moreover, serum levels may remain normal until vitamin A storage capacity in the liver is exhausted.[7]

All patients should be questioned about vitamin intake. Those with abnormal liver function should be carefully screened for hypervitaminosis A.

REFERENCES

1. Strauss MB: Familiar Medical Quotations. Boston, Little, Brown and Co., 1968
2. Council on Foods and Nutrition: Vitamin preparations as dietary supplements and as therapeutic agents. JAMA 169:41-45, Jan 1959
3. White PL: Vitamin preparations. Postgrad Med 60:204-209, Oct 1976
4. Mandel HG: Vitamin A, *In* Goodman LS, Gilman A (Eds): The Pharmacological Basis of Therapeutics, 2nd Ed. New York, Macmillan Publishing Co., 1975
5. Russell RM, Boyer JC, Bagheri SA, et al: Hepatic injury from chronic hypervitaminosis A resulting in portal hypertension and ascites. N Engl J Med 291:435-440, Aug 1974
6. Rubin E, Florman AL, Degnan T, et al:: Hepatic injury in chronic hypervitaminosis A. Am J Dis Child 119:132-138, Feb 1970
7. Muenter MD, Perry HO, Ludwig J: Chronic hypervitaminosis A intoxication in adults. Am J Med 50:129-136, Jan 1971

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Phenytoin Overdose Kinetics

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THE USE OF prescription medications in attempted suicides is a major medical and social problem. Therapeutic difficulties may arise from the fact that the pharmacology of the drugs ingested often differs greatly when comparing therapeutic doses versus overdoses. In addition, massive amounts of drug may overwhelm clearance mechanisms. The purpose of this paper, then, is to emphasize this difference in pharmacokinetics with phenytoin overdose as it influences management.

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Report of a Case

A 54-year-old man was admitted to the detoxification ward at Los Angeles County-University of Southern California Medical Center on January 22, 1976. Upon admission he appeared intoxicated and was described as confused and incoherent. He was crying loudly and passive restraints were required. Vital signs were reported as a pulse of 104 beats per minute, respiratory rate of 20 breaths per minute, temperature of 37.2°C (99°F) (rectally) and blood pressure of 150/100 mm of mercury. His chest was clear to auscultation. There were no focal findings on neurologic examination and there was no evidence of head trauma. The cardiac rhythm was regular. The toxicology report indicated a phenytoin level of 6.9 mg per dl (with therapeutic levels reported as 1 to 2 mg per dl), a phenobarbital level of 6.3 mg per dl (with therapeutic levels reported as 2 to 4 mg per dl) and a negative ethanol level.

Past medical history was obtained from a previous admission. The patient had a history of epilepsy for 18 years following trauma, a history of gastrectomy and previous heavy drinking. Anticonvulsant therapy was begun in 1969 with phenytoin, 100 mg orally three times a day, and phenobarbital, 30 mg orally three times a day.

Hospital Course

On the day of admission the patient was very confused. Body temperature rose to 40°C (104°F). Phenytoin and phenobarbital levels were 6.9 mg per dl and 6.3 mg per dl, respectively (see Table 1). On the second hospital day, he was still lethargic, with slurred speech. He moved all extremities nonpurposefully and remained very agitated. The temperature had fallen to 38.3°C (101°F) without antibiotic or antipyretic drug therapy. On examination the patient had gross nystagmus and ataxia. He was extremely labile emotionally, with episodes of crying and moaning. In addition he was disoriented to person, place and time. Restraints were required for three days. On the third day, the patient remained disoriented and in an apparent psychotic state. He continued to groan loudly and there were periodic bursts of crying. His speech was slurred and unintelligible. The following day serum levels were obtained and indicated a phenytoin level of 6.7 mg per dl and a phenobarbital level of 5.0 mg per dl. Serum level determinations were repeated on the next day, the fifth hospital day, and levels were re-

duced to 5.3 mg per dl for phenytoin and 3.3 mg per dl for phenobarbital. Since the phenobarbital level was in the therapeutic range, administration of the drug was reinstituted at 30 mg given intramuscularly three times daily. The patient's mental status remained unchanged until the sixth day after admission, when he was able to communicate. He was oriented to person and place but continued to be notably agitated. The presence of nystagmus and ataxia persisted but to a lesser degree than on admission. At this time he admitted to taking three phenytoin capsules three times per day and also taking three times the prescribed amount of phenobarbital.

