Clinical observation of childhood urinary stones induced by melamine-tainted infant formula in Anhui province, China

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Abstract

Introduction: The current report detailed an investigation of melamine-linked urinary stones in children exposed to contaminated formula.
Material and methods: A total of 1062 children fed with melamine-contaminated infant formula were screened for urinary stones. Sixty healthy children without melamine exposure were recruited as a control group. Ultrasonography of the urinary tract system was performed. Urinalysis, renal function, liver status, and serum electrolytes were determined.
Results: We encountered 49 affected children from the 1062 screened ones, at a rate of 4.6% per ultrasound performed. Thirty-two were male, and 17 were female. The affected children ranged in age from 1 month to 96 months, with a mean of 25 months. Duration of exposure was from 1.3 months to 84 months, with a mean of 19.5 months. The melamine contents in serum were between 12 mg/kg and 2563 mg/kg, with mean concentration of 1295.3 mg/kg. Most affected children were asymptomatic with no urinary findings. Patients with urinary stones exhibited lower urine pH and serum HCO_3^- than those in the healthy children, whereas for serum uric acid, alanine aminotransferase, aspartate aminotransferase, and anion gap the opposite trends were observed. The stone diameter ranged from 2 mm to 18 mm with a median of 6.5 mm. Multiple stones were noted in all patients. After 1 week of conservative management, stone diameters of 38 cases (77.6%) were significantly decreased. Among them, urinary stones were discharged completely in 21 affected children (42.9%).
Conclusions: The short-term outcome of melamine-linked urinary stones is satisfactory.

Key words: urinary stone, melamine, ultrasound, urinalysis, childhood.

Introduction

Melamine is a nitrogen-rich organic heterocyclic compound belonging to triazines. Its molecular formula is $C_3N_6H_6$ or $C_3N_3(NH_2)_3$, and its molecular weight is 126.12. This substance is used primarily in the synthesis of melamine-formaldehyde resins for the manufacture of laminates, plastics, coatings, commercial filters, glues or adhesives, and molding compounds. Melamine is also reportedly used as a colorant and as a fertilizer. It is currently believed that melamine ingestion can lead to insoluble crystals in the animal urinary system with subsequent physical obstruction or bladder carcinoma [1, 2]. Thus, there are no approved uses for the direct addition of melamine to human or pet food.

Sanlu, a manufacturer of powdered milk, received a complaint of illness in March 2008. Initially, 14 infants suffering from kidney stones were hospitalized in Gansu province. On September 12, 2008, the Chinese government announced that the skyrocketing cases were most likely related to melamine contamination of powdered-milk formula for infants [3]. Because melamine is high in nitrogen (66% by mass versus approx. 10-12% for typical protein), the addition of melamine to a food artificially increased the apparent protein content as measured with the Kjeldahl and Dumas tests, which caused a food to appear to have more protein than it really had [4]. Following inspections conducted by China's national inspection agency, 22 different companies were found to produce the tainted powdered infant formula, and samples from 69 batches of those formulas illegally contained melamine concentrations that ranged from 0.09 mg/kg to 2563 mg/kg [5]. It was truly a disaster. According to a report from the Chinese Ministry of Health, 294,000 infants had been affected by melamine-contaminated infant formula by the end of November 2008. More than 5,000 infants have been hospitalized, and 6 deaths have been confirmed [6]. The outbreak occurred in many regions, but mainly in Gansu, Henan, Ningxia, Hebei, Hunan, Anhui, Jiangsu, Jiangxi, Shanxi, and Shandong province [7].

The current report details an investigation of melamine-linked urinary stones in children exposed to contaminated formula in Anhui, a central province of China. Moreover, a comparative study among our clinical observations and the data from 8 other regions of China was undertaken.

