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## Transplacental Aminophylline Toxicity

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Asthma is a common disorder, with a prevalence of 4% in pregnant women(1) and 10% of them may have exacerbation during labor(2). Aminophylline is frequently used to relieve bronchospasm in

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these women, but little is known about the placental transport and the effects on the fetus and the newborn. We report a case of transplacental aminophylline toxicity in this context.

### Case Report

A twenty-six-year old primigravida; a known case of bronchial asthma, developed an acute exacerbation at forty weeks of gestation. She did not respond to salbutamol and was admitted in a nursing home. She was treated with intravenous aminophylline (250 mg) and hydrocortisone without any improvement and was transferred to our institution. Here, she received two more doses of intravenous aminophylline (250 mg each); the last dose being two hours before delivery. A caesarean section was undertaken for persistent fetal tachycardia (180-190/minute) with poor beat-to-beat variability and non-progression of labor. She delivered a full term female neonate weighing 3150 g with Apgar scores of 3 and 5 at 1 and 5 minutes, respectively.

Within three minutes of birth, the neo-

nate developed multifocal clonic convulsions which failed to respond to intravenous glucose, calcium, phenobarbitone and phenytoin. She had tachycardia, normal blood pressure, poor respiratory drive and was neurologically comatose with flat fontanelle, dilated pupils, hypotonia, depressed deep tendon reflexes and absent neonatal reflexes. Since she had intractable seizures and poor respiratory drive, positive pressure ventilation and diazepam drip were given. She developed coffee colored gastric aspirate at six hours of life. Investigations revealed serum aminophylline levels (measured by HPLC method) of 8.6  $\mu$ g/ml at one hour of life, supraventricular tachycardia on ECG, metabolic acidosis on umbilical cord arterial blood gases, and normal X-ray chest, blood glucose and calcium. There was no evidence of 'other' organ system involvement. Despite ventilatory care and anti-convulsant therapy, she continued to have intermittent seizures and expired forty-eight hours after birth. Postmortem revealed normal brain structure. There was no bleed or evidence of asphyxial brain injury.

#### Discussion

Asthma is the commonest form of chronic airway obstruction seen in pregnant women and aminophylline (theophylline ethylenediamine) is a common bronchodilator used to treat these women. In pregnant women, the half-life of theophylline is prolonged, volume of distribution is increased and more unbound theophylline is available(3). Animal studies have shown that 28% to 40% more unbound theophylline is present in the pregnant rabbit and the fetus than in non-pregnant adult rabbit and the transplacental transfer to the intrauterine fetus occurs in less than one hour(4). As in our case, the fetus was at risk for aminophylline toxicity,

since the mother received three doses of aminophylline, the last dose being two hours before delivery.

The mother and the fetus are a two compartment model, in which the fetus is dependent on the absorptive, metabolic and excretory processes in the mother. In the fetus, the liver is the principal organ of drug metabolism. The most important pathway of theophylline metabolism is the oxidative reactions with the enzymes located in the endoplasmic reticulum. Cytochrome P-450, the terminal hemooxygenase in microsomal drug oxidation of theophylline is present in lower levels in the fetus and at term approaches half the adult values(5). The other major metabolic pathway for theophylline involves methylation.

Though adults are not capable of metabolising theophylline to caffeine(6), fetal liver is capable of methylating theophylline to caffeine as early as the 18th week of gestation(7). A combination of two factors could explain the biotransformation of theophylline to caffeine, *i.e.*, one is deficiency of hepatic cytochrome P-450 monooxygenases and second is presence of N-methylase activity in fetal and neonatal liver. Besides, both the fetus and newborn have lower protein binding capacity(8) and limited excretory capacity for theophylline and caffeine(9) making them more prone to aminophylline toxicity.

The toxic aminophylline levels in neonates have not been well defined and may vary from infant to infant(10). Transplacental aminophylline toxicity at cord serum level of 9.2  $\mu$ g/ml has been mentioned(11). Our case had serum aminophylline level of 8.6  $\mu$ g/ml at one hour of life. As the fetus and newborn both have different metabolic pathways in comparison to adults, it is possible that they can exhibit

signs and symptoms of aminophylline toxicity at normal aminophylline levels, if caffeine levels are also not taken into consideration.

Both caffeine and theophylline have similar pharmacodynamic actions and act on adenosine receptors. The morbidity and mortality from theophylline toxicity result mainly due to hemodynamic and neurological dysfunction. Sinus tachycardia and supraventricular tachycardia may result. The heart rate may become so rapid that myocardium becomes inefficient and the cardiac output falls. Peripheral hypoxemia is accompanied by lactate production. Seizures of various types are associated with its toxicity(8). Our case had persistent tachycardia, refractory seizures and metabolic acidosis, all suggestive of aminophylline toxicity.

The management of aminophylline toxicity in the newborn has not been well defined, but the role of exchange transfusion has been documented(12).

The importance of presenting this case is to highlight that aminophylline should be used judiciously in pregnant women as it is toxic to the fetus and the newborn, manifesting as persistent fetal tachycardia and metabolic acidosis in the fetus and as supraventricular tachycardia and intractable seizures in the neonate. Since the fetus and the newborn metabolize aminophylline to caffeine, they can develop aminophylline toxicity even at the therapeutic aminophylline range, if caffeine levels are not estimated to assess the total methylxanthine load.

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## **Intussusception at the Onset of Acute Lymphoblastic Leukemia in a Child**

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Surgical complication can occur in a child with acute lymphoblastic leukemia (ALL) even at the initial presentation or during treatment and appropriate surgical intervention could be often life saving. Intra abdominal surgical problems can occur in these children while on treatment, due to the disease itself or due to the chemotherapeutic drugs used or due to both(1). Intussusception in ALL has been reported in patients who are receiving chemotherapy. The present report concerns

a child presenting with intussusception as the initial clinical manifestation of ALL.

### **Case Report**

An eight-month-old female baby born to unrelated parents was brought to our center with the history of blood and mucous in stools, vomiting and intermittent crying of 1 day duration. Parents also noticed increasing pallor since 2 weeks for which they did not seek any medical advice.

On examination the child was weighing 8 kg, length was 64 cm and head circumference was 44 cm. She had marked pallor. General examination did not reveal any evidence of bleeding tendency. Small lymph nodes measuring less than 0.5 cm were palpable over cervical, axillary and inguinal region on both sides. Abdomen was protuberant. Liver (5 cm) and spleen (6 cm) were enlarged. A mass was palpable in the left lumbar region which was firm and non-tender. Per rectal examination showed blood stained mucous on the examining finger. Other systems were within normal limits.

The hemoglobin level was 5.1 g/dl, total leukocyte count was 2,52,000 cells/mm<sup>3</sup>, differential count was 88% small lympho-blasts and 12% segmented cells. Platelet count was 40000 cells/mm<sup>3</sup> and ESR was 125 mm/1 hr. The chest X-ray was normal.

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