EXPERIENCE AND REASON—Briefly Recorded

"In Medicine one must pay attention not to plausible theorizing but to experience and reason together. . . . I agree that theorizing is to be approved, provided that it is based on facts, and systematically makes its deductions from what is observed. . . . But conclusions drawn from unaided reason can hardly be serviceable; only those drawn from observed fact." Hippocrates: *Precepts.*
(Short communications of factual material are published here. Comments and criticisms appear as Letters to the Editor.)

Hyperosmolality in Small Infants Due to Propylene Glycol

Propylene glycol (1,2-propanediol) is used in many drug preparations. Although propylene glycol is regarded as having low toxicity in adults, in humans and animals there have been reports of CNS, renal, hematologic, and cardiac toxicity.[1–5] The absorption of propylene glycol through large burn wounds has recently been documented as a cause of serum hyperosmolality.[6,7]

Investigation of the cause of unexplained hyperosmolality in a premature infant led to the finding that several infants in our nursery were hyperosmolar due to administration of propylene glycol in a multivitamin preparation used in parenteral nutrition. This finding raises concern about the relatively large dose of propylene glycol that may be received by very small infants, especially those receiving multiple medications.

CASE REPORT

The index patient, a female infant, was born weighing 890 g, following a 27-week gestation. Parenteral nutrition was begun on the third day after birth. She required some respiratory support for respiratory distress syndrome, and she received phototherapy for hyperbilirubinemia. On the ninth day, a regimen of aminophylline therapy was started for episodes of apnea, and a grade III intraventricular hemorrhage was documented by ultrasound. On the 12th day, she developed unexplained acute renal failure. Serum osmolality was 407 mosm/kg, sodium was 124 mmol/L; potassium, 5.9 mmol/L; chloride, 88 mmol/L; total CO_2, 24 mmol/L. Serum urea nitrogen was 41 mg/dL and serum glucose concentration was 148 mg/dL. Parenteral nutrition was stopped for 48 hours, then resumed. The serum osmolality decreased to about 350 mosm/kg and remained at this approximate level for two weeks; blood lactate level was normal. The cause of the hyperosmolality was identified when a large amount of propylene glycol was detected in the urine by gas chromatography-mass spectrometry. A review of medications revealed that the main source of propylene glycol was MVI-12, a multivitamin preparation (USV Pharmaceutical) that contains 30% propylene glycol. The patient had received 10 mL (3 g of propylene glycol) of this preparation daily in her parenteral nutrition solution. When initially measured, her serum propylene glycol level was 930 mg/dL.

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METHODS

MVI-12 was immediately removed from all parenteral nutrition solutions used in the nursery. Just prior to discontinuation, a blood sample was obtained from all infants receiving MVI-12 for measurement of serum sodium, potassium, chloride, total CO_2, osmolality, and propylene glycol. Serum glucose and urea were not measured simultaneously; however, none of the infants studied had had recent abnormalities in these metabolites. The same measurements were obtained from eight control infants, not receiving parenteral nutrition, who had venipunctures for other reasons. The tests were repeated 36 hours later, on those infants who had been receiving MVI-12. The osmolal gap was calculated as the measured osmolality minus two times the serum sodium measured in millimoles per liter. Propylene glycol was measured by gas-liquid chromatography. Serum was diluted 1:1 with water containing ethylene glycol as an internal standard. An aliquot was injected into a 3 ft x 2 mm (inner diameter) glass column, packed with 0.8% THEED (tetrahydroxyethylenediamine) on Carbopack C. Injector, oven, and detector temperatures were

150°C, 120°C, and 170°C, respectively. Nitrogen at a flow rate of 30 mL/min was used as the carrier gas. Detection was by flame ionization.

RESULTS

Ten infants had each received 10 mL of MVI-12 for at least five days immediately prior to sampling. Of these ten infants, four had a serum osmolality >300 mosmol/kg. The highest osmolalities were found in the smallest babies (Fig 1).

Propylene glycol was not detectable in six control infants who were not receiving parenteral nutrition. Two other control infants had 70 mg/dL of propylene glycol in their serum, which was attributed to therapy with phenobarbital in one infant and Mycostatin cream for diaper rash in the other.

There was a direct relationship between the osmolal gap and serum propylene glycol concentration (propylene glycol = 47.5 times osmol gap + 9.2; $r = .96$). The osmolal gap was somewhat less than the expected osmolality of the measured serum propylene glycol. The decrease in serum propylene glycol level over 36 hours (in one case, 50 hours) is shown in Fig 2. The mean half-life was 19.3 hours, with a range of 10.8 to 30.5 hours (excluding one patient with an unexplained slow decrease in propylene glycol level). This must be viewed as a rough estimate of half-life, as only two sample points were available for all but one patient.