Material and methods

Subjects

A total of 1062 children fed with melamine-contaminated infant formula, no matter how often and how long, were screened for urinary stones in the Department of Pediatrics, the First Affiliated Hospital of Anhui Medical University from September to December 2008. They were 565 males and 497 females, aged from 1 month to 126 months, with a mean of 28 months. Chief complaints, complications, history of exposure to contaminated formula (formula brand, melamine contents, duration of consumption, use of formula alone or in combination with breast milk) were documented. The melamine contents in serum were estimated according to the report by the General Administration of Quality Supervision, Inspection, and Quarantine of China (GAQSIQC) [8]. Sixty healthy children with similar distribution of gender and age were recruited as a control group, in comparison to the patients with urinary stones.

The study was approved by the Bioethics Committee of our Medical Faculty and informed consent was obtained from all subjects before study entry.

Auxiliary examination

Ultrasonography of the urinary tract system was performed in all 1062 children. In patients with urinary stones and 60 healthy children, urinalysis, renal function (blood urea nitrogen (BUN), creatinine (Cr), and uric acid (UA)), liver status (alanine aminotransferase (ALT), aspartate aminotransferase (AST), and γ-glutamyltransferase (GGT)), and serum electrolytes (K^+, Na^+, Cl^-, Ca^{++}, Mg^{++}, P, and HCO_3^-) were determined. Anion gap (AG) was calculated as $AG = (Na^+ + K^+) - (Cl^- + HCO_3^-)$. Because none of our patients were in a serious condition, simple conservative managements were adopted, including fluid infusion, urine alkalinization, increased drinking of water, and increased urination. One week later, the urinary tract system of patients was reexamined with ultrasonography to observe the change in size of stones.

Statistical analysis

Data are presented as mean ± SD and range. Student's *t*-test was performed to determine the significance of differences in urinalysis, renal function, liver status, serum electrolytes, and AG between patients and healthy children. A value of $p < 0.05$ was considered significant. Statistical analysis was performed using the Statistical Package for Social Sciences SPSS version 11.5.

Results

One hundred and sixty-two children who had consumed melamine-contaminated infant formula were screened in our hospital during the study period. Ultrasonography revealed urinary stones in 49 (4.6%) of the screened children. The affected children ranged in age from 1 month to 96 months, with a mean of 25 months. Thirty-two were male, and 17 were female.

In 49 patients, 24 were fed with formula alone, and 25 were fed with formula in combination with breast milk. Duration of exposure was from 1.3 months to 84 months, with a mean of 19.5 months. Six formula brands were consumed by 49 affected children. *Sanlu* was consumed by 25 patients, *Shenyuan* was consumed by 18 patients, *Yili* was consumed by 6 patients, *Shien* was consumed by 3 patients, *Yashili* was consumed by 2 patients, and *Mengniu* was consumed by 1 patient. There were also 4 cases exposed to multiple formula brands consecutively. The melamine contents in serum were between 12 mg/kg and 2563 mg/kg, with mean concentration of 1295.3 mg/kg.

Table I. Clinical characteristics, urinalysis, renal function, liver status, and serum electrolytes of the affected and healthy children

Parameter	Affected children (n = 49)	Healthy children (n = 60)	Value of p
Male/female	32/17	40/20	NS
Age [months]	25.064 ±9.721	28.414 ±6.918	NS
Urine pH	6.322 ±0.663	7.430 ±0.582	0.003
Urine specific gravity	1.015 ±0.006	1.012 ±0.004	NS
BUN [μmol/l]	4.717 ±1.184	4.432 ±0.968	NS
Cr [μmol/l]	22.761 ±8.966	20.530 ±6.432	NS
UA [μmol/l]	354.991 ±74.816	263.296 ±69.922	0.001
ALT [U/l]	25.180 ±8.763	17.365 ±3.207	0.001
AST [U/l]	35.667 ±9.551	22.743 ±6.520	< 0.001
GGT [U/l]	15.718 ±2.294	12.477 ±2.031	NS
Serum K^+ [mmol/l]	4.532 ±0.449	4.371 ±0.267	NS
Serum Na^+ [mmol/l]	139.551 ±2.306	140.925 ±2.739	NS
Serum Cl^- [mmol/l]	103.400 ±2.461	101.991 ±2.231	NS
Serum Ca^{2+} [mmol/l]	2.547 ±0.122	2.393 ±0.148	NS
Serum Mg^{2+} [mmol/l]	0.939 ±0.076	1.060 ±0.145	NS
Serum P [mmol/l]	1.812 ±0.196	1.761 ±0.163	NS
Serum HCO_3– [mmol/l]	19.476 ±2.419	26.893 ±3.476	0.001
AG [mmol/l]	21.186 ±2.441	13.384 ±1.935	0.001

