Acute and Chronic Toxicity of Antiepileptic Medications: a Selective Review

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Abstract: Acute and chronic toxicity complicates all antiepileptic medications (AED) and is idiosyncratic. Acute toxicity can be categorized into 1) acute brain dysfunction or 2) acute organ dysfunction when AED's are started. Despite promising *in vitro* lymphocyte testing, anticipation of acute reactions cannot be offered. Furthermore, screening for AED toxicity by routine blood and urine tests in asymptomatic patients is of doubtful value and should be abandoned. Patients should be informed of possible reactions and immediately report early symptoms. Treatment for acute reactions is largely unstudied. It is unclear how to reintroduce AED's following acute reactions. Often patients are sensitive to drugs with a similar chemical structure. The "desensitization" protocol of Purvis may be of merit. Three major chronic toxicities of AED's have been noted – soft tissue and gum hypertrophy, progressive ataxia, and peripheral neuropathy. New AED's require careful post-marketing surveillance since long term toxicity data are not yet available.

Résumé: Toxicité aiguë et chronique des anticonvulsivants. La toxicité aiguë et chronique complique toute médication antiépileptique (MAE) et est idiosyncrasique. La toxicité aiguë peut être classifiée en 1) dysfonction cérébrale aiguë ou 2) dysfonction organique aiguë en début de traitement. Bien qu'il existe des épreuves lymphocytaires *in vitro* qui soient très prometteuses, on ne peut prédire les réactions aiguës. De plus, une épreuve sanguine ou urinaire de dépistage de la toxicité à la MAE chez des patients asymptomatiques a une valeur douteuse et devrait être abandonnée. Les patients devraient être informés qu'ils peuvent avoir des effets secondaires dont ils doivent rapporter les symptômes précocement. Le traitement des réactions aiguës a été peu étudié. La façon de réintroduire les MAEs après une réaction aiguë n'est pas claire. Les patients sont souvent sensibles à des médicaments qui ont une structure chimique semblable. Le protocole de "désensibilisation" de Purvis a peut-être de la valeur. Trois catégories de toxicité chronique par les MAEs ont été notées: l'hypertrophie des tissus mous et des gencives, l'ataxie progressive et la neuropathie périphérique. Les nouveaux MAEs doivent fiare l'objet d'une surveillance attentive après la mise en marché parce que leur toxicité à long terme n'est pas connue.

Can. J. Neurol. Sci. 1994; 21: Suppl. 3-S7-S11

This article concentrates on selected controversies about drug toxicity and is meant to be provocative rather than inclusive. We present our impressions based on published data and clinical experience. Readers are referred to several reviews of acute and chronic anti-epileptic drug (AED) toxicities for a more general perspective.[1-3]

Acute toxicity can be divided into acute brain dysfunction and acute organ failure. The frequency of severe acute reactions to antiepileptic medication with organ failure is uncertain but is estimated at 1 of 50,000 treated patients.[4]

Less severe "organ failure" reactions and acute brain dysfunction occur more frequently. About 15% of patients will have a biologic, cognitive or behavioral reaction to their first AED that is sufficient to warrant drug discontinuation.[5,6]

Acute toxicity – description and prediction

Acute organ failure

Acute organ failure generally occurs within the first 6 months of antiepileptic drug use. The reactions fall into two groups. With carbamazepine, phenytoin, phenobarbital and lamotrigine there is a so-called "allergic reaction" associated

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Presented in part at the Canadian Congress of Neurological Sciences Satellite Symposium, Toronto, Ontario, June 15, 1993.
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with rash, fever, and lethargy. It is unclear if these reactions are truly allergic. Most are fortunately mild.[7] On the other hand, there may be life-threatening illness involving one or more organ systems resulting in hepatotoxicity, bone marrow failure, nephritis, Stevens-Johnson syndrome or other systemic complications.[1] The mechanism for these catastrophic reactions is still unknown but could also be "allergic". Valproic acid is particularly associated with hepatic failure and pancreatitis, although nearly all AED's except benzodiazepines have been associated with a wide spectrum of severe reactions.

