trol subjects,[20] we have seen a clear relationship between pubertal development (Tanner stage) and increased daytime sleepiness in the absence of any changes in total nighttime sleep. Multiple sleep latency test scores showed a significant increase in daytime sleepiness at Tanner stages 3 and 4. From these data we have hypothesized that this period of maturation might be a particularly vulnerable stage in the development of narcolepsy. In the present case the signs and symptoms of narcolepsy were first seen at Tanner stage 4, supporting this hypothesis. The findings in this case suggest the possibility of an additive effect wherein a preexisting tendency toward daytime sleepiness and the pubertal augmentation of sleepiness lead to an unequivocally pathological level of sleepiness.

Summary

A 12-year-old girl whose mother has narcolepsy was evaluated with sleep-habits questionnaires, Tanner staging, nocturnal sleep recordings and multiple sleep latency tests at yearly intervals for three consecutive years. In the first year the child reported no symptoms of narcolepsy. In the third year all symptoms were present. Nocturnal sleep recordings showed reduced REM latencies in years 1 and 3, with one sleep onset REM period in year 3. Results of multiple sleep latency tests each year showed an excessive tendency to fall asleep; however, abnormally short REM latencies were not seen until year 3. Sleep onset REM periods were seen on 13 of 18 sleep latency tests in year 3. The signs and symptoms of narcolepsy developed when the child was at Tanner stage 4.

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A Prolonged Severe Intoxication After Ingestion of Phenytoin and Phenobarbital

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THE ANTICONVULSANT DRUGS phenytoin and phenobarbital are often prescribed concomitantly in the treatment of epilepsy. Despite this association, few cases of severe combined overdose with these agents have been reported. Further, cases of fatal

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poisonings with phenytoin alone are rare in the literature.[1-3] In the case reported here, that of a woman without epilepsy, there was delayed absorption and prolonged severe toxicity after combined phenytoin and phenobarbital ingestion.

Report of a Case

A 22-year-old mentally retarded woman, who was not epileptic and who had been in good health previously, was brought to the University of California Davis Medical Center emergency room on August 22, 1980. The patient said she had taken an unknown amount of phenobarbital and phenytoin, which belonged to a friend, earlier in the day. On examination, the patient was noted to be lethargic but was able to answer questions. Vital signs were as follows: temperature 37°C (98.6°F), blood pressure 104/58 mm of mercury, pulse 96 beats per minute and respirations 12 per minute. Nystagmus was notably absent. The rest of the physical examination findings were unremarkable. The initial laboratory examination showed normal values for electrolytes, glucose and blood urea nitrogen. The leukocyte count was 9,200 per cu mm, with a hemoglobin of 14.7 grams. A blood drug screen showed a trace of either tolbutamide or chlorpropamide, a small amount of caffeine, and phenobarbital and phenytoin levels of 15 and 18 mg per liter, respectively. Phenobarbital and phenytoin were measured in serum using high-performance liquid chromatography.[4] Confirmation of serum results was made by gas chromatography.[5] Initial treatment consisted of gastric lavage with more than 3 liters of normal saline followed by administration of activated charcoal and magnesium citrate. No pill fragments were recovered.

The patient was evaluated by a psychiatrist and then observed for several hours without change in her status. Because of an outstanding warrant, she was discharged to jail. While incarcerated and after being searched, the patient was noted to become extremely agitated over the next day. She was returned to the emergency room almost 24 hours after her first visit for reevaluation. On physical examination, she was afebrile with vital signs as follows: blood pressure 110/60 mm of mercury, heart rate 88 beats per minute and respirations 20 per minute. She was agitated and disoriented with lateral gaze nystagmus. Serum values for electrolytes and glucose were normal. A urine screen for phencyclidine was negative. A repeat blood drug screen showed only phenytoin

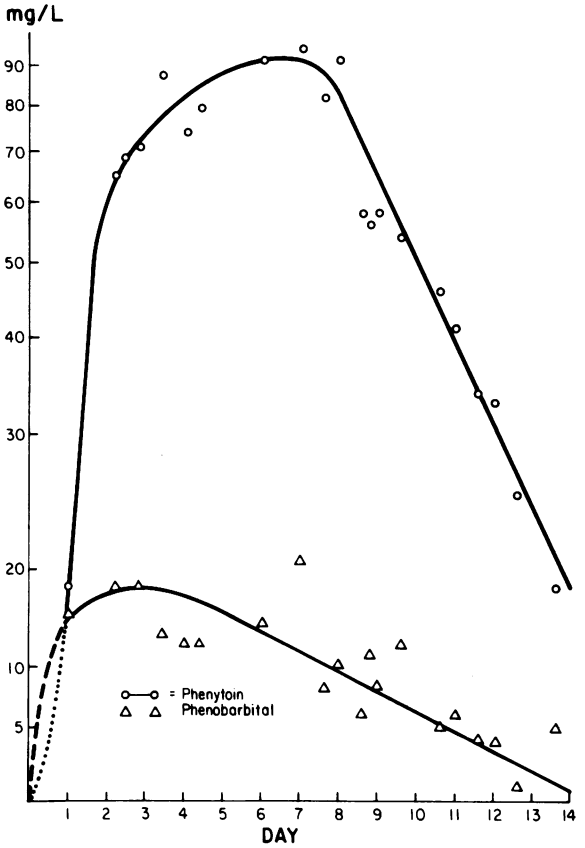

Figure 1.—Serum levels of phenytoin and phenobarbital are plotted against days in hospital. The initial presentation to the emergency room is considered day 1. Solid lines represent an approximate best fit, and the broken lines represent estimated curves.

