selves, your families, your patients and to society which gives you your license to practice. You are entering practice at a time of unprecedented challenge and excitement. It should be both fun and satisfying for you to face and meet these many challenges. I wouldn't mind being one of you!

—MSMW

Seizures From Theophylline Use

IN A RECENT two-year study of theophylline toxicity,[1] 17 percent of 3,112 serum theophylline concentrations were greater than 20 μg per ml, the upper limit of the usual therapeutic range. Of 87 patients with serum theophylline concentrations higher than 20 μg per ml, almost all had one or more symptoms or signs of toxicity, including tachycardia, tremor, nervousness, irritability, nausea, vomiting, diarrhea, headache and seizures. Of 19 patients who had values of more than 40 μg per ml, four had seizures. None of the patients with values below 40 μg per ml had seizures. Seizures from theophylline can result in status epilepticus and can have a fatal outcome. In one series[2] four of eight patients with seizures due to theophylline use died. Seizures have been reported with intravenously given aminophylline, orally given theophylline[3] and aminophylline given by suppositories.[4] Suicide attempts have been made by ingesting an overdose of theophylline. Of nine such suicide attempts described in one report, three of the nine patients had seizures and those three died.[5] The six who did not have seizures survived.

Seizures from theophylline use usually occur with serum theophylline concentrations above 35 μg per ml.[2] Other side effects clearly occur with concentrations within the therapeutic range of 10 to 20 μg per ml.[6] Several individual cases have now been reported in which patients had seizures due to theophylline use, with theophylline concentrations of less than 35 μg per ml.[2,7] Nakada and colleagues in this issue of the journal add three more patients to this group; their three patients had seizures likely from theophylline use with theophylline values of 17, 20.5 and 24 μg per ml at the time of the seizures. Results of an autopsy done on two of the patients showed no structural lesion in the brain to explain the seizures. One possible explanation for seizures occurring at low theophylline concentrations is decreased binding of theophylline to plasma proteins, making more free drug available for diffusion into tissues.[8] Nakada and co-workers did not measure the amount of theophylline bound to protein, though all three of their patients had low serum albumin levels.

Treatment of seizures from theophylline toxicity is difficult, making prevention of paramount importance. The seizures are refractory to anticonvulsive medication. Theophylline therapy should be stopped immediately and the theophylline concentration should be decreased as soon as possible. Resin and charcoal hemoperfusion has been reported to reduce theophylline concentration, but a recent review of renal dialysis for theophylline toxicity points out that even with rapid reduction of the serum theophylline value the outcome has not always been favorable.[9] For attempted suicide with theophylline overdose, vomiting should be induced, then activated charcoal and cathartics given.[9]

Prevention of theophylline toxicity requires some knowledge of pharmacokinetics of theophylline. The half-life varies in asthmatic adults who are otherwise healthy from 2.9 to 12 hours.[7] Similar variation occurs in children. Thus, one dosage schedule is not applicable to all patients. Serum theophylline values should be used to guide therapy. Guidelines for theophylline therapy have been published,[7,9,10] and a patient's past experience with theophylline should be considered.

Diseases that prolong the theophylline half-life and thus require a decreased dose include congestive heart failure, liver disease, influenza and possibly other respiratory and febrile illnesses.[7] A growing number of drugs that are being reported to delay theophylline metabolism also require a reduction in the dose. Troleandomycin,[11] erythromycin[12] and cimetidine[13] are well-documented examples. Furosemide,[14] thiabendazole,[15] allopurinol at a dose of 600 mg per day but not at 300 mg per day,[16] propranolol but not metoprolol,[17] hydrocortisone[18] and influenza immunization[19] have all been reported to delay theophylline metabolism and thus could cause toxicity in patients on stable theophylline regimens.

Seizures are an uncommon but serious complication of theophylline therapy. Most of these seizures result from toxic theophylline serum concentrations and can be prevented by application of pharmacokinetic knowledge of theophylline use and by monitoring therapy with measurement of serum theophylline values.

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