EDITORIAL

Melamine-tainted milk product (MTMP) renal stone outbreak in humans

The outbreak in China

The 'outbreak' of renal stones associated with consumption of melamine-tainted milk products (MTMP) in infants and young children in China, is truly a disaster. By mid October 2008, 47 000 individuals were reported hospitalised with kidney problems related to MTMP-contaminated infant formula consumption, at least four of whom died.[1] The outbreak occurred in many regions, but mainly in Ganzu, Henan, Ningxia, Hubei, Hunan, Anhui, Jiangsu, Jiangxi, Shaanxi, and Shandong provinces. Many of the stones were rather 'loose' and 'soft'; and after copious water drinking, they could be passed out as sand and sediments, which made the urine slightly turbid and cloudy.[1,2] The stones were radiolucent and could be detected by ultrasound. Seriously affected patients had urinary obstruction with acute renal failure, but many individuals with smaller stones were virtually asymptomatic and only picked up after ultrasound of the kidneys. Apparently the severity of the affliction was dose-related; the great majority being associated with the consumption of 'Sanlu' (三鹿) milk, which had very high melamine concentration (up to >2.5 g/kg). Large-scale ultrasound screening in China has resulted in the detection of thousands of stones of varying sizes, and resulted in variably severe to mild effects on the health of the respective infants and young children.

Outbreaks in cats and dogs

Hitherto the MTMP problem had never been reported in humans. However, in 2004 and 2007 outbreaks did occur in cats and dogs following contamination of pet food, resulting in acute renal failure on a large scale with many deaths.[3,4] Melamine and cyanuric acid were identified in kidney tissues of affected animals, and were considered responsible for crystal formation in distal renal tubules that resulted in urinary obstruction. Kidney histology revealed unique polarisable crystals with striations, and there were also associated changes of acute and chronic interstitial nephritis, characterised by the presence of fibrosis and inflammation. In such animal studies it was also reported that by themselves melamine and cyanuric acid appeared to be innocuous, but in combination they formed an insoluble precipitate in renal tubules, which lead to progressive tubular blockage and degeneration.[5] In rats a carcinogenic effect on the bladder was also noted, though its relevance to humans is unclear.[6]

Screening in Hong Kong

In Hong Kong, after reporting of suspected cases of renal stones associated with MTMP consumption, 18 designated clinics (DCs) and nine special assessment clinics (SACs) were set up to screen children 0 to 12 years old. Such screening included urinalysis, renal function tests, and ultrasound examinations.[7] By 14 November 2008 (after 8 weeks of screening), the total numbers of young persons attending the DCs and SACs amounted to 50 314 and 19 714, respectively. In all only seven patients with renal stones were picked up by the SACs, at a rate of 0.036% per ultrasound performed, which is extremely low. There were another five patients with MTMP consumption–associated renal stones who presented in emergency departments, out-patient clinics, and private institutions. In all 12 of these cases, both urinalysis and renal function were normal. In the initial 3000 screened subjects, mild renal impairment was present in only a few, and was unrelated to this condition. It can therefore be inferred that in Hong Kong the consequences of MTMP-associated renal stones were small. There is definitely no outbreak as in mainland China.

Ultrasound for diagnosing renal stones

In China, ultrasound examination is regarded as acceptable for the diagnosis of renal stones of size equal to or exceeding 4 mm in diameter, which is the guideline set for reporting. For small renal stones, especially those below 4 mm in size, the specificity and sensitivity of ultrasound as a diagnostic tool is not high. Vessels and other structures cannot be differentiated definitely. Though computed tomography (CT) is able to identify structures in more detail and can pick up smaller stones of density different from the surrounding tissues, the radiation hazard it presents to children needs to be considered. A non-contrast CT scan is estimated to entail 200 times the radiation dose of a plain chest X-ray, depending on the machine and patient's size. Thus, the benefit of confirming suspicion of a small stone needs to be carefully weighed. If on copious water drinking, small stones can be passed out, for suspicious small stones it may be worth repeating an ultrasound of the kidneys a few weeks later rather than opting for CT. However, if there is pelvi-calyceal dilatation suggesting obstruction, further evaluation for stones smaller than 4 mm may be necessary. Such an approach has been adopted in the diagnosis and management guidelines from the Department of Health and the Hospital Authority.[8,9]

Evaluation of stones

Unlike mainland China, in Hong Kong only 12 patients with renal stones associated with consumption of MTMP have been detected; mainly these were related to consumption of 'Yili' (伊利) milk and 'Mengniu' milk (蒙牛), which had a much lower melamine concentration than 'Sanlu' (三鹿). The stones were mostly 4 to 7 mm in size, and they were calcified in three patients. Investigations to exclude other causes of stones included determination of urinary calcium/creatinine, metabolic screening, and blood for urate, chloride, calcium, phosphate, venous astrup, as well as studies of renal tubular function (beta-2 microglobulin in urine). For stones that were passed out and recovered, their composition was analysed. Other than one patient who had hypercalciuria, investigation results were all normal, and the majority were asymptomatic.