(65 mg per liter) and phenobarbital (18 mg per liter). An electrocardiogram showed sinus tachycardia with diffuse nonspecific ST-T wave changes. Arterial blood gas determinations while the patient was breathing 2 liters of oxygen were as follows: oxygen pressure (Po_2) 97 and carbon pressure (Pco_2) 31 mm of mercury, and pH 7.32. The patient received magnesium citrate a second time and was admitted to hospital.

The serum levels of phenytoin and phenobarbital and the patient's clinical course are summarized in Figure 1 and Table 1, respectively. The patient became less agitated and more lethargic as phenytoin serum levels increased. On the third hospital day, a barium swallow test was done, which showed no evidence of retained pills. By the sixth and seventh days, the patient was comatose, with disconjugate gaze, decreased deep tendon reflexes and absent gag reflex. Nystagmus was not noted. Because of the increase in serum levels of phenytoin, the patient was given mag-

TABLE 1.—*Hospital Course and Neurological Status of Patient Following Combined Phenytoin and Phenobarbital Ingestion*

	Hospital Day*													
	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Hospital course														
Gastric lavage	x†	..	..	..	..	..	..	..	..	..	..	..	..	..
Charcoal	x	..	..	..	..	x	x	x	..	..	..	..	..	..
Magnesium citrate	x	x	..	x	..	x	x	x	..	..	..	..	..	..
Elevated temperature	..	..	..	..	..	..	x	x	x	..	..	..	..	..
Cephalosporin	..	..	..	..	..	..	x	x	x	x	x	x	..	..
Lactic dehydrogenase (units/liter)	207	275	233	242	223	..	399	387	..	..	..	268	..	..
Serum aspartate aminotransferase (units/liter)	28	32	31	33	32	..	54	121	..	..	..	31	..	..
Total bilirubin (mg/dl)	0.5	0.4	0.4	0.4	0.4	..	0.4	0.2	..	..	..	0.2	..	..
Albumin (grams/dl)	4.6	4.3	4.2	4.1	4.1	..	4.0	3.6	..	..	..	3.7	..	..
Neurological status														
Coma	..	..	..	..	x	x	x	x	..	..	..	..	..	..
Agitation	..	x	x	..	..	..	..	..	x	x	x	x	..	..
Ataxia	x	..	..	x	..	..	..	..	..	..	..	..	x	..
Nystagmus	..	x	x	..	..	..	..	..	x	x	x	x	x	..

*The initial presentation to the emergency room is considered day 1.
† x indicates that on a given day the procedure was done, the drug was given or the symptom was noted.

nesium citrate on day 4 followed by three additional doses of charcoal and magnesium citrate on days 6, 7 and 8.

On the seventh day a fever developed. Blood cultures were negative; however, urine culture grew more than 100,000 colonies of *Enterococcus*. The patient defervesced during antibiotic treatment over the next 48 hours. On day 9 the patient's serum phenytoin levels began to fall, which was accompanied by a return of nystagmus and agitation. Liver function tests gave only minimally elevated results by day 9 (Table 1). She continued to improve neurologically as serum phenytoin and phenobarbital levels decreased. The patient was discharged 14 days after she had ingested the drugs. She was oriented and without nystagmus.

Comment

This case represents a unique demonstration of severe phenytoin intoxication after combined phenytoin and phenobarbital ingestion. Extremely slow absorption of phenytoin was observed with peak serum levels not attained until the seventh hospital day. This delay occurred despite gastric lavage and the administration of activated charcoal and cathartics on the day of ingestion. Most previous reports of phenytoin toxicity have reported levels that declined from the initial serum determination.[6-9] Two patients[10,11] were found to have a prolonged plateau phase followed by a slow decline phase in serum levels. One of these cases[11] involved an alcoholic man with a history complicated by gastrectomy and chronic anticonvulsant therapy. The patient presented with a phenytoin level of 64 mg per liter and a phenobarbital level of 63 mg per liter. There was no mention of emesis, gastric lavage or activated charcoal administration in the case report. The only other reported case of prolonged phenytoin levels occurred in a 6-year-old child despite treatment with emesis, gastric lavage and administration of activated charcoal and cathartics.[10] A single report observed phenytoin levels that continued to increase after ingestion.[12] A 5½-year-old boy accidentally received 500 mg a day of phenytoin and 100 mg a day of phenobarbital for approximately 20 days while in hospital. An initial phenytoin level of 85.2 mg per liter was obtained three hours after the last dose. This rose to 108.5 mg per liter 24 hours later but rapidly decreased over the next three days.[12]

