Treatment of Diphenhydramine Cardiac Toxicity with Phenytoin: Implication of Treatment of Type 1a Antiarrhythmic Toxicity

Michael B. Gutman, MD, PhD, FRCPC, FACEP

Department of Traumatology and Emergency Medicine, University of Connecticut, Hartford, CT, USA

Robert Noseworthy, MD, FRCPC

Department of Emergency Medicine, Royal Columbian Hospital, New West Minister, BC, Canada

Roy Pursell, MD, FRCPC, FACEP

Department of Surgery, Division of Emergency Medicine, and British Columbia Poison Center, University of British Columbia, Vancouver, BC, Canada

Address for Correspondence:
Michael Gutman, MD, PhD, FRCPC, FACEP
Department of Emergency Medicine St. Francis Hospital and Medical Center
114 Woodland Street
Hartford, CT 06105 USA
Tel: +(860) 714-4017
Fax: +(860) 714-8046
E-mail: mgut@comcast.net

Abstract

Case Report: A 30 year old female ingested a large amount of diphenhydramine. Shortly after, she exhibited seizure activity and wide-complex tachycardia. Seizure activity was successfully treated with intravenous benzodiazepines and orotracheal intubation. Wide-complex tachycardia initially resolved with intravenous sodium bicarbonate but later recurred despite alkalinization to a pH of 7.52 and arterial pCO_2 28 mmHg. The wide complex tachycardia resolved shortly after the intravenous infusion of phenytoin 750 mg.

Drug screening for tricyclic overdose as well as other common toxic ingestants was negative.

Conclusion: Phenytoin may have had therapeutic value in this case of cardiac toxicity from diphenhydramine that was refractory to alkalinization with sodium bicarbonate.

Introduction

Diphenhydramine ingestion resulting in toxicity has been reported very commonly (1). There is some evidence to suggest that the cardiotoxicity of diphenhydramine is similar to tricyclic anti-depressant (TCA) toxicity, in that it has type 1a antiarrhythmic properties (2). We will present a case in which the usual modalities for type 1a antiarrhythmic toxicity were unsuccessful in treating a diphenhydramine cardiotoxicity but phenytoin was. We will then review the literature and discuss the use of phenytoin in treating type 1a antiarrhythmic toxicity.

Case Study

The patient, a 30 year old Korean female, awoke her boyfriend lying beside her with noisy labored breathing. Her eyes were open but she was not responding to touch or voice. She had last been seen awake and well one hour before. The patient had attempted suicide with Sominex™ (diphenhydramine) one month before. The patient had no other medical problems and aside from Sominex™ was on no medication.

One hour and fifteen minutes after last being seen well the patient began having generalized seizures lasting at least thirty five minutes. Paramedics treated the patient pre-hospital with Valium™ 20 mg IV, midazolam 5 mg IV and endotracheal intubation. They also administered 100 ml of D50W IV, even though a chemstrip™ showed normal fingerstick glucose range, thiamin 50 mg and Narcan 0.8 mg IV.

Initially when the paramedics arrived and were beginning to treat the seizure, a sinus tachycardia at a rate of 120 was noted on the cardiac monitor. The systolic blood pressure was 120 mmHg. As the seizure progressed the QRS complex was noted to widen. An online order was given to administer NaHCO3 88 meq, IV. The QRS narrowed shortly thereafter.

The paramedics arrived with the patient to the emergency department (ED) 45 minutes after the first patient contact at the scene. At that time, in the ED, the oxygen saturation was 100%; glucometer showed serum glucose at 11 mmol/l (198 mg/dl); pulse 130/min wide complex; blood pressure 110/70; ventilated @ 16/min. Her temperature was 38.8°C. The patient's weight was approximately 50 Kg. Her neck was supple. There were no signs of head or neck trauma. There was good air entry bilaterally. The heart sounds were normal with good peripheral pulses. The abdomen was soft and no

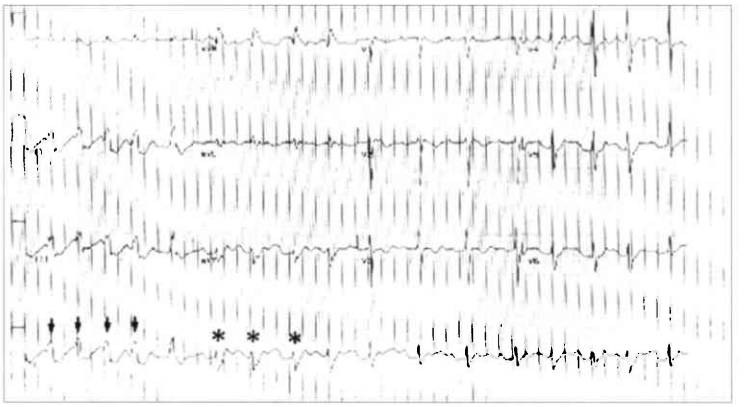

Figure 1. This is a 12 lead ECG of the patient discussed in this report prior to treatment with phenytoin. It illustrates the runs of wide complex tachycardia (arrows). The asterisks indicate likely fusion beats. This ECG was interpreted by two cardiologists as likely representing runs of Ventricular Tachycardia.