On the sixth day, the reported phenytoin and phenobarbital serum levels were 4.8 mg per dl and 3.4 mg per dl, respectively. At this time the patient was still drowsy but no longer very agitated. On the ninth day, nystagmus was no longer present but ataxia was observed. The phenytoin level was 4 mg per dl. On the 14th day, the phenytoin level was 0.4 mg per dl and a maintenance dose of 300 mg per day was started. At this time the patient continued to be slightly unstable while walking, possibly due to chronic alcohol-induced cerebellar disease.

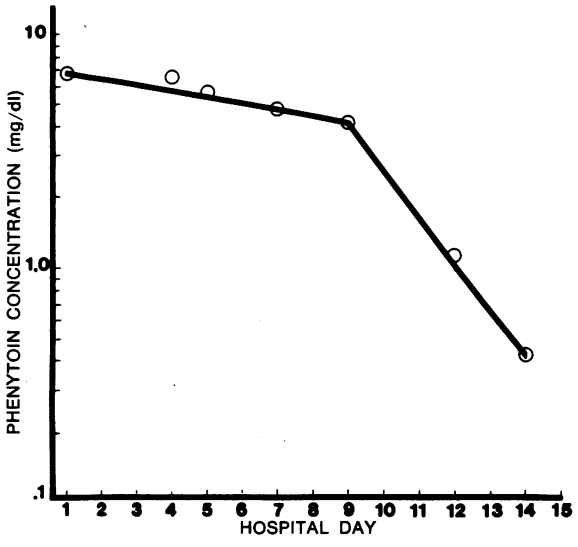

Figure 1.—Plot of the log of the serum phenytoin concentration versus time in days.

Treatment consisted of supportive care until the patient became less confused and agitated. No medications were administered during the acute psychotic phase. Hard restraints were employed to prevent injury to the patient. Hydration was maintained by intravenous administration of fluids. After 15 days in hospital, the patient was discharged and continued on a regimen of anticonvulsant medications.

Discussion

Our premise is that an understanding of the pharmacokinetics of phenytoin will influence therapeutic decisions in an overdose situation. The plasma half-life of phenytoin has been shown to be dose dependent in man.[1] In other words, the time required for the plasma level to halve itself increases as the concentration of the drug increases. An explanation for the nonexponential decline of phenytoin is that the biotransformation mechanism approaches saturation at higher plasma levels.[2] Therefore, the disappearance of the drug is not a simple exponential process and does not follow apparent first order kinetics. According to Atkinson and Shaw, the elimination follows a fixed rate at high plasma concentrations or zero order kinetics (as seen with ethanol).[3] This would explain the persistence of symptoms for several days at high plasma concentrations of the drug. The half-life of phenytoin for healthy adults averages 22(±9) hours (range 7 to 42 hours).[1] In our patient the plasma half-life was 9.6 days for that period of time when the plasma level fell from 6.9 mg per dl to 4.3 mg per dl (see Figure 1). During this ten-day interval, phenytoin elimination is best described as showing Michaelis-Menton kinetics. However, once the phenytoin level fell below 4.0 mg per dl (on the ninth hospital day) various metabolic pathways were no longer as saturated. After this time, the phenytoin half-life was 30 hours and was con-

TABLE 1.—*Symptoms of Phenytoin Toxicity in Conjunction With Phenytoin and Phenobarbital Serum Levels*

	HOSPITAL DAY															
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Nystagmus	4+(*)	→		3+	→		2+	→			1+	→				
Confusion	4+	→		3+	→	2+	→		1+	→						
Ataxia	4+	→				3+	→		2+	→						1+
Serum phenytoin (mg/dl)	6.9			6.7	5.3	4.8			4.2		1.2		0.4			
Serum phenobarbital (mg/dl)	6.3			5.0	3.3	3.4			3.1		3.0					

*This is an attempt to quantitate subjective signs and symptoms: 4 = severe, 3 = moderate, 2 = mild, 1 = minimal.

sistent with a faster rate of decline. The patient exhibited the classical signs of phenytoin dose dependent side effects (nystagmus, ataxia and confusion) for nearly ten days after entering the hospital. Were the elimination rate unchanged in the overdose situation, the patient would have been asymptomatic after three days. Therefore, when a patient enters the hospital after taking an overdose of phenytoin, toxicity may persist for many days until the metabolic rate of elimination increases and phenytoin levels fall below the toxic range.