The rise in serum phenytoin levels that occurred in our case can best be explained by decreased gastrointestinal motility, which prolonged the time available for absorption. Because our patient was searched and incarcerated in isolation, we feel comfortable that she had no further opportunity to ingest phenytoin and phenobarbital. The barium swallow test done on the third day failed to show any evidence of pill bezoar or gastric-outlet obstruction. This reduces the likelihood of any serious gastric retention of pill fragments. Although a significant enterohepatic-loop exists, it

is the pharmacologically inactive hydroxylated metabolite of phenytoin that is reabsorbed after bacterial deconjugation, and this compound would not contribute to the rise in serum levels seen in this patient.[6,13] Wide variation in the rate of phenytoin absorption have been reported.[14-16] In healthy volunteers given a single dose of 900 mg of phenytoin by mouth, the time to reach peak plasma levels varied from six to eight hours.[16]

Peak phenytoin levels obtained in this patient are consistent with levels reported in previous cases of severe poisoning and intoxication.[3,6-12] Laubscher[3] reported a fatal case of pediatric phenytoin ingestion with an initial serum level of 94 mg per liter. The level had decreased to 45 mg per liter at the time of vascular collapse and death. In contrast, phenytoin levels of 89 mg per liter have been associated with only minimal neurological findings in some patients.[17] This variability in response to serum levels was less pronounced in a large series of phenytoin-intoxicated patients.[18] Kutt and co-workers[18] found that phenytoin levels of 20 to 30 mg per liter were associated with nystagmus, 30 to 40 mg per liter led to ataxia and levels greater than 50 mg per liter progressed to further mental changes and coma. The increased side effects of phenytoin seen in patients with hypoalbuminemia are thought to be a result of increased circulating unbound phenytoin in these patients.[19] Booker and Darcey[20] have noted a closer correlation with free or unbound phenytoin levels and clinical intoxication. As can be seen in Table 1 and Figure 1, the neurological findings correlated with the total serum levels in our patient both during the ascending and descending phases. However, a small decrease in serum albumin and possible phenobarbital-binding competition complicates estimation of unbound phenytoin in this patient.

The few cases in the literature that report simultaneous phenytoin and barbiturate ingestion do not address their potential interactions.[8,11,21] Phenobarbital is both a known inducer of the enzymes that metabolize phenytoin and a competitive inhibitor of the same enzymes.[22] The effect of phenobarbital on phenytoin levels is varied. Kutt[22,23] has reviewed several clinical studies with therapeutic doses of each drug and concluded that the balance between the stimulating and inhibiting effects of phenobarbital on phenytoin metabolism is difficult to predict for the individual patient. Genetic variability in phenytoin metabolism has been shown[24,25] and may play an important role in the phenobarbital-phenytoin interaction in any individual toxic patient.

The elimination half-life ($T_{1/2}$) of approximately 96 hours in this patient is substantially longer than the average $T_{1/2}$ of 22 hours (range 7 to 55 hours) seen in healthy volunteers given therapeutic doses.[26] Patients with phenytoin intoxication have been reported to have a wide spectrum of $T_{1/2}$ values varying from 24 to 230 hours.[9-11] The wide range of $T_{1/2}$ values is in part due to the probable continued absorption and saturation kinetics seen with toxic serum levels. Metabolite or product feedback inhibition has not been conclusively shown in humans.[27]

Several authors have questioned the use of hemodialysis in the treatment of acute phenytoin overdoses.[10,28] The few case reports in which successful hemodialysis or peritoneal-dialysis has been described do not provide adequate documentation of clinical benefit or significant recovery of phenytoin in the dialysate.[21,28-31]

In a recent review of one hospital's drug-related hemoperfusions, phenytoin was not one of the "severe" cases of drug intoxication treated with this technique.[32] Lorch and Garella[32] stated "in view of the low morbidity and mortality observed in our patients we cannot support the widespread use of hemoperfusion for most common intoxicants." Certainly this is true for most moderate and severe phenytoin intoxications.

This case shows that significant absorption of phenytoin can occur despite emesis, gastric lavage, and treatment with activated charcoal and cathartics at first presentation. Thus, efforts should be focused on supportive care and the prevention of further absorption of phenytoin. Repeat administration of both activated charcoal and cathartics may be necessary to prevent the prolonged and delayed absorption seen in this case.

Summary

A 22-year-old nonepileptic woman ingested an unknown amount of phenytoin and phenobarbital. Peak serum levels of 95 and 21 mg per liter for phenytoin and phenobarbital, respectively, were observed seven days after gastric lavage, charcoal and cathartics had been administered. Blood levels of phenytoin began to decrease only after repeat multiple doses of charcoal and cathartics were given. An elimination half-life of approximately 96 hours for phenytoin was found. The prolonged

phenytoin toxicity seen in this case is probably secondary to delayed intestinal absorption and to saturation kinetics seen with toxic serum levels leading to the long phenytoin elimination $T_{1/2}$. Therapeutic efforts in cases of massive phenytoin ingestion should be focused on supportive care and the prevention of further phenytoin absorption with repeat administration of activated charcoal and cathartics.

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