CASE REPORT

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Dicyclomine in the Sudden Infant Death Syndrome (SIDS)—A Cause of Death or an Incidental Finding?

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ABSTRACT: We report a case of a small infant apparently dying of the Sudden Infant Death Syndrome (SIDS) with a postmortem blood dicyclomine level of 200 ng/mL. Review of the literature and the comparison with blood dicyclomine values from four rabbits given equivalent doses suggests that a blood dicyclomine value of 200 ng/mL probably is in the therapeutic range for infants. Although safely used for years for infantile colic, recently, the administration of dicyclomine has been related to acute episodes of apnea, seizures, and coma. In the absence of those acute reactions, we feel that a 200-ng/mL blood dicyclomine level in a child dying of apparent SIDS should not prevent categorization of the death as SIDS.

KEYWORDS: pathology and biology, Sudden Infant Death Syndrome, dicyclomine

A plethora of causes and mechanisms of death have been postulated for the Sudden Infant Death Syndrome (SIDS). The diagnosis of SIDS, however, still rests on the autopsy and toxicologic exclusion of all possible causes of death in the appropriate age and historical setting. The diagnosis of SIDS is in question whenever there are pathological or toxicological findings that could represent another potential cause of death.

We recently investigated the death of a nine-and-one-half-week-old child in which the circumstances surrounding the death and the autopsy examination both were consistent with SIDS. Historical data, however, indicated that the child was taking dicyclomine (Bentyl®—Merrell-Dow) for infantile colic. Subsequent postmortem toxicologic analysis confirmed the presence of dicyclomine. The presence of dicyclomine was alarming since there have been at least fourteen reported instances of potentially life-threatening episodes of apnea, seizures,

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and coma following administration of dicyclomine [*1–3*]. Two deaths have also been reported associated with dicyclomine use [*4*].

Unfortunately, no therapeutic dicyclomine blood values for infants have been published or are available from the manufacturer. Although Garriott et al. [*4*] do report postmortem blood dicyclomine values, only one of their two cases was an obvious overdose situation.

In an effort to categorize the blood dicyclomine level found in our case as either therapeutic or overdose, we compared our autopsy dicyclomine value with those from four rabbits given an equivalent dose.

Case Report

The decedent was a 9½-week-old male infant. The 25-year-old mother is gravida two, para two with the most recent pregnancy uneventful as was the delivery. The decedent remained healthy with the exception of infantile colic until he died. At 3 weeks of age, dicyclomine syrup was prescribed by a physician to be administered as needed at 5-mg doses up to 4 times a day.

On the day of death the child appeared normal and healthy. He received two 5-mg doses of dicyclomine on the day of death, one at 8:30 a.m. and the other at 1:00 p.m. following a noon meal. Nothing unusual was noted when the child was put down for a nap at 2:00 p.m. The infant appeared to be sleeping normally at 3:15 p.m., but was dead when rechecked again at 4:15 p.m.

Autopsy on the refrigerated, unembalmed body began at 8:00 a.m. on the following day. The infant weighed 5750 g. No gross or microscopic pathologic changes were seen during the postmortem examination. Blood for toxicologic examination was removed directly from the right atrium and ventricle.

Method

Four domesticated rabbits weighing 2380, 2250, 2625, and 3110 g (Rabbits A, B, C, and D, respectively, in Fig. 1) were given commercially available dicyclomine syrup orally via a plastic pipette. No external spillage was noted of the red syrup nor was there evidence of aspiration. Each rabbit received the same dose that the child in the case report reportedly received (0.86 mg/kg of body weight). The rabbits were allowed free access to food and water before the dosing but not afterwards. Blood for dicyclomine determination was removed from each rabbit by pericardial puncture at 30 min, 1 h, 2 h, and 3 h after the dicyclomine was administered. The whole blood samples were stored frozen at −70°C until assayed approximately three weeks later.

Reagent grade methanol, ethyl acetate, isobutyl alcohol, hydrochloric acid, sodium hydroxide, and ammonium hydroxide were used without further treatment. Ethyl ether was USP grade and reagent water was provided by a Barnstad RO/Nanopure system. Procaine (Sigma) and dicyclomine (Bexar County Medical Examiner's Office, San Antonio, Texas, and Merrell-Dow Pharmaceutical Company) were screened for contaminants but used without further purification. Extraction tubes and concentrator cups were washed with detergent, water rinsed, cleaned with hydrochloric acid, water rinsed, methanol rinsed, and allowed to air-dry. Concentrator cups were then silylated, water rinsed, and allowed to air-dry.

Frozen clotted blood samples, 5 mL, in 10-mL plastic tubes were thawed and transferred to an all glass tissue grinder. Ammonium hydroxide (10%) solution, 5 mL, and 0.05 mL of internal standard were added to the blood. The mixture was then ground for 30 s and transferred to a 50-mL test tube with Teflon® lined screw cap. Ethyl ether, 10 mL, was then added and the tube vortexed for 1.0 min. The mixture was centrifuged and the ether layer transferred to a 20-mL test tube containing 5 mL of hydrochloric acid (1*N*). This mixture was vortexed, centrifuged, and the ether layer discarded. Another 5 mL of ether was added to the

tube and vortexed, centrifuged, and the ether discarded. Approximately 0.6 mL of sodium hydroxide (10*N*) was added to the extraction tube with 10 mL of extraction solvent (ethyl acetate:isobutyl alcohol, 9:1). After vortexing, the tubes were centrifuged and the organic layer transferred to a 20-mL conical concentrator tube and evaporated to dryness at 50°C under a stream of air. The residue was dissolved in 0.025 mL of makeup solvent (toluene:methanol, 96:4) before injection of 3.0 μL into the gas chromatograph.