The possibility of delayed absorption cannot be excluded since three days passed between the first two determinations of phenytoin levels. In fact, this has previously been described.[4] In our patient there could have been a continued rise in phenytoin levels secondary to persistent absorption during the second and third hospital days.

Although there are insufficient data to determine a representative lethal drug concentration, Laubscher reported a fatal phenytoin ingestion associated with a peak plasma level of 9.4 mg per dl.[5] In general, phenytoin levels in excess of 10 mg per dl may require measures beyond supportive care. If the patient cannot tolerate toxic phenytoin concentrations, other measures should be undertaken to increase the elimination rate. Dialysis is one means and has been advocated by some,[6-8] but found to be relatively ineffective by others.[9]

In conclusion, the successful management of a patient with phenytoin overdose is enhanced by good clinical judgment, successive plasma drug level determinations and an appreciation of phenytoin kinetics.

REFERENCES

1. Arnold K, Gerber N: The rate of decline of diphenylhydantoin in human plasma. Clin Pharmacol Ther 11:121-134, Jan 1970
2. Gerber N, Wagner JG: Explanation of dose dependent decline of diphenylhydantoin plasma levels by fitting to the integrated form of the Michaelis-Menton equation. Res Commun Chem Pathol Pharmacol 3:455-466, May 1972
3. Atkinson AJ, Shaw JM: Pharmacokinetic study of a patient with diphenylhydantoin toxicity. Clin Pharmacol Ther 14:521-528, Jul 1973
4. Holcomb R, Lynn R, Harvey B, et al: Intoxication with 5,5-diphenylhydantoin (Dilantin). J Pediatrics 80:627-632, April 1972
5. Laubscher FA: Fatal diphenylhydantoin poisoning—A case report. JAMA 198:1120-1121, Dec 1966
6. Schreiner GE: The role of hemodialysis in acute poisoning. Arch Intern Med 102:896-913, Dec 1958
7. Tenckhoff H, Sherrard DJ, Hickman RO, et al: Acute diphenylhydantoin intoxication. Am J Dis Child 116:422-425, Oct 1968
8. Blair AA, Hallpike JF, Lascelles PT, et al: Acute diphenylhydantoin and primidone poisoning treated by peritoneal dialysis. J Neurol Neurosurg Psychiat 31:520-523, Oct 1968
9. Adler DS, Martin E, Gambertoglio JG, et al: Hemodialysis of phenytoin in a uremic patient. Clin Pharmacol Ther 18:65-69, Jul 1975

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Ventricular Tachycardia in a Young Adult With an Apical Aneurysm

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FINDING THE CAUSE of frequent ventricular extrasystoles in a young, presumably healthy patient is difficult. Often, no pathologic condition can be found to account for the arrhythmia despite extensive cardiac evaluation. This paper reports the unusual finding of frequent ventricular extrasystoles and ventricular tachycardia in a young adult with an apical cardiac aneurysm. The cause of the aneurysm was felt to be infection with the parasite Trypanosoma cruzi (Chagas disease). Surgical removal of the left ventricular aneurysm ablated the arrhythmia. Surgical removal of the apical aneurysm for control of arrhythmia has not previously been reported in Chagas disease.

Report of a Case

A 23-year-old woman from El Salvador was referred to the Los Angeles County-University of Southern California Medical Center for investigation of an abnormal heart rhythm. The patient had no serious illnesses and had had a normal baby two years before admission. There was no history of heart disease, chest trauma, rheumatic fever, hypertension or diabetes mellitus. She had lived in the United States for three years.

On examination, the patient appeared well. Her blood pressure was 120/70 mm of mercury, pulse 60 and irregular and respirations normal. The lungs were clear, and there was no neck vein distention. The heart was not enlarged, and the

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