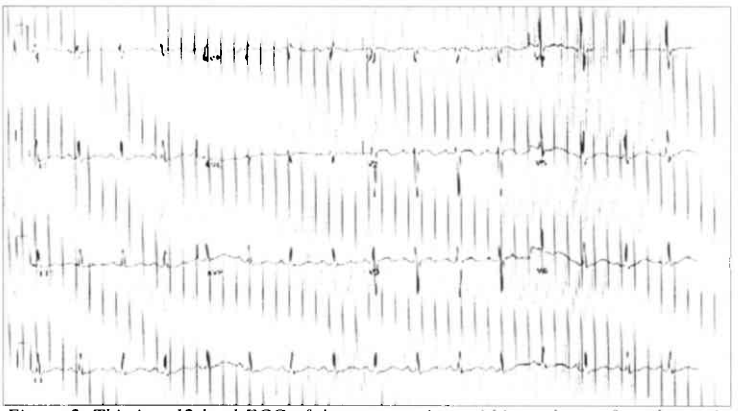

Figure 2. This is a 12 lead ECG of the same patient within an hour after phenytoin infusion had stopped. There are no longer runs of wide complex tachycardia. Note that the QT interval is still abnormally long.

masses were felt. The pupils were 4 mm and non-reactive. Fundi were normal. Her eyes were closed and she was flexing all four limbs to pain. There were no gag or corneal reflexes and no doll's eye movement. No skin lesions were observed.

A 12 lead electrocardiogram (**figure 1**) showed a wide complex tachycardia which was interpreted at the time, and later confirmed by two cardiologists, as likely being a ventricular tachycardia (VT).

Within 15 minutes of arrival to the ED $NaHCO_3$ one ampule (50 ml, 88 meq) and two ampules in 1 L D5W @ 250 cc/h was administered. She also received activated charcoal, 50 g by nasogastric tube.

Arterial blood gases (ABG) five minutes after administration of $NaHCO_3$ were pH 7.52; pCO_2 28 mmHg; $O_2$234 mmHg; and -$HCO_3$23 meq/L. A chest x-ray was normal.

A half hour after arrival to the ED, initial blood work-up showed sodium (Na) 139 meq/L; Potassium (K) 2.6 meq/L; Chloride (C1 100 meq/L and serum glucose 15.1 meq/L.

Alcohol, acetylsalicylic acid and acetaminophen levels were not detected. A tricyclic antidepressant screening was negative. Urine toxicology screening was not done.

Thirty five minutes after arriving in the ED, runs of VT continued. Over the next 45 minutes, despite lidocaine, a 3 mg/Kg IV bolus, followed by 4 mg/min infusion and another ampule of $NaHCO_3$ being administered, runs of VT continued. KC1 40 meq IV was administered and a repeat ABG showed pH 7.53; $pCO_2$26 mmHg; $O_2$188 mmHg; -$HCO_3$22 meq/L and K 3.4 meq/L.

In order to treat the VT, phenytoin 750mg IV was administered over 30 minutes, the infusion beginning two hours after arrival in the ED. No further VT was observed once the infusion had stopped.

Procainamide, amiodarone and bretylium were not considered for treatment because the ECG had a prolonged QT interval suggestive of type Ia antiarrhythmic toxicity and these drugs are contraindicated in this circumstance.

A CT scan of the head was normal.

One hour after the phenytoin infusion began the BP was noted to be only 87/51 mmHg. Following IV NS 500 ml bolus, the BP was 92/78 mmHg with a sinus tachycardia of 100 beats/min. (**Figure 2**). A repeat dose of activated charcoal 50 g was given and the patient was transferred to the intensive care unit.

She was extubated later that day. She admitted to taking more than twenty 50mg caplets of Sominex™. Eventually she was transferred to psychiatry with no known long term neurologic or cardiac sequelae.

Discussion

Diphenhydramine is an H1 antagonist. It's toxic actions with exception to its cardiac effects, are primarily due to its anticholinergic properties (3). Toxicity is common (4). Anticholinergic poisoning usually predominates (4).