The basic tenet of acute toxicity is that it is idiosyncratic and unpredictable. An accurate method to predict acute organ failure toxicity would be highly desirable. Spielberg and associates suggested that a lymphocyte based assay might eventually identify those at risk before treatment.[8] They suggested that patients with severe adverse reactions to certain AED's have a genetically determined abnormality in arene oxide metabolism. Their studies demonstrated such abnormalities in the lymphocytes of patients with phenytoin-induced hepatotoxicity and aplastic anemia due to phenytoin and carbamazepine.[8,9]

Spielberg's hypothesis for the AED hypersensitivity acute organ failure syndrome is interesting. Some AED's are metabolized by the liver cytochrome P-450 enzyme system to an arene oxide. This compound is presumed toxic and capable of causing acute reactions. Normally, arene oxide is unstable and rapidly metabolized by epoxide hydrolase to a nontoxic compound. Spielberg, therefore, proposed that a relative deficiency in epoxide hydrolase would lead to high levels of arene oxide and acute toxic reactions.

A bioassay was developed in which mouse microsomes were used as a source of P-450 enzyme. When the AED is added, these microsomes metabolize the drug to its arene oxide. The patient's own live lymphocytes are added as a source of epoxide hydrolase. If the epoxide hydrolase is deficient, the lymphocytes are killed. The assay, therefore, counts numbers of surviving lymphocytes. Spielberg et al. studied 53 patients who had 80 reactions to phenobarbital, carbamazepine, or phenytoin – a number of these patients had reactions to two or all of these drugs. It was possible to correctly categorize 74 of the 80, although 6 of 80 were incorrectly categorized.

Using the same assay, family studies showed that parents of reacting patients had numbers of killed lymphocytes greater than controls but less than patients. This suggests that the proposed deficiency of epoxide hydrolase might be inherited in an autosomal recessive fashion.

Could this test, in its current form, be useful in clinical practice? Unfortunately, it has a sensitivity of only 75%. No prospective studies have been reported and the test is complex and expensive. The proposed mechanism for these toxic reactions may be correct and the lack of further research is disappointing.

An epidemiologic approach to predicting valproic acid hepatotoxicity was reported by Dreifus and coworkers in 1987.[10] They described the American experience with fatal liver failure associated with valproic acid in 37 patients. At that time, estimates from the pharmaceutical industry suggested that about 400,000 patients had been treated with valproic acid. Based on the age distribution of these patients, it was suggested that children under 2 years of age receiving polytherapy had a risk of fatal hepatitis of 1 in 500. For those older than 2 years, the estimate of risk was 1 in 12,000. Those on monotherapy and less than 2 years of age had a rate of 1 in 7,000, and if the child was older than 2 years, the rate was 1 in 45,000. Surprisingly, there were no cases in children older than 10 years of age. The analysis of these data was reported without statistical testing and the risk estimates were without confidence intervals. Given the small number of cases, the results should not be overly interpreted.

It is quite likely that a number of these young patients had an underlying disorder. It is thought that some had an inborn error of fatty acid metabolism, while others had the fatal syndrome described by Huttenlocker consisting of liver failure plus severe epilepsy with cortical atrophy.[11] Because their epilepsy is so severe, these patients are often treated with valproic acid in combination with other medications. Since their disorder is fatal without valproic acid, it is easy to overestimate the role of this AED in hepatic related deaths in small children.

Even though the Dreifuss paper has been widely quoted, there is another side to the controversy concerning the frequency of fatal hepatotoxicity. Scheffner reported similar data from the former West Germany.[12] From 1977-1986, there were 24 patients who died from valproic acid-associated hepatatoxicity. Scheffner personally reviewed 16 of the deaths.

The profile in the German series was not the same as the American experience. Five of 24 patients (21%) received monotherapy valproic acid; only 2/24 (8%) were under 2 years of age; and 1/24 (4%) was 17 years of age.

Therefore, risk factors for valproic acid-associated fatal hepatatoxicity are not clear cut. It is of interest that both Dreifus and Scheffner noted a similar clinical syndrome when their patients developed liver failure – nausea, vomiting, lethargy, anorexia, and edema prior to their final demise. An additional point emphasized by Dreifus was that "biochemical tests ... provided no clear evidence of hepatic injury in progress ...".

In summary, there are no currently available tests that accurately predict AED severe toxic reactions. The epidemiologic profile is not clear cut for those who die from valproic acid-associated hepatitis.