In the past 10 years, an average of about five to six symptomatic kidney stone patients aged 0 to 12 years were being admitted into Hospital Authority hospitals per year. Lack of a confirmatory test for MTMP stones makes establishment of a definitive diagnosis difficult, and can only be inferred by exclusion. For the 12 current patients with stones reported so far, the relationship to MTMP remains a suspected diagnosis only.

Melamine as a diagnostic test

The Toxicology Reference Laboratory at Princess Margaret Hospital has developed a method to measure melamine in urine and stones. However, the test is very sensitive and can detect melamine in the urine of normal subjects (without symptoms or stones), who are taking food products contaminated by low doses of melamine. The half-life of melamine in the body is 3 to 4 hours, and about 80% is cleared within 24 hours. Criteria need to be developed in order to interpret the significance of melamine detected in urine, and what level should be considered abnormal. Whilst it is also possible to measure its presence in stones, what concentration to regard as clinically significant also has to be worked out. Measurement of melamine concentration is possibly a helpful investigative tool, but its clinical application needs further study.[10]

Treatment

The first step in management is to cease consumption of contaminated milk products. Copious water drinking can help pass out MTMP stones, which should be first tried in all patients without urinary obstruction. Intravenous fluid supplementation may be given in addition to oral intake, up to about double the usual maintenance fluid requirement,[9] but plasma electrolyte concentrations need to be monitored. In China, 12 out of 14 stones analysed had uric acid, for which reason alkali therapy was used with a view to help dissolve the uric acid in these stones.[2] However, as melamine and cyanuric acid are more soluble in acid, further studies are required before making a recommendation, and may well depend on the actual composition of the stones in question.

Failing medical treatment, the presence of significant urinary obstruction requires surgery. Drainage can be via cystoscopic retrograde catheterization, using double J catheters, which can also enable some of the stones to be dislodged and passed out. Failing which, percutaneous nephrostomy guided by imaging may be required. For definitive stone removal, mini percutaneous nephrolithotripsy, ureteroscopy or extracorporeal shockwave lithotripsy can be considered as second-line treatment.[9]

Outcome

After passage or removal of stones, renal function recovers even in renal failure patients, so long as obstruction was not prolonged. However, since MTMP disorders have not been reported in humans before, long-term effects cannot be ruled out. The following caviats nevertheless apply. First, if the stones are not passed out and remain in situ, the patients need to be closely monitored lest they develop obstruction and/or infections, in which case surgical intervention may become necessary. Second, as tubulo-interstitial nephritis has been encountered in animals exposed to melamine, its possible occurrence in exposed humans cannot be ignored. Such individuals warrant close follow-up, especially if they have renal stones, urinary abnormalities, and/or they consumed milk products with high melamine content. Third, possible carcinogenic effects on the bladder (in animals) need further investigation, although their relevance to humans is not established.

Food safety

Melamine contamination of food is the Government's responsibility. The Food and Drug Administration (FDA) had recommended melamine's tolerable daily intake (TDI) to be kept below 0.63 mg/kg-bw,[11] based on a 13-week study to determine melamine toxicity in rats.[12] The European Food Safety Authority recommends melamine's TDI to be 0.5 mg/kg-bw. In Hong Kong, the Centre for Food Safety adopts the FDA's recommendation: 0.63 mg/kg-bw for adults and 0.32 mg/kg-bw for children below age 3 years. These recommendations take into consideration melamine contamination in the environment (eg in plastic resins, dishes, industrial coatings, and flame retardant fibres). The legal upper limit set for melamine is 1 ppm for milk and food mainly intended for children younger than 3 years old and pregnant or lactating women, and 2.5 ppm for foods intended for all others.[13] Continuous food surveillance is therefore required and needs to be enforced. Melamine has been found to exceed the above concentrations in a great variety of foods other

than milk, including: ice bars, chocolates, cheese packs, instant coffee, and biscuits containing dairy products. Recently melamine has also been found in eggs (possibly due to contamination of poultry food), and in fish feed. Notably, melamine by itself does not cause much harm. Its combination with cyanuric acid or the latter's analogues, like ammeline and ammelide appear to cause crystallisation in renal tubules. To ensure food safety, it therefore seems necessary to also look into the presence of cyanuric acid–related analogues in food. In October 2008, the FDA has applied an additional 10-fold safety factor to compensate for this uncertainty (related to combined exposure), such that the TDI of melamine has been revised to 0.063 mg/kg-kw.[14]

