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Editorial

The Scare of Melamine Tainted Milk Products

In the past weeks, the public as well as paediatrician colleagues were intensely concerned about the problem of melamine in infant formulae and dairy products and its adverse effects on the health of children. The renal toxicity of melamine on human has not been reported before, and any proposed management of such patients is based on the understanding of stone management, experience from China, understanding of how it had affected pets in the previous outbreaks, and lots of common sense. No one can claim expertise for this unknown disease in human.

Background

Melamine, or 1,3,5-triazine-2,4,6-triamine, is a industrial chemical derived from urea ($(NH_2)_2CO$) through decomposition to cyanic acid (HCNO) and polymerization to melamine ($C_3H_6N_6$)[1]

$$6\ (NH_2)_2CO \rightarrow 6\ HCNO + 6\ NH_3 \rightarrow C_3H_6N_6 + 3\ CO_2 + 6\ NH_3$$

It is 66% nitrogen (by weight) and is used to manufacture fire-resistant plastics, glues, cleansing agents, fertilisers. In its industrial production, cyanuric acid, ammeline, ammelide are also produced and these melamine derivatives are important in determining the solubility and harmful effects as discussed later.

Melamine was also used as a non-protein nitrogen additive to animal feeds, to give the appearance of increased protein content of this food, initially in the belief that ruminant stomach can hydrolyze and utilise it to synthesise protein, though later studies have proven otherwise.

In 2007, an outbreak of nephrotoxic renal failure and death occurred in dogs and cats,[1] and detailed study suggested that the toxin was melamine and cyanuric acid in the pet food. This was traced to the melamine compounds added to the wheat gluten, rice protein and corn gluten.

The recent baby milk incident started with reports of increased incidence of renal stones in infants in China. The Chinese Ministry of Health revealed on 21 September 2008 that 12,892 children were admitted to hospital after taken tainted milk, and 104 had serious symptoms. About 40,000 infants and children exposed to tainted milk were screened and found to be healthy.[2] It was found by subsequent analysis that melamine had been added to milk which was diluted with water, in an attempt to increase the nitrogen content and hence evaded the government regulatory quality tests that only tested protein (nitrogen) content.

Toxicity of Melamine after Acute and Chronic Exposure

Little is known about the toxicity of melamine in humans. Material safety database reported possible hazards of irritation on acute skin and eye contact or after ingestion and inhalation. Chronic exposure may have adverse effects on fertility, fetotoxicity, carcinogenicity, and mutagenicity based on animal data. In rats, the LD50 of acute oral exposure was >3161 mg/kg, and in rabbits, the LD50 of acute dermal exposure was >1000 mg/kg.[3]

Detailed studies of dogs and cats which died after being fed on melamine contaminated pet food in 2007 showed that they all had typical symptoms and biochemical abnormalities of uraemia.[4] Renal histology showed the presence of unique polarisable crystals in distal tubules and collecting ducts. The tubules were dilated with evidence of necrosis and regeneration. There were signs of tubulitis, interstitial fibrosis and lymphoplasmacytic inflammation. The crystals were analysed to be melamine-cyanurate crystals.[5] This was confirmed by various animal studies in hogs, sheep and rats deliberately fed melamine and cyanuric acid.[6] Thus melamine and cyanuric acid caused acute renal failure with crystal deposition and tubulointerstitial nephritis in animals.

However, preliminary reports from the present outbreak in China suggested that most affected infants had renal stones and complications due to obstruction. Of the children screened (including asymptomatic children), the risk of detecting stones was between 0.3-5.0% and varied from region to region (personal communication). The exposure threshold (daily intake and duration) was not clearly identified, yet most of the severe cases having obstruction were associated with the ingestion of milk products that were reported to be highly contaminated. On the other hand, their screening protocol only looked for renal stones by ultrasound and their consequences, but not interstitial nephritis or renal impairment without stones.

Proposed Mechanism of Renal Injury

Animal studies showed that most of the problem with crystal deposition is in the renal distal tubules and collecting ducts, which if extensive leads to calculi formation. From pharmacokinetic studies of intravenous melamine injection, the chemical is rapidly and completely cleared by the kidneys with a half-life (T1/2) of 4 hours in pigs and 2.7 hours in rats. There is no significant tissue binding or retention in the body. However, it persists and accumulates in the kidneys (its T1/2 in kidneys may be 7-fold greater than in the plasma).[7] Melamine deposition then leads to crystallisation when the urine is saturated. The crystals can also lead to stone formation, or mucosal ulceration and inflammation and tumour in the long run.