Screening for AC Reactions

Much effort and expense has been devoted to screening blood and urine from patients receiving AED's with the hope of recognizing the early stage of severe reactions. Screening is advocated on the basis of three assumptions – however, each appears tenuous and not scientifically substantiated. The first assumption is that there are identifiable patients at special risk. As discussed above, severe reactions are idiosyncratic and unpredictable in the individual patient. Therefore, all patients would have to be screened.

Second, it is assumed that there is a presymptomatic phase occurring before the clinically apparent reaction which can be detected by screening blood or urine. To our knowledge this assumption has not been proven for any antiepileptic drug, and in most cases the onset of the reaction is sudden. For example, Fenichel described a child with a normal physical examination and serum aspartate aminotransferase (SGOT) level one week before dying from fatal valproic acid-associated hepatitis.[13]

Third, if a reaction is detected in the presymptomatic phase, then the severity of the reaction is assumed to be limited after the AED is stopped. Again, this assumption has not been directly

https://doi.org/10.1017/S0317167100040750 Published online by Cambridge University Press

tested. In fact, in some cases it appears that the reaction cannot be altered once it begins.[14]

Two studies of screening for AED reactions have been published, one in children and another in adults. In Halifax, 199 children with newly treated epilepsy were studied prospectively.[15] All were placed on AED's which included either phenobarbital (n=62), carbamazepine (n=73), phenytoin (n=21), valproic acid (n=29) and other (n=14). Blood and urine screening was carried out before treatment and at 1, 3, 6, 12, 18, and 24 months. Blood tests included routine measures of haematologic, liver and pancreatic function.

There were no serious toxic reactions. However, there were many minor abnormalities in all laboratory tests seen equally with all AED's, *even* before medication was started. For example, 5 of 757 white blood counts were less than 3000/ml, but 3 of those 5 were before the drug was actually started. Two of 757 neutrophil counts were less than 1500; one before treatment was begun.

The same type of screening "errors" occurred with the SGOT. Overall, 14% of the SGOT (107/786) assessments were abnormal. For an individual patient, the original level did not change over the following 24 month period, and no patient developed toxic hepatopathy. Any abnormal SGOT was religiously repeated and always became closer to normal – without any reduction in the anticonvulsant dosage. Overall, the incidence of all screening abnormalities was the same for children on monotherapy or polytherapy.

It was interesting to note that these children also received a number of other medications. During the 24 month study period, they took 114 courses of antibiotics, 99 courses of antipyretics, and 66 courses of cold remedies. Therefore, when minor screening abnormalities are discovered, it becomes difficult to interpret which of the medications is the real culprit or if it was due to an intercurrent illness.

If screening is to detect the early, presymptomatic phase of a severe reaction, then any abnormal test must be repeated. Since the normal range of most laboratory tests will be exceeded by 3% of the healthy population, many screening tests must be repeated. We found that 6% of tests required a repeat determination. Does this matter? Certainly. It is inconvenient and anxiety provoking for the child and parent and may be expensive. Occasionally, it may also interfere with the child's treatment. For example, in the above study, a 10-year-old boy received phenytoin for post-traumatic epilepsy. His one month visit coincided with a bout of pharyngitis associated with a fine maculopapular rash. The white blood count was 1900/ml with only 2% neutrophils. Other screening tests were normal. Phenytoin was immediately discontinued but was restarted by a sceptical family physician 2 weeks later. Repeat CBC's were normal. This child's epilepsy control might have been seriously compromised by the discovery of a screening abnormality likely caused by viral pharyngitis.

The same conclusions concerning AED toxicity screening were reached by Mattson et al.[16] In the Veterans Administration Collaborative Study, 622 patients were randomized to either phenytoin, carbamazepine, phenobarbital or primidone. They were screened for at least 6 months. Nine percent of patients developed rash. None of the patients stopped the medication because of drug related laboratory changes. The authors concluded that "routine monitoring is not cost effective and of doubtful clinical value in the asymptomatic patient".

