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Methanol Toxicity in a Newborn

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ABSTRACT

Background: Methanol poisoning during human pregnancy rarely has been described. We report the first human newborn with a documented methanol concentration resulting from maternal exposure. *Case Report:* A 28-year-old pregnant woman EGA 30 weeks with HIV infection and asthma presented to the emergency department in respiratory distress. She was acidotic (pH 7.17) with an anion gap of 26, and fetal bradycardia was noted. Her son was delivered by emergent C-section (birthweight 950 g, Apgars 1 and 3) and required aggressive resuscitation. During his hospital course, acidosis (initial pH 6.9) persisted despite fluid, blood, and bicarbonate administration. His mother also had persistent metabolic acidosis despite fluids, bicarbonate, and dopamine. Results of other laboratory tests on the mother included undetectable ethanol and salicylates and an osmolar gap of 41. An ethanol drip was initiated for the mother 36 h after admission when a methanol level of 54 mg/dL was reported. When consulted on hospital day 3, our regional poison center recommended hemodialysis for the mother and administering fomepizole and testing the methanol level of the newborn (61.6 mg/dL). Because the infant developed a grade 4 intraventricular bleed, no further therapy was offered, and he died on day 4. His mother died on day 10. *Conclusion:* Fatal neonatal methanol toxicity can result from transplacental exposure.

Key Words: Methanol; Acidosis; Neonate; Newborn; Pregnancy.

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INTRODUCTION

Few reports of methanol poisoning during human pregnancy have been published (1,2) and knowledge is limited about both risk to the fetus from maternal methanol exposure and appropriate treatment. We report what we believe is the first human newborn with a documented plasma methanol concentration resulting from maternal exposure.

CASE REPORT

A 28-year-old woman, gravida 3, para 2, EGA 30 weeks with HIV infection, asthma, and history of cocaine use and hospitalization two months earlier for unexplained metabolic acidosis presented to our emergency department (ED) lethargic and in respiratory distress. Her initial vital signs were remarkable for tachycardia (heart rate 120) and tachypnea (respiratory rate 28). She was afebrile and had a normal blood pressure. The initial diagnosis was status asthmaticus, and bronchodilator and oxygen therapy was initiated. Because of fetal bradycardia, an emergent caesarian section was performed. Results of pertinent laboratory tests obtained in the ED included an arterial pH of 7.17 (normal 7.35–7.45), sodium 136 mEq/L, potassium 3.6 mEq/L, chloride 105 mEq/L, bicarbonate of 7 mEq/L (normal 23–29 mEq/L) with an anion gap of 24 mEq/L (normal 8–12 mEq/L), glucose 163 mg/dL (normal 70–105 mg/dL), osmolar gap of 41 mOsm (normal −2±6 mOsm), and a negative urine drug screen. The mother's medical record from a prenatal visit during this pregnancy five weeks earlier documented normal ultrasound findings and a gestational age of 24 weeks. During a brief hospitalization 2 months earlier for unexplained metabolic acidosis, she was treated with sodium bicarbonate and showed improvement.

A 950-g male was delivered. Apgar scores were 1 at 1 min and 3 at 5 min. He was intubated in the delivery room and given two doses of epinephrine because of a heart rate (HR) of 70–90, cyanosis, agonal respirations, and capillary refill longer than 3 sec. On initial examination in the neonatal intensive care unit (NICU), the newborn was pale with poor tone, peripheral and central pulses were weak, capillary refill was longer than 3 sec, and minimal hepatomegaly was present. A Ballard score estimated him to be 30 weeks gestational age. Results of initial NICU laboratory tests included sodium 138 mEq/L, potassium 4.2 mEq/L, chloride 103 mEq/L, bicarbonate 7 mEq/L, calcium 6.9 mg/dL (normal 7–11.5 mg/dL), glucose 126 mg/dL (normal 40–60 mg/dL), C-Reactive Protein<0.5 (normal 0–0.5 mg/dL), lactate 19.2 mEq/L (normal<3.8 mEq/L) and a high anion gap metabolic acidosis (Table 1). Initial management included administering sodium bicarbonate and intravenous fluids, which increased his HR to the 150s. Blood and urine cultures were obtained, and ampicillin and gentamicin were started.

