barbiturates enhance GABA-mediated inhibition. Other mechanisms of antiepileptic drug action include inhibition of calcium influx, inhibition of excitatory receptors, or excitation of inhibitory receptors. Glutamate and aspartate are the major excitatory neurotransmitters in the central nervous system and glutamate binds to excitatory receptors, including N-Methyl D-aspartate (NMDA). NMDA receptors which regulate channels permeable to sodium and calcium and are blocked by magnesium play a role in the pathogenesis of some forms of epilepsy. Lamotrigine is an NMDA antagonist with antiepileptic potential. (Talwar D. Mechanisms of antiepileptic drug action. Pediatr Neurol Sept/Oct 1990; 6:289-295).

COMMENT. This excellent review of antiepileptic drug action might also include acetazolamide, a carbonic anhydrase inhibitor with an anticonvulsant mechanism that is unique and not shared by the drugs noted in the review. Acetazolamide is a sulfonamide containing a free-SO_2NH_2 group which is essential for inhibition of carbonic anhydrase. The anticonvulsant effect of acetazolamide is not abolished by nephrectomy and is independent of the action of the drug on the kidney and the resultant metabolic acidosis. The anticonvulsant effect is correlated directly with the inhibition of brain carbonic anhydrase. (Millichap JG et al. Mechanism of the anticonvulsant action of acetazolamide, a carbonic anhydrase inhibitor. J Pharm Exp Ther 1955; 115:251-258). The inhibition of carbonic anhydrase located in glial cells results in CO_2 accumulation and changes in acid-base and electrolyte balance that reduce neuronal excitability.

GENERIC SUBSTITUTIONS FOR ANTIEPILEPTIC DRUGS

The hazards and problems of generic substitutions for antiepileptic drugs are reviewed in a Report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology (Neurology Nov 1990; 40:1641-1643) and are discussed by Nuwer MR et al (Neurology Nov 1990; 40:1647-1651). According to the present Federal guidelines for manufacturers a generic product may be approved as equivalent to a brand name product even if it produces widely varying bioavailability in some individuals. Implicit in the FDA guidelines is the assumption that a ± 20% change in mean steady-state serum concentration of antiepileptic drugs can be tolerated safely. However, there is no scientific evidence to support this assertion. When substitution of different formulations of an antiepileptic drug occurs, the patient is put at risk of drug intoxication or breakthrough seizures. Generic substitution of drugs such as phenytoin and carbamazepine which have a narrow therapeutic range is especially problematic.

COMMENT. Economic benefits because of lower cost of generic substitutions may be outweighed by the need for more frequent serum concentration determinations and costs of follow-up visits.