Conclusion

Melamine-tainted milk product disease is a newly recognised entity in humans, about which very little is known, except that it causes renal stones. This is somewhat different from the crystallisation in the renal tubules that occurs in animals. It is postulated that the crystals so formed serve as nidus for deposition of other chemicals like uric acid, and in the process give rise to stone formation. The missing link is the role of cyanuric acid or other analogues, which may explain the pathogenesis. Such analogues actually inhibit hepatic uric acid oxidase, an effect that increases circulating uric acid levels[5] that may explain the composition of stones containing uric acid. The possible development of tubulo-interstitial nephritis also needs looking into. Much work still needs to be carried out on this condition, especially in China where its impact has been enormous. In Hong Kong, after massive screening by ultrasound, very few patients with stones have been encountered. The stones identified were small and did not cause obstruction, whilst their relationship to MTMP still needs confirmation. Though further follow-up studies are necessary, it is certain that there is no local 'outbreak', such that the initial scare about MTMP stones should be over. With the very low stone pick-up rate, the policy of ultrasound screening needs revisiting. What is also needed is the vigilant enforcement of standards to control food products, and thereby ensure food safety for people's health.

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References

1. Melamine-contamination event, China, September - October 2008. World Health Organization website: http://www.who.int/foodsafety/fs_management/infosan_events/en/index3.html. Accessed 11 Nov 2008.
2. Sanlu Infant Milk Formula Incident Public Consultation Guidelines. Chinese Center for Disease Control and Prevention website: http://www.chinacdc.net.cn/n272442/n272530/n3226631/index.html. Accessed 11 Nov 2008.
3. Brown CA, Jeong KS, Poppenga RH, et al. Outbreaks of renal failure associated with melamine and cyanuric acid in dogs and cats in 2004 and 2007. J Vet Diagn Invest 2007;19:525-31.
4. Cianciolo RE, Bischoff K, Ebel JG, Van Winkle TJ, Goldstein RE, Serfilippi LM. Clinicopathologic, histologic, and toxicologic findings in 70 cats inadvertently exposed to pet food contaminated with melamine and cyanuric acid. J Am Vet Med Assoc 2008;233:729-37.
5. Dobson RL, Motlagh S, Quijano M, et al. Identification and characterization of toxicity of contaminants in pet food leading to an outbreak of renal toxicity in cats and dogs. Toxicol Sci 2008;106;251-62.
6. World Health Organization, International Agency for Research on Cancer (IARC), V73. Monographs on the evaluation of the carcinogenic risk of chemicals to man. International Agency for Research on Cancer website: http://monographs.iarc.fr/ENG/Monographs/vol73-17.pdf. Accessed 17 Sep 2008.
7. Wong SN, Chiu MC. The scare of melamine tainted milk products [Editorial]. Hong Kong J Paediatr (New Series) 2008:13:230-4.
8. Case definitions of renal diseases associated with consumption of melamine tainted milk products (MTMP). DH SEB NCE/17/10/2008. Centre for Health Protection website: http://www.chp.gov.hk/view_content.asp?lang=en&info_id=13990. Accessed 12 Nov 2008.
9. Hospital Authority Expert Group on MTMP related disorders. Updated Guidelines for Assessment and Treatment of Melamine Tainted Milk Product Related Disorders (version 3). Hospital Authority website: http://ha.home/qns/mtmp/man.htm. Accessed 12 Nov 2008.
10. Mak T. Melamine measurement for clinical application. Melamine Tainted Milk Product (MTMP) Symposium; 2008 Oct 18; Princess Margaret Hospital, Hong Kong.
11. Interim Melamine and Analogues Safety / Risk Assessment. (May 25, 2007) U.S. Food and Drug Administration website: http://www.cfsan.fda.gov/~dms/melamra.html. Assessed 14 Nov 2008.
12. NTP Technical Report on the Carcinogenesis Bioassay of Melamine (CAS NO.108-78-1) in F344/N Rats and B6C3F1 MICE (Feed Study). National Toxicology Program. March 1983. US Department of Health and Human Services, Public Health Services, National Institutes of Health.
13. Harmful Substances in Food (Amendment) Regulation 2008. Centre for Food Safety website: http://www.cfs.gov.hk/english/whatsnew/whatsnew_fstr/whatsnew_fstr_harmful_substances_regulation.html. Accessed 12 Nov 2008.
14. Interim Safety and Risk Assessment of Melamine and its Analogues in Food for Humans (3 October 2008). U.S. Food and Drug Administration (FDA) website: http://www.cfsan.fda.gov/~dms/melamra3.html. Accessed 12 Nov 2008.