Tachyarrhythmias, bradyarrhythmias, ventricular tachycardia, ventricular fibrillation, bundle branch blocks, hypotension and complete cardiovascular collapse have been

observed following large diphenhydramine ingestion (5). In most reported fatal or life threatening cases, the cardiac toxicity presents following seizure activity (3,4,6).

In 1992 Clark and Vance (2) reported a diphenhydramine intentional overdose resulting in progressive loss of consciousness, seizure activity, and then ventricular tachycardia with a normal blood pressure. Presuming initially that the TCA overdose was the cause of the clinical presentation, they alkalinized (pH>7.45) the patient with an IV $NaHCO_3$ bolus and infusion and observed an abolition of the VT. No TCA ingestion was found on serum analysis or history. As a result the authors introduced the concept of diphenhydramine toxicity being caused by a quinidine like or type 1a antiarrhythmic toxicity similar to TCA poisoning. Diphenhydramine is a "membrane stabilizer" because of its fast Na^+ channel blockade properties, resulting in intrinsic pacemaker suppression, AV node blockade and re-entrant ventricular tachydisrrhythmias (2). $NaHCO_3$ may combat diphenhydramine cardiotoxicity by "antagonizing" Na^+ channel blockade either by the provision of hypertonic saline and/or an alkaline environment (2,8,9). Thus it seems that diphenhydramine is similar to other type 1a antiarrhythmic toxicities both in its electrophysiologic properties and the ability of $NaHCO_3$ to treat its cardiotoxicity. But what if $NaHCO_3$ doesn't work?

In the early 80's, phenytoin was advocated as the antiarrhythmic of choice for digoxin and TCA overdose (10,11,12). Since then, Digibind ™ has become primary therapy for serious digoxin overdose. Many authorities do not recommend phenytoin in TCA overdose (13) and thus, by inference for, all other type 1a antiarrhythmic toxicities. This recommendation is based on two animal studies. These studies involved an intravenous amitriptyline infusion model in dogs (14) and rabbits (15). In the dog study, one group was given phenytoin 19mg/Kg and the control group, none. The number of episodes of VT per animal and the duration of VT was significantly greater in the phenytoin group. The plasma levels of amitriptyline were not compared in the phenytoin versus the control group. But the authors did report that there were higher plasma levels of amitriptyline in the group with VT. The authors concluded that: 1. phenytoin causes increased VT in TCA overdose, 2. there are no clear indications for phenytoin in TCA toxicity and 3. phenytoin may have similar "negative effects" on other type 1a antiarrhythmic toxicities. In the Rabbit study, phenytoin prophylaxis did not prevent death from amitriptyline infusion and a "rescue" (authors used quotes) phenytoin infusion reversed only two of twelve animals' cardiac arrhythmias. These authors concluded that phenytoin prophylaxis or "rescue" doesn't delay or treat cardiac arrhythmia or prevent death. However, the observation described above could be interpreted differently and might lead to different conclusions as described below.

There is poor clinical applicability of a constant toxic infusion model compared to real life scenarios involving usually single large ingestions. In the dog study the authors noted that phenytoin resulted in more TCA being required before VT was elicited. It is possible that the increased incidence of VT and mortality was caused by a greater level of amitriptyline in the group with phenytoin. Furthermore, the blood pressure was not controlled in either study. In the rabbit study, the authors admit that the blood pressure was not monitored and in the dog study the phenytoin group had "substantially" lower BPs than the control group. It is possible that the hypotension in the phenytoin group resulted in myocardial hypoperfusion and thus increased ventricular irritability. These interpretations suggest that these two animal studies should be viewed with caution as being the basis for prohibition of phenytoin in TCA or any other type 1a toxicity.

There is some evidence from other studies that phenytoin has therapeutic effects in TCA and type 1a antiarrhythmic toxicities. Hagerman et al, 1981 (16) described a case series involving 10 patients with TCA overdose resulting in varying degrees of conduction block and QRS widening that had a reversal of cardiotoxicity after 5 to 7 mg/Kg phenytoin IV.

Maxwell et al, 1994, reported two cases of neonates given bupivacaine for spinal anesthesia resulting in VT refractory to alkalinization and usual ACLS protocol, including lidocaine and bretylium, which converted to sinus rhythm soon after the

administration of phenytoin. Bupivacaine is similar to TCA and diphenhydramine toxicity in that it blocks the fast Na^+ channel.

There are three possible mechanisms underlying the therapeutic effect of phenytoin in type 1a cardiotoxicity: 1. phenytoin decreases ventricular automaticity, probably due to a decrease in slope of phases 0 and 4 in the Purkinje fibers and thus increases in effect the refractory period of the conducting action potential, 2. it has central antiarrhythmic properties as suggested by decreased sympathetic discharge and 3. phenytoin increases AV node conduction, therefore decreasing likelihood of reentrant ventricular arrhythmias (17).

