Fatalities Following Intravenous Use of Sodium Diphenylhydantoin for Cardiac Arrhythmias
Report of Two Cases

Allen H. Unger, MD, and Herschel J. Sklaroff, MD

In 1950 Harris and Kokernot reported that sodium diphenylhydantoin (Dilantin Sodium) is effective in the treatment of cardiac arrhythmias in the experimental animal. Since then, several reports have been published which demonstrate the efficacy of diphenylhydantoin given intravenously in abolishing arrhythmias in dogs and humans.

There have been no reported fatalities due to intravenous use of diphenylhydantoin in treating cardiac arrhythmias in humans. The purpose of this report is to present two cases of patients who died following intravenous administration of diphenylhydantoin.

Report of Cases

Case 1.—A 67-year-old white woman with a 30-year history of diabetes mellitus and a ten-year history of angina pectoris was admitted to the Mount Sinai Hospital on Feb 8, 1966, with an acute myocardial infarction (inferior wall) complicated by pulmonary edema. The pulmonary edema responded to treatment including administration of digitalis. Anticoagulants were also administered. The hospital course was then uncomplicated except for occasional episodes of angina pectoris. Six weeks after admission the patient had crushing, substernal chest pain,

which lasted several hours and was again followed by frank pulmonary edema. An electrocardiogram revealed more marked ST segment depression in leads V1 through V4. One hour later the pulse rate increased and an ECG then revealed atrial flutter with a ventricular response of 150. The patient had been on a maintenance dose of digoxin and an additional 0.4 mg of lanatoftuide C was given intravenously but no ventricular slowing occurred over the next two hours. The patient's clinical condition deteriorated as substantiated by increasing pulmonary edema and gradually falling blood pressure. Diphenylhydantoin, 250 mg, was given intravenously for two minutes with electrocardiographic monitoring. Within one minute after the completion of the administration of the diphenylhydantoin, sinus rhythm was restored but was soon followed by sinus arrhythmia, ventricular escape, idioventricular rhythm, and cardiac arrest (Figure). The patient could not be resuscitated.

Case 2.—A 70-year-old white man with chronic lung disease for many years and angina pectoris for six months was admitted to the Mount Sinai Hospital on Feb 1, 1966, because of increasing congestive heart failure despite digoxin and diuretic therapy.

On admission the patient manifested evidence of some left-sided and marked right-sided congestive heart failure with tricuspid regurgitation. The ECG revealed regular sinus rhythm with an S1S2S3 pattern. The patient responded well to bed rest, oxygen, antibiotics, bronchodilators, and expectorants. A maintenance dose of digoxin was continued. Two days after admission he suddenly experienced pulmonary edema and atrial flutter with a ventricular response of 150. Diphenylhydantoin, 250 mg, was given intravenously for a period of three minutes. The atrial flutter persisted, but with a high degree of atrioventricular block, followed by asystole three minutes after the completion of the administration of diphenylhydantoin. All attempts at resuscitation failed.

Comment

Harris and Kokernot demonstrated that, in dogs, ventricular tachycardia produced by ligation of the anterior descending ramus of the left coronary artery could be prevented or abolished by therapy with diphenylhydantoin. Two dogs in this series died following rapid intravenous injection of di-
phenyldantoin. In these animals respiratory arrest preceded cardiac standstill. A dose of 20 mg/kg of body weight proved fatal when injected quickly, but doses as large as 50 mg/kg were given repeatedly without incident once the necessity for slow administration was appreciated.

Covino et al studied the effect of diphenyldantoin upon ventricular fibrillation in dogs made hypothermic by pentobarbital anesthesia. Asystole resulted from the combination of diphenyldantoin and hypothermia, whereas the same degree of hypothermia by itself induced ventricular fibrillation.

Scherf et al, in studying the effect of diphenyldantoin upon the ECG, were able to produce cardiac standstill in dogs by giving very large doses (66 to 69 mg/kg of body weight) of diphenyldantoin.

Dreifus and associates state that cardiac standstill can be produced by toxic doses of diphenyldantoin in the experimental model, but the effect is only transient and can be readily reversed by several minutes of normal perfusion.

Conn administered diphenyldantoin intravenously in 24 patients with a variety of cardiac arrhythmias. He used 250 mg of diphenyldantoin diluted in 5 ml of solvent and gave it in a period of one to three minutes. Toxicity developed in two patients in this series. In one, treatment for premature ventricular contractions resulted in transient hypotension with a ventricular rate of 30, but the blood pressure and pulse rate returned to normal a few seconds after administration of atropine. In a second patient, with atrial tachycardia, the injection of diphenyldantoin was followed by 4:1 and 6:1 atrioventricular block which lasted three minutes. Conn therefore cautioned against the use of diphenyldantoin in patients with bradycardia and advanced atrioventricular block.

Dreifus et al recommended a larger dose (5- to 10 mg/kg of body weight) of diphenyldantoin to be injected over a longer period of time (15 minutes) for the treatment of supraventricular and ventricular tachycardias.

In treating digitalis-induced arrhythmias, Lang and associates recommend that an initial dose of diphenyldantoin should be 6 mg/kg of body weight, given intramuscularly; if the toxic arrhythmia is not improved within 40 minutes, diphenyldantoin is given intravenously (1 mg/kg/min) until the arrhythmia is corrected or the maximal dose of 15 mg/kg of body weight is reached.

The use of diphenyldantoin for treatment of atrial flutter may be open to question. Scherf et al have demonstrated that, in dogs, diphenyldantoin was effective in transiently abolishing atrial flutter produced by aconitine or delphinine in all their experiments. Conn administered diphenyldantoin intravenously to only two patients with atrial flutter and observed no effect in either. Atrial flutter, seen in a patient in this institution, was converted to regular sinus rhythm following the intravenous administration of diphenyldantoin. Fulop et al recently reported a case in which supraventricular tachycardia (180 to 190 beats per minute), without atrioventricular block, developed in a patient with atrial flutter with varying 2:1 and 4:1 atrioventricular block during the intravenous injection of diphenyldantoin.

Both of our patients had severe cardiac disease with progressive cardiac decompensation complicated by atrial flutter. Each patient had received digitalis but electrical cardioversion was not undertaken since in the presence of the amount of digitalis needed to produce desired therapeutic effects, it is thought to be hazardous. Further, the possibility of rapid conversion of atrial flutter by diphenyldantoin, not seen with other drugs and seen in one patient in this institution, prompted the use of diphenyldantoin in these emergency situations. The diphenyldantoin was given in doses recommended by Conn, ie, 250 mg given intravenously for two to three minutes. The adverse response in these two patients indicates that caution should be observed in the dose and rapidity of intravenous administration of diphenyldantoin.

Summary

Cardiac arrest developed in two patients given sodium diphenyldantoin (Dilantin Sodium) intravenously for atrial flutter. Caution should be used in the intravenous administration of this drug.

Generic and Trade Names of Drugs

Sodium diphenyldantoin—Denny! Sodium, Dilantin Sodium, Diphenylan Sodium.

Pentobarbital—Nembutal.

References