On day 2 of hospitalization, the newborn's tone, activity, color, and capillary refill were slightly better. His urine drug screen was positive only for opiates. Urine was obtained for organic acids because of persistent acidosis despite aggressive therapy. He had leukopenia with 35% neutrophils and 53% lymphocytes

Table 1. Vital signs and laboratory data of a methanol-exposed newborn during his hospitalization.

Hospital day	HR	MAP	WBC	Hgb	pH	pCO_2	Base deficit	CO_2	Anion gap
1	70–150	30–36	NA	NA	6.90	29	26	7	28
2	150–160	36–42	2.0	14.7	7.37	26	8	9	28
3	150–165	36–45	1.3	9.1	7.27	52	3.5	16	30
4	130–160	28–49	0.7	11.0	7.51	34	NA	20	NA
Reference values (3,4)	120–160 bpm	34 mm Hg	4.4 cells/mm^3	14.5 g/dL	7.26–7.29 (birth), 7.37 (>24 h)	55 (birth), 33 (>24 h) mm Hg	<4 mEq/L	17–24 mEq/L	8±4 mEq/L

HR=heart rate
MAP=mean arterial pressure
WBC=white blood cell count
Hgb=hemoglobin
pCO_2=partial pressure of carbon dioxide
CO_2=serum bicarbonate
NA=not available

(Table 1). Blood and urine cultures were negative at 48 h.

On day 3 of hospitalization, the infant received a red blood cell transfusion because of decreasing hemoglobin (Table 1). He was given phenobarbital after generalized seizures (length of time not documented). A cranial ultrasound revealed a grade 4 intraventricular hemorrhage (IVH).

The mother had persistent metabolic acidosis (pH<7.1) during the first 2 days of hospitalization despite fluids, bicarbonate, and dopamine. An evaluation of her acidosis began on hospital day 2: salicylates, ethanol, and acetaminophen undetectable; lactate 2.9 mEq/L (normal<2 mEq/L), normal beta hydroxy-butyrate, and pending ethylene glycol and methanol levels. On hospital day 3, the mother's ethylene glycol level was reported to be undetectable, and her methanol level from hospital day 2 was 54 mg/dL. Ethanol therapy began 36 h after her hospital admission.

Our regional poison center was consulted on hospital day 3 when the mother's toxic alcohol analysis results became available. For the mother, we recommended urgent hemodialysis, adjustment of ethanol dosing, leucovorin (folinic acid), and a repeat methanol level (10 mg/dL, hospital day 3). For the newborn, the poison center recommended a methanol level (61.6 mg/dL, hospital day 3) and fomipezole administration. Because of his grade 4 IVH, the family elected to withhold fomepizole therapy and to withdraw cardiovascular and respiratory support on hospital day 4. The infant died shortly after withdrawal of support. The mother developed acute respiratory distress syndrome and renal failure and died on day 10 of hospitalization.

DISCUSSION

To our knowledge, this is the first documented case of a toxic plasma methanol concentration in a human newborn. One other published case report of a human infant born after exposure to methanol during pregnancy (1) differed in a number of ways from our report: a documented time of exposure (5 h) before therapy, no maternal drug history, gestational age was term, no maternal acidosis or fetal distress, successful treatment of the mother with ethanol and dialysis, no need for emergency delivery, and no detection of methanol in the infant at birth.

In our case, because the mother's mental status remained altered and the one available family member had no knowledge of the mother's exposure to methanol, the reason and time of her exposure remain unknown.

Earlier recognition of the cause of the mother's acidosis in this case might have decreased the risk to herself and her newborn. The history of a previous hospitalization with an undiagnosed acidosis might have suggested a repetitive behavior such as methanol ingestion.

