged may seem a bit farfetched, but ultrastructural analysis has revealed that the metabolic apparatus of the skeletal muscle cell is probably abnormal [2]. The idea that the attacks are caused by some form of autointoxication was formulated as early as 1891, but it remains difficult, and perhaps impossible, to prove such a postulated mechanism. Nevertheless, we believe that a high P_{Na} scheme fits the data far more closely than does the low P_K hypothesis.

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