A Hewlett-Packard 5880A series gas chromatograph fitted with a flame ionization detector (FID) was used. A Level IV data processor provided reports. A 50-m fused silica SE-54 capillary column was used. The temperature of the oven was 190°C, the detector 275°C, the injector port 225°C; the carrier gas was helium at a flow rate of 2.0 mL/minute, the makeup gas was nitrogen at a flow rate of 30 mL/minute, the FID air flow rate was 400 mL/minute, and the hydrogen flow rate was 30 mL/minute. The internal standard was procaine (0.1 mg/mL). Retention times under these conditions were procaine 5.8 min and dicyclomine 7.2 min. Recovery of dicyclomine and internal standard was established by comparative analysis of methanol and drug-free blood each containing 250 and 500 ng/mL of dicyclomine, respectively. Recovery of dicyclomine was only 80%; however, good precision indicated consistent recoveries of dicyclomine and internal standards were obtained.

Results

The infant's postmortem blood dicyclomine level was 200 ng/mL. The dicyclomine whole blood values obtained from the four rabbits are shown in Fig. 1.

Discussion

The blood dicyclomine values from the four test animals (Fig. 1) demonstrate marked variability. Clearly, in our test rabbits, there is considerable variation in dicyclomine absorption and distribution. We cannot explain the widely divergent blood values in the test rabbits other than to postulate marked variations in absorption as a result of the nonfasting state. Although no representative "average" therapeutic blood dicyclomine level could be derived from data peak values, some peak values did approximate the level seen in our autopsy case. Garriott, et al.'s [*4*] first case represented a death suggestive of SIDS with an associated, probably therapeutic, use of dicyclomine. The postmortem blood dicyclomine level in that case was 221 ng/mL. The blood dicyclomine level in the apparent overdose case was 505 ng/mL. As a cautionary note, we do recognize the hazards of extrapolating between drug blood levels in animals and humans, particularly when only small numbers of animals are used and marked unexplained variability occurs in the observed results.

The highest reported adult therapeutic blood dicyclomine level is 80 ng/mL [*5*]. Garriott et al. [*4*] were concerned that their 221-ng/mL blood dicyclomine value dramatically exceeded the known adult therapeutic level. However, the maximum pediatric daily dose is only half of the maximum daily adult dose [*6*]. In a 70-kg adult, the dose is only 0.14 mg/kg of body weight compared to the "therapeutic" dose of 0.86 mg/kg of body weight in our case. The observed and reported pediatric blood dicyclomine values appear realistic in view of the marked difference in dosing between adults and children.

The reported cases of apnea, seizures, and coma following dicyclomine use all occurred within 30 min of administration [*1–3*]. The authors of these reports speculated that the reaction to the dicyclomine dose was secondary to an immediate local irritation or aspiration or both and not an overdose phenomenon.

Although of questionable efficacy for infantile colic [*7*], dicyclomine has been used safely for many years with no reported adverse effects until quite recently. In view of dicyclomine's safety record, the recovery of an apparent therapeutic blood dicyclomine level (as suggested by concordance of our maximum rabbit blood levels with human postmortem levels follow-

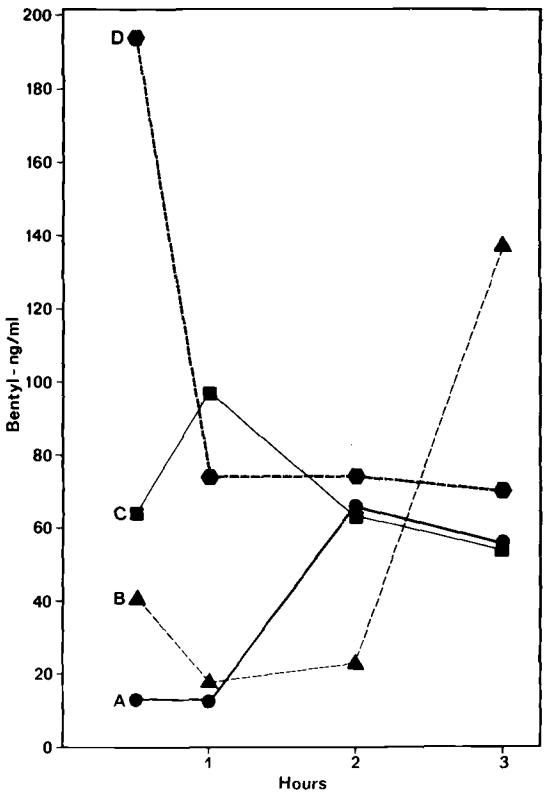

FIG. 1— *Whole blood dicyclomine (Bentyl) levels of four rabbits at* (A, B, C, *and* D) *at 30 min, 1 h, 2 h, and 3 h after receiving an oral dose of dicyclomine of 0.86 mg/kg of body weight.*

ing apparent therapeutic dosing both in our case and that reported by Garriott et al. [*4*]), and the absence of an immediate reaction to the dicyclomine dose, we conclude that the dicyclomine did not materially contribute to the death in our case. The cause of death in our case was certified as SIDS, although the possibility of an adverse dicyclomine reaction cannot be absolutely excluded.

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