NS – not significant

Most affected children were asymptomatic (15 cases; 30.6%). Three main clinical presentations, including unexplained crying when urinating (9 cases), oliguria (8 cases), and abdominal pain (6 cases), were found to occur in 18.4%, 16.3%, and 12.2% of childhood urinary stones induced by melamine-tainted formula, respectively. On the basis of urinalysis, 6 cases had microscopic hematuria (12.2%), and 5 cases had leukocyturia (10.2%). The longest duration of illness was 48 weeks, with a mean of 5 weeks. Nineteen patients were without any complications. But the others had at least one or more complications, such as respiratory tract infection (20 cases; 40.8%), hydronephrosis (8 cases; 16.3%), urinary tract infection (3 cases; 6.1%), liver lesion (3 cases; 6.1%), and diarrhea (1 case; 2.0%).

Urinalysis, renal function, liver status, and serum electrolytes of the affected and healthy children are given in Table I. Patients with urinary stones exhibited lower urine pH and serum HCO_3^- than those in the healthy children ($p < 0.01$), whereas for serum UA, ALT, AST, and AG the opposite trends were observed ($p < 0.01$).

In the 49 affected children, the stone diameter ranged from 2 mm to 18 mm with a median of 6.5 mm. Almost half of them (25 cases; 51.0%) had small stones less than 5 mm in diameter. Multiple stones were noted in all patients. Stones in the bilateral urinary tract were found in 11 cases (22.4%), of whom 10 had bilateral kidney stones; only one had left kidney and right ureter stones. Stones in the unilateral urinary tract were found in 38 cases (77.6%), of whom 16 had left kidney stones, 16 had right kidney stones, 2 had right kidney and ureter stones, 1 had left kidney and ureter stones, 2 had right ureter stones, and 1 had left ureter stones. Because none of our patients were in a serious condition, simple conservative managements were adopted. One week later, the urinary tract system of patients was reexamined with ultrasonography to observe the change in size of stones. Stone diameters of 38 cases (77.6%) were significantly decreased with a range from 2 mm to 9 mm, a median of 3.8 mm. Among them, urinary stones were discharged completely in 21 affected children (42.9%). But unfortunately, B-ultrasound examinations after treatment showed that no change in stone diameter was observed in 11 affected children (22.4%) after 1 week of conservative therapy.

Comparison between our clinical observations and the data from 8 other regions of China (Beijing [9], Gansu [10], Guangdong [11], Hebei [12], Hong Kong [13], Shandong [14], Taiwan [15], and Zhejiang [16]) is presented in Table II.

Discussion

In the current study, we encountered 49 affected children from the 1062 screened ones with a histo-

Table II. Comparison among our clinical observations and the data from 8 other regions of China