In 1989, the Canadian Association of Child Neurologists approved a position statement on routine screening of blood and urine in asymptomatic patients.[17,18] Overall the position paper concludes that routine screening is of doubtful value. There were five additional detailed conclusions:

1. Before anticonvulsant therapy is started, patients should be informed, preferably in writing, of the possible severe reactions and their early symptoms. They should be warned to contact their physician immediately if any of the symptoms develop. We suggest that patients be given handouts with this information to take home. We use them regularly and they are much appreciated by families.
2. 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 laboratory tests later. There is still disagreement amongst neurologists in Canada concerning the usefulness of this recommendation, because there are frequent screening abnormalities at the time of initiation of antiepileptic medications. In our personal practice we perform baseline tests less and less frequently.
3. Routine screening of blood and urine for severe reactions to anticonvulsant drugs has no proven value and is not recommended in asymptomatic patients.
4. Blood and urine tests could be considered if a patient reports a rash or unexplained illness. In other words, if a patient has symptoms, such as lethargy, vomiting, fever, or rash, this is the moment to request screening tests and to stop the medication if there is sufficient concern.
5. Further research is needed to identify patients at risk for severe reactions to anticonvulsant drugs.

Following the development of these recommendations, Pelekanos et al. evaluated the clinical features and management of allergic rash due to antiepileptic drugs.[7] A clinic population of 50 patients was identified with 68 allergic reactions to AED's. Thirty-six children had reacted to one drug, 10 to 2 drugs, and 4 to 3 drugs. Forty-six reactions were mild (rash only); 18 moderate (systemic symptoms or other organ system involvement); and 4 were life threatening – incidentally, all with phenobarbital. These rashes generally developed 2-3 weeks after the AED had been started. The frequency of a preceding history of medication or non-medication allergic reactions was similar to controls.

When these patients presented with an drug reactions, in most cases[59] the AED was stopped abruptly. In 5 cases it was tapered and in 4 the drug was continued. No patient developed status epilepticus. Later, 7 of these patients were rechallenged and 6 had recurrence of their reaction.

Presently, we approach an acute drug reaction with rash by stopping the medication immediately – the risk of status epilepticus seems to be very small. Treatment of the acute reaction depends on severity but prednisone should only be used with caution.[19] In general, we recommend restarting a different AED only after the rash is gone because of the confusion that arises from cross reactions. If a new AED is started before the rash has resolved, persistence or worsening of the rash may be the result of the original reaction or a cross reaction with the new drug – the new AED will need to be stopped, perhaps

unnecessarily. Rechallenge with the offending AED does not seem to be of any benefit in most patients, unless there is real doubt as to causality. If the reaction has been very severe with carbamazepine, phenobarbital or phenytoin, we try to choose a drug with a different chemical structure; usually valproic acid or clobazam.

Desensitization has been attempted following carbamazepine skin rash.[20-22] In 1988, Purvis described 5 patients with previous severe skin reactions to carbamazepine, but ongoing poorly controlled epilepsy. A desensitization protocol was used starting with a dose of 2.5 mg/day orally, plus an antihistamine. The dose was doubled every 3 days. If the rash reappeared, the dose was decreased to its previous level for 6 days before increasing it once again. In 4 of 5 cases, an average normal adult dosage was reached and maintained with no serious complications. This protocol appears safe and may benefit patients who with previous serious reactions and no effective alternative to the offending AED.

Acute brain dysfunction

Many neurologists have had the experience of prescribing a large dose of an AED in an effort to stop difficult seizures. Seizure control may be achieved but the patient becomes ataxic and somnolent. This somnolence represents an acute brain dysfunction but is not mysterious! However, four more surprising examples of acute brain dysfunction are of special interest.

First, there are occasional patients who take a small dose of valproic acid and develop remarkable somnolence, even to the level of coma.[23] The underlying causes are unknown but may include an underlying defect in fatty acid metabolism, the formation of unusual metabolites, or an abnormal response in the target organ. In some patients the serum ammonia may be moderately elevated without other signs of liver dysfunction. In general the elevations of ammonia do not seem adequate to explain the degree of somnolence.

A second group of patients have remarkable fatigue or confusion from carbamazepine, despite what seems to be a very low maintenance dose and a gentle and gradual introduction of the drug. This is a truly idiosyncratic problem.[24]

A third group of patients have personality disintegration from phenobarbital or benzodiazepines.[25,26] Much of the literature on phenobarbital side effects in children has emphasized hyperactivity as a problem; however, clinical experience suggests that some children have a much more severe behaviour deterioration, not just hyperactivity. They become extremely agitated, aggressive, confused and sometimes self abusive. Clobazam apparently may rarely induce a similar catastrophic reaction.[26] The literature about this problem is very limited. In our experience, this frightening reaction may occasionally be familial – seen in siblings and other generations.