It might be argued that the arrhythmia reported in this case report was not VT, but rather a supraventricular tachycardia with aberrant conduction. Several points can be made against this possibility. First, even in the ECG following phenytoin (**figure 2**), the QT interval was abnormally long suggesting that diphenhydramine was having type 1a antiarrhythmic effects, which, if it acted as other type 1a cardiotoxicities, causes VT. Second the ECG showed AV dissociation consistent with VT. Thirdly, two cardiologists, one of whom was an electrophysiologist, said that the ECG was likely consistent with VT. The only way of unequivocally proving that this rhythm was VT would have been to observe it in an electrophysiology laboratory, obviously an impossibility. Finally, even if this rhythm was not VT, phenytoin nevertheless appeared to have a therapeutic effect on abolishing it.

In the case reported here it cannot be unequivocally stated that phenytoin resulted in the abolition of VT. It is possible that the VT would have resolved with time regardless of the therapy. However, despite very adequate alkalinization, the VT continued and only ended very shortly after the phenytoin infusion. A controlled animal study with a single large dose ingestion of diphenhydramine model in which hypotension was prevented would help answer the question of whether phenytoin is effective against this drug's cardiotoxicity.

Conclusion

This case report suggests that there may be a role for phenytoin in treating refractory VT resulting from diphenhydramine toxicity. It is possible that phenytoin may also be effective in other type 1a cardiotoxicities. This assertion requires more study.

References

1. Litovitz TL, Schmitz BF, Bailey KM. Annual Report for the American Association of Poison Control Centers National Data Collection System. Am J Emerg Med 1990;8:394-442
2. Clark RF and Vance MV. Massive Diphenhydramine Poisoning Resulting in a Wide-Complex Tachycardia: Successful Treatment with Sodium Bicarbonate. Ann Emerg Med 1992;21:318-321
3. Winn RE, and McDonnell KP. Fatality secondary to Massive Overdose of Dimenhydrinate. Ann Emerg Med 1993;22:1481-1484
4. Clark RF and Vance M. Massive Diphenhydramine Poisoning Resulting in a Wide-Complex Tachycardia: Successful Treatment with Sodium Bicarbonate. Ann Emerg Med 1992;21:318-321
5. Hausmann E, Wewer H, Wellhoner HH, Weller JP. Lethal Intoxication with Diphenhydramine Report of a Case with Analytic Follow-up. Arch Toxicol 1983;53:33-39
6. Hestand HE and Teske DW. Diphenhydramine hydrochloride intoxication. J Ped 1977;90:1017-1018
7. Kopel C and Ibe K. Clinical Symptomology of Diphenhydramine Overdose: An evaluation of 136 Cases in 1982 to 1985. Clin Toxicol 1987;25:53-70
8. Hoffman JR, Votey SR, Bayer M and Silver L. Effect of Hypertonic Sodium Bicarbonate in the treatment of Moderate-to-severe Cyclic Antidepressant Overdose. Am J Emerg Med 1993;11:336-341
9. Pentel P and Benowitz N. Efficacy and Mechanism of Action of Sodium Bicarbonate in the Treatment of Desipramine Toxicity in Rats. J Pharmacol Exp Ther 1984;230:12-9
10. Rosen M, Lisak R, Rubin I. Diphenylhydantoin in Cardiac Arrhythmias. 1967;20:674-678
11. Bigger JT, Schmidt DH, Kutt H. Relationship Between the Plasma Level of Diphenylhydantoin Sodium and its Cardiac Antiarrhythmic Effects. Circ 1968; 38:363-374
12. Cantrill SF. Emergency Case Records: Prophylactic Phenytoin in Tricyclic Overdose. J Emerg Med 1983;1:169-177
13. Pentel PR, Benowitz NL. Tricyclic Antidepressant Poisoning: Management of Arrhythmias. Med Toxicol 1986;1:101-121
14. Callaham M, Schumaker H, Pentel P. Phenytoin Prophylaxis of Cardiotoxicity in Experimental amitriptyline Poisoning. J Pharmacol Exp Ther 1988;245:216-220
15. Mayron R, Ruiz E. Phenytoin: Does it Reverse Tricyclic Antidepressant Induced Cardiac Conduction Abnormalities? Ann Emerg Med 1986;15:876-880
16. Hagerman GA, Hanashiro PK. Reversal of Tricyclic Antidepressant Induced Cardiac Conduction Abnormalities By Phenytoin. Ann Emerg Med 1981;10:82-86
17. Maxwell LG, Martin LD, Myron Y. Bupivacaine Induced Cardiac Toxicity in Neonates: Successful Treatment with Intravenous Phenytoin. Anesthes 1994;80:682-686