Author	Region	Exposure history	Epidemiology	Clinical characterization	Ultrasonography	Management	Outcome
Hu *et al.* (this study)	Anhui	Content: 1295.3 mg/kg; duration: 19.5 months	Prevalence: 4.6% (49/1062); mean age: 25 months; 36 patients were younger than 3 years (73.5%); male/female: 1.9	Asymptomatic patients: 30.6%; complaint: unexplained crying when urinating (18.4%), oliguria (16.3%), and abdominal pain (12.2%), etc; complication: respiratory tract infection (40.8%), hydronephrosis (1.63%), urinary tract infection (6.1%), liver lesion (6.1%), and diarrhea (2.0%); urinalysis: hematuria (12.2%), leukocyturia (10.2%); renal dysfunction: none	Mean diameter: 6.5 mm; multiple stones were noted in all patients; bilateral/unilateral stone: 0.3	All patients underwent conservative therapy	Complete discharge: 42.9%; no change: 22.4%
Guan *et al.* [9]	Beijing	High content (> 500 ppm): 23 patients; moderate content (< 150 ppm): 19 patients; no-melamine: 8 patients; duration: at least 30 days	Prevalence: 8.5% (50/589); all patients were younger than 3 years; male/female: 1.5	Asymptomatic patients: 93.6%; complaint: 6.4% patients with oliguria; complication: urinary tract obstruction (8.0%); urinalysis: hematuria (5.9%), leukocyturia (2.9%); renal dysfunction: 9.8%	Most stones were localized in the renal pelvis	Not mentioned	Not mentioned
Ren *et al.* [10]	Gansu	Melamine content was not mentioned; duration: 6.3 months	Mean age: 10 months; all patients were younger than 3 years; male/female: 0.8	Asymptomatic patients: 6.3%; complaint: dysuria (37.5%), anuria (31.3%), and fever (31.3%), etc; complication: hydronephrosis (81.3%); urinalysis: hematuria (6.3%); renal dysfunction: 25.0%	Mean diameter: 8.0 mm; 87.5% patients had multiple stones; bilateral/unilateral stone: 3.0	Conservative therapy (25.0%), ureteral retrograde catheterization (75%)	Complete discharge: 33.3%; no change: 8.3%
Zhu *et al.* [11]	Guang Dong	Melamine content consumed by 91.7% patients was from 955 to 2563 ppm, and consumed by 8.3% patients was from 6.2 ppm to 17.0 ppm; duration: 1 to 24 months	Prevalence: 1.1% (12/1091); mean age: 19 months; 11 patients were younger than 3 years (91.7%); male/female: 5.0.	Asymptomatic patients: 50.0%; complaint: dysuria (50.0%), polyuria (8.3%), and crystalluria (8.3%); urinalysis: hematuria (8.3%), proteinuria (33.3%); renal dysfunction: none	Mean diameter: 3.4 mm; 58.3% patients had multiple stones; bilateral/unilateral stone: 0.1	All patients underwent conservative therapy	Complete discharge: 100.0%
Liu *et al.* [12]	Hebei	Content: 1351 mg/kg; duration: 10 months.	Prevalence: 0.61% (48/7933); mean age: 19.8 months; all patients were younger than 3 years; male/female: 3.1	Asymptomatic patients: 89.6%; complaint: oliguria and unexplained crying when urinating; complication: hydronephrosis (50.0%); urinalysis: hematuria (2.1%), leukocyturia (2.1%), proteinuria (2.1%)	Not mentioned	No specific treatment was undertaken (95.8%)	Complete discharge: 85.4%
Lam *et al.* [13]	Hong Kong	Estimated melamine was between 0.01 mg/kg day and 0.2 mg/kg day; duration: at least 30 days	Prevalence: 0.03% (1/307)	This patient was asymptomatic, without associated hydronephrosis, urine abnormalities, and renal dysfunction	The diameter of a single stone was 7 mm	No specific treatment was undertaken	Not mentioned

Table II. Continue

Author	Region	Exposure history	Epidemiology	Clinical characterization	Ultrasonography	Management	Outcome
Chen *et al.* [14]	Shan Dong	Estimated melamine was 0.9 mg/kg day; duration: 17 months	Prevalence: 1.6% (63/3976); mean age: 27 months; male/female: 1.9	Most patients were asymptomatic, but prevalence was not mentioned; complication: hydronephrosis (32.7%); urinalysis: hematuria (8.2%)	Not mentioned	Not mentioned	Not mentioned
Wang *et al.* [15]	Taiwan	Melamine content exceeded 0.05 ppm; duration: 7.2 months	Prevalence: 1.1% (12/1129); all patients were younger than 3 years	Most patients were asymptomatic, but prevalence was not mentioned	Not mentioned	Not mentioned	Not mentioned
Zhang *et al.* [16]	Zhe Jiang	Melamine content exceeded 12 mg/kg; duration: 15.7 months	Prevalence: 3.6% (562/15577); male/female: 0.7	Most patients were asymptomatic, but prevalence was not mentioned; complications: polyuria (18.7%), unexplained crying when urinating (14.3%), fever (11.3%); complications: hydronephrosis (7.9%) and ureter distention (2.5%); urinalysis: hematuria (19.1%), leukocyturia (12.2%); renal dysfunction: 2.1%	Mean diameter: 20 mm; 86.2% of patients had multiple stones; bilateral/ /unilateral stone: 0.6	Conservative therapy (90.7%), operation (9.3%)	Complete discharge: 90.7%; no change: 3.7%