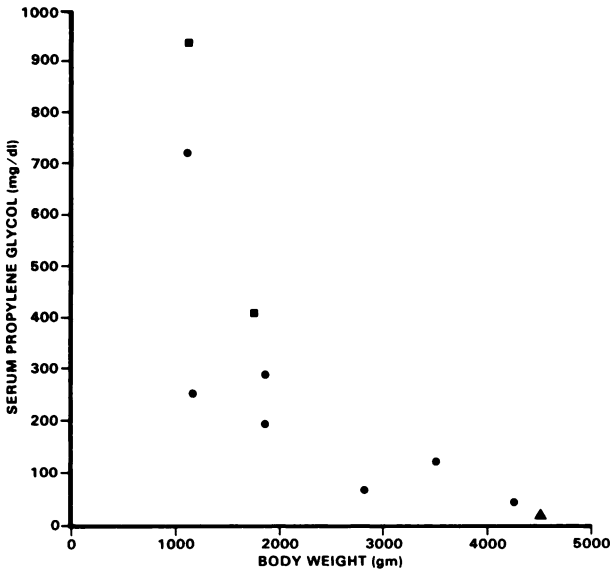

Fig 1. Propylene glycol levels and body weight. All patients had received 10 mL of MVI daily for at least five days. Circles indicate patients not receiving drugs containing propylene glycol; squares indicate patients receiving phenobarbital; triangle indicates patient receiving Digoxin, Bactrim, phenobarbital, and hydralazine (containing 2.64 mL of propylene glycol) in addition to MVI-12.

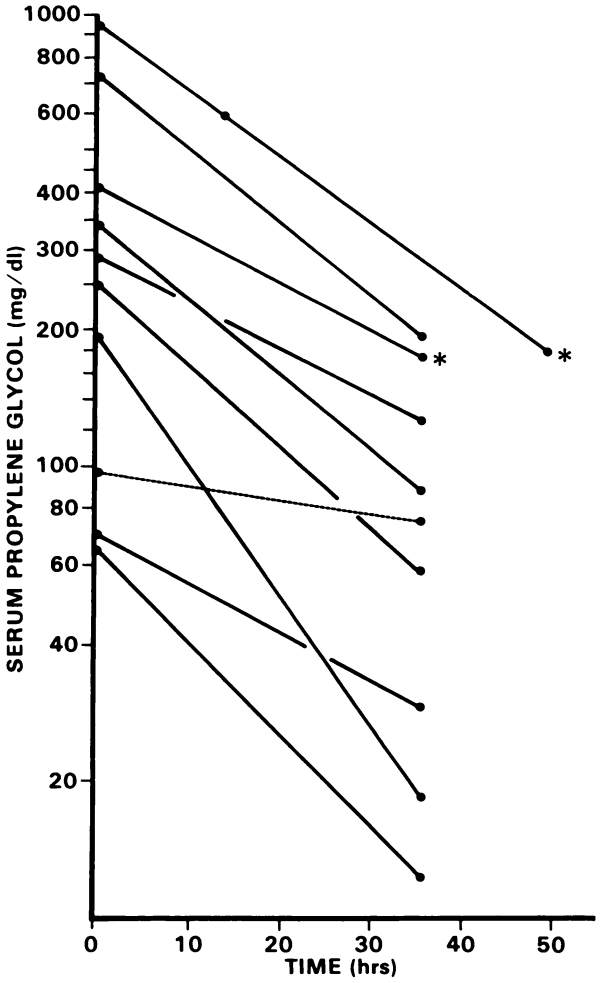

Fig 2. Change in serum propylene glycol levels after discontinuation of MVI-12. Asterisk indicates patients who continued to receive phenobarbital; dashed line indicates patient with unexplained long half-life.

DISCUSSION

We have found, in small infants, marked serum hyperosmolality caused by propylene glycol in a parenteral multivitamin preparation. Communication with other centers indicates that the dose of this multivitamin preparation may be higher than that generally used. The package insert indicates that MVI-12 is intended for patients 11 years of age and older; yet it was chosen because it is the only parenteral-use preparation containing Biotin. This dose was chosen to provide adequate amounts of vitamins relative to estimated requirements. Hyperosmolality may not occur with lower doses of this preparation.

On the other hand, many other drugs contain propylene glycol. Many of these drugs are commonly used in the nursery: Digoxin, Bactrim, phenobarbital, phenytoin, diazepam, vitamin D, hydralazine, and Mycostatin cream. It is not uncommon for small sick infants to receive multiple drugs

in addition to parenteral multivitamins. It is likely that some of these infants would receive sufficient propylene glycol to result in substantial levels being shown in serum concentrations. As all infants in this study received the same daily dose (10 mL) of MVI-12, the smaller infants received a greater dose per kilogram of body weight. Our limited data do not suggest that the half-life of serum propylene glycol is related to size or gestational age.

Propylene glycol has been associated with CNS depression.[4,5] It has been estimated that on a weight-for-weight basis it is approximately one third as intoxicating as ethanol.[1] Depression due to this intoxication could impair respiratory function in infants. Rapid intravenous injection of propylene glycol has been associated with circulatory collapse and arrhythmia in calves.[2] Intravenous injection in sheep produces intravascular hemolysis.[3] As propylene glycol is metabolized to lactate, it may produce lactic acidosis in susceptible individuals.[8] Finally, propylene glycol may cause a diuresis, and there is concern about possible renal and hepatic toxicity.[1]

Some of our patients demonstrated some of these problems. However, we cannot as yet ascribe any clinical problems other than hyperosmolality to propylene glycol. As propylene glycol is diffusible into all body water the hyperosmolality would not be expected to have the same consequences as hyperosmolality due to nondiffusible substances such as sodium and glucose. For the present, it would seen prudent to be cautious when using drugs containing propylene glycol, and to try to limit the amount of propylene glycol administered to very small infants.

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