

Kidney Disease from Powdered Infant Formula-based Melamine Exposure in Chinese Infants.

Introduction

Over the past weeks, there has been world wide concern about kidney disease stemming from melamine-contaminated powdered infant milk formula in China. This statement from the Pediatric Nephrology community is intended to provide a brief overview of this topic, and an approach for physicians who may see affected children.

Melamine, $C_3H_6N_6$, also known as cyanuramide, is a synthetic product that forms resins with formaldehyde, and is used in a variety of products in which resin-based coatings are found. It is not intended for human or animal consumption as food. Melamine and related substances such as hexamethylmelamine were explored as potential anti-cancer agents in the 1960s and 1970s, but were abandoned due to toxicity and insufficient benefit. The urinary metabolites recovered after administration of hexamethylmelamine in phase I studies indicated that the s-triazine ring is very stable and does not undergo cleavage in vivo [1]. In experimental murine and rat models, chronic melamine exposure resulted in the production of kidney stones, bladder stones, and possibly, transitional cell carcinoma of the bladder [2]. There appears to be a gender difference in the appearance of stones, at least in experimental animals, with a much greater incidence in males compared to females. Chemical analysis of the calculi in experimental animals demonstrated equimolar amounts of melamine and uric acid, accounting overall for 61-81% of the stone weight [3]. Other studies have demonstrated equal parts of melamine and cyanuric acid. Furthermore, stone formation appears to be dose-, threshold-, and concentration-dependent, that would not be relevant to long-term, low-dose exposure settings. Pet-food associated kidney disease due to melamine in cats and dogs in the United States in the past two years demonstrated similar urinary stone composition to that noted in experimental rodent models. Additionally, tubulointerstitial nephritis was noted in some affected dogs that came to necropsy [4].

Melamine and Disease in Infants in China.

In late September, 2008, the United States Food and Drug Administration (FDA) and the World Health Organization (WHO) learned of a total of over 52,000 cases of kidney stones and a number of instances of acute kidney failure linked to consumption of powdered milk formula contaminated with melamine. By report, there were over 13,000 hospitalizations, and at least three confirmed deaths. Eighty-two % of the affected children were below two years of age; no cases involved adults. No cases were associated with liquid infant formula. An investigation conducted within China (AQSIQ) revealed that 22 different companies produced the tainted powdered infant

formula, and that samples from those formulas contained melamine concentrations that ranged from 0.1 to 2500 ppm.

Melamine-related illness related to contaminated powdered infant formula was reported from multiple regions of China, including Anhui, Gansu, Henan, Hubei, Hunan, Jiangsu, Jiangxi, Ningxia, Shaanxi, and Shandong provinces. Chinese medical authorities released information that 14 kidney stones had sufficient information to comment about composition, and demonstrated uric acid dihydrate and or struvite. Stones were not uniformly radio-opaque, but were easily visualized by ultrasound or CT study.

From anecdotal reports at present, a variety of signs and symptoms have been observed in infants in China affected by the melamine-contaminated infant formula, ranging from nonspecific findings to acute obstructive oligo-anuric kidney failure, due to urinary obstruction from melamine-containing stones [Table 1].

TABLE 1 SIGNS AND SYMPTOMS REPORTEDLY ASSOCIATED WITH MELAMINE EXPOSURE FROM POWDERED INFANT FORMULA IN CHINESE INFANTS

- Unexplained crying in infants, especially when urinating.
- Vomiting.
- Unexplained fever secondary to urinary tract infection/bacteremia secondary to urinary stasis resulting from obstruction.
- Macroscopic or microscopic hematuria.
- Acute obstructive oligo-anuric kidney failure.
- Stones discharged while passing urine.
- High blood pressure, edema, elicitable flank pain.

Suggested Key Diagnostic Criteria for Likely Melamine-associated Kidney Disease.

The key diagnostic criteria that suggest melamine-associated kidney and urinary tract disease include both demographics and supporting clinical and laboratory data. These are detailed in **Table 2**.

TABLE 2. DIAGNOSTIC CRITERIA TO SUSPECT POWDERED INFANT FORMULA-ASSOCIATED MELAMINE KIDNEY DISEASE

Possibly Affected Children

- Infants from China who were fed with melamine-contaminated powdered infant milk formula in late 2007 or during 2008.
- Infants with one or more of the clinical manifestations noted in Table 1.

Laboratory Test Results Supporting Exposure

- Routine Urinalysis that reveals hematuria which is eumorphic.
- Abnormalities in kidney function tests that estimate glomerular filtration, such as serum creatinine levels.
- Absence of abnormalities in urinary excretion ratio of calcium to creatinine; blood parathyroid hormone levels; levels of hepatic enzymes.

Radiographic Imaging Studies Supporting Exposure

- Kidney ultrasound demonstrating bilateral enlargement, increased echogenicity, normal parenchymal thickness, slight pyelectasis and caliectasis, blunted calyces.
 - Presence of nephrolithiasis on plain radiograph, ultrasound or CT study.
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Recommendation for Physicians for Evaluation of Infants Possibly Exposed to Melamine from Powdered Infant Formula

The recommendations for assessment are based on a common-sense approach. These are noted in Table 3.

- Asymptomatic, thriving infants have little to no likelihood of powdered infant formula-based melamine-associated kidney disease in our opinion. Therefore, testing should not be performed on asymptomatic infants who may have been living in the geographic areas of China noted to have melamine-associated kidney disease found in late 2007 or during 2008.
- Infants from China who may have been exposed to powdered formula, and who have unexplained fussiness, unexplained vomiting, renal colic, macroscopic hematuria, stone passage, urinary tract infection, hypertension, edema, and/or oliguria, should undergo the screening and management noted in **Table 3**.

TABLE 3. SUGGESTED PHYSICIAN ASSESSMENT FOR INFANTS SUSPECTED OF POWDERED INFANT FORMULA MELAMINE EXPOSURE.

- A complete physical examination including measurement of blood pressure, assessment of general nutritional status and hydration.
- Complete urinalysis (including a microscopic examination of the urine).
- Measurement of creatinine, BUN and serum electrolytes ("renal function panel") and estimation of glomerular filtration rate.
- Performance of an abdominal ultrasound that includes the kidneys and the urinary bladder.
 - ↳ Note that the preferable ultrasound examination should include an ultrasound B exam of urinary system.
 - ↳ If necessary, an abdominal CT scan and rarely, intravenous urography (not to be used in case of anuria or renal failure)
 - ↳ might be considered.
 - ↳ Radionuclide renal scans may be considered to evaluate renal function if there is a question of renal dysfunction.
- Referral to a pediatric nephrologist or pediatric urologist is suggested children with suggestive signs and symptoms or who have abnormal kidney function tests, and/or abnormal ultrasound findings.
 - Management of kidney and urinary tract stones will depend on findings.
 - Management of kidney dysfunction, if present, should be supportive.

22 October 2008 from the American Society of Pediatric Nephrology Committee Members:

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