ry of exposure to melamine-tainted formula, at a rate of 4.6% per ultrasound performed. The prevalence of childhood urinary stones in Anhui was higher than that in Guangdong [11], Hong Kong [13], Shandong [14], Taiwan [15], and Zhejiang [16], which might be attributed to the consumption of melamine-tainted formula being in parallel with lower social and economical levels. Consistently, the incidence of urinary stones induced by melamine-contaminated formula observed in the present study was also elevated markedly, when compared with the overall incidence (3.2%) of urinary stones (not melamine-induced ones) in 10 407 children of Anhui province [17]. However, the investigation from Beijing [9], the capital of China, disclosed the highest prevalence. Guan *et al.* [9] considered that there might be enrollment bias for two reasons: screened children mainly came from nearby provinces, such as Hebei and Henan, in which the melamine contamination was reported as being more serious than elsewhere. In addition, children screened in other hospitals, especially those who had urinary stones or were suspected of having stones, may have been sent for further evaluation to Beijing, resulting in referral bias and an overestimate of the incidence of urinary stones. To our surprise, the prevalence in Hebei was not as high as anticipated, according to the report by Liu *et al.* [12]. The population-based screening and household investigation may be reasonable explanations.

Our study also showed that male infants who were younger than 3 years were more susceptible to urinary stones than their opposites. The boys have a longer and narrower ureter than the girls and the ureter in boys has three physiological narrow segments and two bending parts, and hence it is difficult for stones to be expelled [18]. Why are infants a high risk group for melamine-related health effects? First, infants may consume contaminated formula as their primary food source. Second, the smaller lumen of the infant urinary tract may lead to easier irritation of tubular and urinary tract walls, and easier occlusion by uroliths [19]. Third, infants have a lower glomerular filtration rate than older children and adults. This may decrease the flow of urine through the tubules, thus predisposing crystals to clump together and co-crystallize [20]. Lastly, uric acid is excreted into the urine at a much higher rate in infants relative to older children and adults. It is possible that uric acid may co-crystallize with melamine in infants [2].

Some affected children were exposed to multiple formula brands consecutively, or fed with formula in combination with breast milk. Moreover, we were unable to test the melamine contents of milk formula ourselves. It was difficult for us to obtain the exact data of serum melamine contents. In this study, we estimated the exposure levels according to the feeding style, the exposure dura-

tion, and the melamine contents reported by GAQSIQC. The melamine contents in serum were between 12 mg/kg and 2563 mg/kg, with mean concentration of 1295.3 mg/kg, which greatly exceeded the tolerable daily intake according to the Food and Drug Administration (FDA) [21].

Childhood urinary stones induced by melamine-tainted formula were asymptomatic with no urinary findings. One hypothesis is that a melamine-containing kidney stone that has no proteinaceous matrix and does not react with urinary epithelium will not produce urinary findings [3]. However, there are also several nonspecific clinical signs occurring in some patients. In the present study, three main clinical presentations, i.e. unexplained crying when urinating, oliguria, and abdominal pain, were noted in 18.4%, 16.3%, and 12.2% of patients, respectively. Interestingly, our results revealed that respiratory tract infection was the most prevalent complication of affected children, which might be related to the lower nutritional and immune status secondary to hypo-protein ingestion. Unexpectedly, liver lesion was found in 3 cases in this investigation. This is similar to the report of Zhang *et al.* [16], in which 5 children with urinary stone induced by melamine-tainted formula exhibited abnormalities of liver including hepatomegaly, elevated AST, and gallstone. But the mechanism associated with secondary liver lesion is unknown. Further studies on the metabolic procedure of melamine in the human body should be undertaken to elucidate these confusing observations [22].