Transplacental Drug Transfer and Metabolism

Transplacental drug transfer and metabolism influence the cause and extent of fetal drug toxicity. Drug characteristics that favor transfer across the placenta include low molecular weight (<1000 daltons), high lipid solubility, low protein binding, and nonionized state (5). Methanol has a low molecular weight, low protein binding, is unionized at physiologic pH (pKa of 15.3), (6), and should cross the placenta. On the other hand, formic acid, the toxic metabolite of methanol, has a pKa of 3.75 and is ionized at physiologic pH (7) so its passage from mother to fetus would be hindered. Therefore, for fetal acidosis and toxicity to occur, the fetus would have to generate formic acid.

The metabolic capability of the fetal liver changes as the fetus matures. Alcohol dehydrogenase (ADH) activity in 10- to 16-week human fetuses is only 10% of adult levels and probably increases over time (8). Thus, an immature fetus would produce little formic acid and would be relatively protected from the maternal methanol. As ADH activity increases during the second half of pregnancy, the production of formic acid and its associated toxicity would be expected to increase, also (9).

High Anion Gap Metabolic Acidosis

There are many potential causes of a high anion gap metabolic acidosis in a newborn. Maternal acidosis of short duration is unlikely to lead to significant fetal acidosis because of the bicarbonate pool in the placenta (10) but prolonged maternal acidosis may be a risk to the fetus (9). In our patient, the duration of maternal acidosis was unknown.

In a critically ill newborn, a high anion gap acidosis is highly specific, but not very sensitive, for lactic acidosis (3). In a newborn, lactic acidosis from tissue hypoxia is commonly caused by sepsis or an anoxic event. Sepsis or an anoxic event was not documented in our patient. Lactic acidosis is the most common organic acidosis in newborns because of a limited capacity to form ketones (11) and intoxication

with exogenous anions (e.g., metabolites of methanol, salicylates) is rare. The increase in the anion gap with methanol poisoning is secondary to the accumulation of formic acid; however, in the late stages of a severe exposure, other anions such as lactate may increase due to formate's inhibition of the cytochrome oxidase chain (12).

Another possible cause of an infant with a high anion gap acidosis is an inborn error of metabolism such as isovaleric acidemia and methylmalonic acidemia (13). The results of our patient's urine organic analysis were not consistent with an inborn error of metabolism.

The high anion gap metabolic acidosis in our newborn was likely due to several factors: 1) formic acid from the fetal metabolism of methanol, 2) prolonged maternal acidosis, 3) lactate produced from methanol metabolism, and 4) poor tissue perfusion. A formic acid level was not measured on our newborn so we cannot comment on the extent of that metabolic process.

Management

Little evidence exists about the optimal management of a pregnant woman after a methanol exposure, regardless of the infant status, or management of the methanol-exposed neonate. We feel strongly that the metabolism of methanol should be inhibited. In one case report, use of ethanol and hemodialysis was effective for a mother and her nondistressed fetus after an intentional methanol exposure (1). However, ethanol administration during pregnancy is not without risk. Ethanol crosses the placenta and can concentrate significantly in the fetus (14), ethanol is a known tetratogen (15), and neonatal hypoglycemia has been reported following maternal administration of ethanol (16).

Emergent delivery of the distressed fetus should be strongly considered because hemodialysis or alkali therapy in the mother would have negligible immediate impact upon the acidotic fetus (9).

Fomepizole (4-methylpyrazole) is an alternative to ethanol as an antidote in treating methanol poisoning (17–20). However, the risk to the fetus of maternal fomepizole adminstration has not been studied (15). Theoretically, treating pregnant women with fomepizole is safer than treating them with ethanol. Successful treatment of a pregnant woman with fomepizole for methanol poisoning due to inhalant abuse on two separate occasions has been described (2). Similarly, although indications have not been established for the use of fomepizole in a methanol-exposed neonate, fomepizole theoretically would be safer than ethanol. Unfortunately, we did not have the opportunity to administer fomepizole to our newborn patient.

In conclusion, we believe this is the first reported case of neonatal methanol toxicity from transplacental exposure. Persistent acidosis in a newborn may suggest maternal drug toxicity. Although there are no established recommendations for treating a methanol-toxic newborn, correcting acidosis, blocking methanol metabolism, and using dialysis to remove methanol and formic acid would be appropriate interventions.

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