It is noteworthy that melamine or cyanuric acid alone did not cause any renal toxicity or precipitates in kidney tubules. The water solubility of melamine was 3240 mg/L and that of cyanuric acid 2000 mg/L. However, melamine and cyanuric acid form a highly ordered lattice structure held

together by multiple hydrogen bonds between each pair of molecules which makes the complex practically insoluble in water. Other melamine derivatives also contribute to form the lattice, such that ammeline may substitute for melamine and ammelide for cyanuric acid. The solubility of melamine-cyanurate complex was only 2.2 mg/L.[6,8]

From animal studies, Dobson et al proposed that the melamine-cyanurate complex in contaminated food were dissociated in the acid gastric lumen. The dissociated compounds were differentially absorbed in the stomach and small intestine. How melamine and cyanuric acid remained dissociated in the blood stream, excreted in the urine and became precipitated in the renal tubules remained to be elucidated. The two molecules reached a critical concentration in renal filtrate as the filtrate became concentrated in the renal medulla. It is also possible that melamine and cyanuric acid are inhibitors of hepatic uric acid oxidase and they cause raised uric acid levels which may precipitate in the tubules, providing a nidus for melamine-cyanurate deposition.[8]

Indirect Exposure of Meat of Animals Fed on Contaminated Feed

Based on available data, the FDA issued a statement in May 2007 that there is "very low risk to human health from consuming meat from hogs and chickens known to have been fed animal feed supplemented with pet food scraps that contained melamine and melamine-related compounds." In the most extreme risk assessment scenario, when scientists assumed that all the solid food a person consumes in an entire day was contaminated with melamine at the levels observed in animals fed contaminated feed, the potential exposure was still about 2500 times lower than the dose considered safe.[1]

Tolerable Levels of Melamine Intake

In June 2007, the European Food Safety Authority provisionally recommends to apply a tolerable daily intake (TDI) of 0.5 mg/kg BW for the total of melamine and its analogues.[9] The US FDA recommended a TDI of 0.63 mg/kg BW.[1] In Hong Kong, the Government has made an emergency amendment of the Harmful Substance in Food Regulation to set the acceptable level of melamine compounds to below 1 mg/kg in food intended for consumption principally for young children below 36 months or pregnant or lactating women, and to 2.5 mg/kg for other food.[10]

Some Suggestion on Evaluating Children for Melamine-related Renal Diseases

The pre-requisite criterion for starting the evaluation is a confirmed history of exposure – by documenting the brand of formula, the duration, and amount taken. A reasonable criteria, though not evidence-based, of "regular consumption of tainted milk for at least one month" was adopted by the Hospital Authority.[11] A updated list of formulae contaminated with melamine and their melamine content could be found on the following two websites:

The General Administration of Quality Supervision, Inspection and Quarantine of the People's Republic of China website at:

http://www.aqsiq.gov.cn/zjxw/zjxw/zjftpxw/200809/t20080916_89958.htm

and locally the Hong Kong Food and Environmental Hygiene Department website at:

http://www.cfs.gov.hk/english/whatsnew/whatsnew_fstr/whatsnew_fstr_Test_results_of_dairy_product_samples_2008_09_18.html

Evaluation is focussed on renal, ureteric and bladder stones and possibly tubulo-interstitial nephritis. Reference was made of the protocol by the Chinese Ministry of Health and Hong Kong Hospital Authority.[11,12]

Symptoms: (1) Unexplained crying, especially on urination (renal colic and dysuria); abdominal and loin pain (obstructive colic); (2) passing red or turbid urine (haematuria, crystalluria); (3) passing sand in urine (stones); (4) sudden decrease in urine output (acute obstruction); (5) pallor and puffiness of face (fluid retention and uraemia); (6) fever (urinary tract infection UTI complicating obstruction).

Signs: (1) pallor and cafe-au-lait complexion (uraemic

look); oedema; (2) kidney and bladder masses; 3) loin pain on percussion; (4) blood pressure, if child is cooperative (hypertension).