Sixty healthy children without melamine exposure were recruited as a control group, in comparison to the patients with urinary stones. The biomedical parameters of the affected and healthy children were determined. Our results demonstrated that the affected children exhibited lower urine pH and serum HCO_3^- than those in the healthy children, whereas for serum UA and AG the opposite trends were observed. We postulated that melamine consumption could lead to the disturbance of homeostasis, especially to metabolic acidosis, and then contribute to the acceleration of urinary stone formation. Furthermore, melamine, a substance related to UA, actually inhibits hepatic UA oxidase, and plays an important role in the increase of circulating UA levels [23].

Ultrasound examination is simple and easy to perform, it may provide accurate and reliable results, and does not apply any radiation. Therefore, ultrasound examination can be used to determine the size, number, and location of stones. A high frequency transducer can show fine gravel-like calculi 0.1-0.2 cm in size [24]. In this study, urinary stones were diagnosed according to the ultrasound findings in combination with the exposure history of melamine. Stones in the unilateral urinary tract were found in 77.6% of the patients, including kidney and ureter stones, but no bladder stones were present. Multiple stones were noted in all patients. Almost half of our patients had small stones less than 5 mm in diameter. The development of urinary stones showed a considerable dose-effect relationship with the serum melamine contents, while no correlation existed between stone diameter and duration of exposure [25]. These above findings were compatible with the observations from human and animal model studies [26, 27]. However, it is possible that species differences in renal physiology might have contributed to variable stone composition. Jia *et al.* [24] analyzed specimens of melamine-associated stones from 12 affected children by using liquid chromatography-mass spectrophotometry and found that the stones were composed primarily of melamine and UA. The molar ratio of melamine to UA was 1 : 2. In contrast, chemical analysis of the stones in experimental dogs demonstrated equal parts of melamine and cyanuric acid [28].

Since most melamine-associated stones were small or sand-like [9, 18], and none of our patients were in a serious condition, simple conservative managements were adopted, including fluid infusion, urine alkalinization, increased drinking of water, and increased urination. One week later, the urinary tract system of patients was reexamined with ultrasonography to observe the change in size of stones. Stone diameters of 38 cases (77.6%) were significantly decreased. Among them, urinary stones were discharged completely in 21 affected children (42.9%). Therefore, conservative therapy should be preferred and effective in all patients without serious urinary obstruction and renal failure. The short-term outcome was satisfactory. In the study by Shen *et al.* [29], after the 24-72 h clinical intervention, 4 of the 13 affected children still had small kidney stones at hospital discharge, 2 had kidney stones expelled within 1 month during the follow-up and 2 others had kidney stones expelled within 2 months after discharge from the hospital. It seems that the deadline of our observation might be so short that no change in stone diameter was noted in 11 affected children (22.4%) at hospital discharge. Further follow-up is warranted to evaluate the long-term outcome of childhood urinary stones induced by melamine-contaminated infant formula [30].

In conclusion, a comparative study between our clinical observations and the data from 8 other regions of China was undertaken. The common nature of childhood urinary stones induced by melamine-tainted formula includes the following aspects. i) Children from the Chinese mainland were exposed to higher content of melamine than ones from Hong Kong and Taiwan; ii) the prevalence of urinary stones was diverse among different regions, and infants younger than 3 years old were more sus-

ceptible than other children; iii) most of the patients were asymptomatic, with sporadic urinary findings, metabolic acidosis, renal and liver disorders; iv) small (< 5 mm in diameter) and multiple stones were noted in the majority of patients examined by ultrasonography; v) conservative therapy should be first tried in all patients without serious urinary obstruction and renal failure; vi) the short-term outcome was satisfactory.

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