Lastly, psychosis induced from vigabatrin has recently been described.[27] This phenomenon occurs in about 4% of patients and may be more frequent in those with a previous unprovoked psychotic episode. It has been suggested that "forced normalization" may have a role in causing the psychoses with vigabatrin; however, the mechanism remains unclear.[28] In addition to enhancing brain GABA levels, vigabatrin undoubtedly has effects on other neurotransmitter systems. Anecdotal discussion suggests that these psychotic episodes eventually resolve; however, concern about this idiosyncratic reaction may limit the use of the drug.

Chronic toxicity of antiepileptic drugs

Most anticonvulsants have been available in Canada for many years and their toxicities are well known. Phenobarbital was first used in 1912, phenytoin in 1940, carbamazepine in 1960, and valproic acid in 1978. Phenytoin induced gingival and soft tissue hyperplasia is well known and the best recognized chronic AED toxicity. Reynolds reviewed this issue in 1975[29] and concluded that the incidence was between 50-90% of patients. There is some suggestion that the degree of the problem is related to dose, serum phenytoin levels and oral hygiene.[30] Despite a very large literature on management, we are unaware of any randomized trials.

There are surprisingly few other clear cut chronic AED toxicities. Because some AED's may interfere with vitamin D metabolism, there has been concern that AED's may exacerbate osteoporosis. Remarkably little literature addresses this issue directly in the past ten years. The most clear cut effect of AED's on bone is the induction of rickets or decreased bone density in a small number of institutionalized, mentally disabled patients taking multiple AED's.[31] The effect of AED's on bone metabolism in more normal children and adults remains unclear.[32]

Two other chronic toxicities have been recently emphasized.

Phenytoin, carbamazepine, and phenobarbital have been associated with mild sensory neuropathy, often asymptomatic, in about 10% of patients.[33] The mechanism is unknown and it is unclear how long the drug exposure must be to cause this clinically often inapparent toxicity. It is also unknown if the signs and symptoms disappear if the drug is stopped.

Cerebellar degeneration in patients receiving AED's is also of concern. When a patient with chronic AED treatment becomes ataxic, there are often a number of potential causes other than chronic AED toxicity – such as hypoxic-ischemic or other injury from multiple seizures or alcoholism. In 1980, McLain and others described five patients with irreversible ataxia and CT findings of cerebellar atrophy.[34] All had elevated serum levels of phenytoin (mildly above the usual therapeutic range of 20-40 micromoles/litre) for varying periods of months to years, and all had received phenytoin plus other AED's. No patient had a generalized seizure within several years of development of cerebellar signs. Therefore, it was thought unlikely that the cerebellar difficulties were caused by seizures.

Two cases have helped to support a direct relationship between high levels of phenytoin and cerebellar degeneration. Masur in 1989 reported a 21-year-old who had chronic epilepsy although he had both a normal neurologic exam and CT scan.[35] Carbamazepine and phenytoin were prescribed together. In a suicide attempt, he took 7 grams of phenytoin. Four weeks later his CT scan showed remarkable cerebellar atrophy and 18 months later he continued to be very ataxic.

Lindvall described a 32-year-old man with a subarachnoid hemorrhage who had an aneurysm clipped.[36] His neurologic recovery was complete. He received phenytoin prophylaxis at a dose of 400 mg/day. One month later severe ataxia developed in association with an extremely high serum level – 340 micromoles per litre. The phenytoin was stopped. The ataxia improved but was still present 6 years later, when the CT scan showed cerebellar atrophy.

The cause of cerebellar atrophy and chronic ataxia from long-term toxicity from AED's is unclear. It does seem clear

that high levels of phenytoin can cause cerebellar degeneration. Other studies of patients who were not acutely intoxicated are contaminated by the confounding issues of seizure severity, multiple AED's and failure to exclude alcoholism. If a patient is clinically normal with well controlled seizures, it would seem unwise advice to encourage a change in medication based on information currently available.

There is a cadre of new medications for epilepsy coming to the Canadian market with toxicities that remain to be defined and explored. Severe acute reactions to these new drugs seem infrequent but uncertainty about long term toxicity will hopefully prompt careful post marketing surveillance.

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