Investigations: (1) Urine for haemastix and albustix, and, if patient has fever and UTI symptoms, leucocyte esterase and nitrite. (2) Renal function test (serum creatinine should be interpreted with age appropriate reference range). (3) Ultrasound scan of urinary system (Expected findings include bilateral enlarged kidneys, increased echogenicity, dilated pelvicalyceal system and ureters if obstruction, perinephric or peri-ureteric oedema. Any echogenic focus of 4 mm or more with acoustic shadow would be diagnosed as urinary calculus. Melamine stone was not radiopaque). CT scan would be reserved for patients being considered for surgical intervention.

Treatment of affected patients: Little is known about any specific treatment for melamine toxicity. Until more information is available, the following general measures are appropriate. (1) The source of exposure should be stopped as soon as possible. (2) Most renal stones can be managed conservatively. Medical treatment includes maintenance of adequate hydration and electrolytes, acid-base homeostasis, and encouraging diuresis to enhance chance of spontaneous passing of stones. (3) Paediatric urologists should be consulted for surgical intervention in case of obstruction. (4) Patients with renal impairment / acute renal failure should be referred to paediatric dialysis centre urgently for further care. (5) Patients should be followed up to ensure spontaneous passage of stones and complete renal recovery.

Colleagues are encouraged to refer all patients with melamine-related renal stones or renal impairment to special Designated Treatment Centres of the Hospital Authority. The Centre for Health Protection has also requested all medical practitioners to report young children diagnosed to have renal diseases including stones AND a history of consuming melamine containing dairy products. It is hoped that by collecting such data and concentrating the management of these children, we can gain useful information of the epidemiology and health effect of melamine on humans.

Experience in Hong Kong and China

In Hong Kong, screening of stones was started on 20 September for children from 0-12 years, and 18 Designated Clinics (DC), and 9 Special Assessment Clinics (SAC) had been set up. Until 3 October, there were altogether 25,474 and 4,912 children who have attended the clinics respectively. Only 5 cases having history of ingestion of melamine tainted milk products (MTMP) were reported to have small stones without obstruction, of which one was screened out from the SACs. It seems the problem of MTMP affecting Hong Kong is not big, both in incidence and severity as compared to that of China.

From experience in China, many of the stones were rather loose, which could easily be broken; and with adequate hydration alone, some of them could be passed out as sand, making urine cloudy and turbid. As a general measure, fluid should be encouraged, and for genuine cases, copious fluid was to be administered if without significant obstruction. As uric acid has been identified in the stones, alkali therapy has been tried to help dissolve the stones, keeping urine pH around 6.5-6.8 in some centres in China. For severe cases, failing medical treatment and with significant obstruction, surgical intervention is necessary. As these stones seem rather loose, if the site of the stone is in the renal pelvis accessible by the retrograde cystoscopic approach, it may first be tried. Percutaneous approach may be necessary if the stone is at other sites. Lithotrypsy has been recommended only as second line treatment.

More Questions Than Answers

As of today, there are still many questions and few answers. On the basic science level, it is uncertain whether the proposed mechanism of renal injury in animals can be applied to humans, and whether there may be species difference in the pharmacokinetics or susceptibility to the toxic effects of melamine mixtures. The dose-response curve and toxic dose threshold will certainly be different and need to be studied.

On a clinical level, melamine-related disease in humans is largely unknown – Are there any extra-renal manifestations? Are there any biomarkers of renal injury apart from stones? What is the best treatment to "dissolve" the stones and crystals apart from general supportive measures and surgical intervention for obstructing stones. Currently the effectiveness of urine

alkalinisation needs evaluation, for the melamine-cyanurate complex is being more soluble in acid medium.

On a service provision level, the population of children who presented for screening has already imposed a huge burden on our paediatric services. It requires the wisdom of our health administrators to decide on the extent of screening. To screen for renal stones by ultrasound alone would miss potential cases of interstitial nephritis without visible stones. To screen for all melamine-related renal diseases needs renal function test and urinalysis which would impose extra resources not only of the tests themselves, but also the need to manage incidental abnormalities, such as haematuria and/or proteinuria, that are to be expected from any mass screening projects. The potential long term harmful effect of melamine and other associated analogues or substances may also be kept in mind. It is noteworthy that only melamine is measured in the current screening of milk products whereas ideally measurement of melamine, cyanuric acid, melamine cyanurate, ammeline and ammelide in the contaminated samples will give a full picture. A method has been developed to simultaneously measure these products by high performance liquid chromatography in the food industry.[13]

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