Nephrolithiasis associated with the use of topiramate in children

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Topiramate (TPM) has been widely used in epilepsy and migraine. Its use, however, has been associated with development of metabolic disturbances such as acidosis, hypokalaemia, hyperuricaemia, and renal stone disease.[1] The routine use of ultrasonography (USG) of the urinary system to screen for nephrolithiasis remains controversial.

We performed a single-centre retrospective survey of nephrolithiasis associated with TPM use. Medical records of children with epilepsy who had ever been prescribed TPM between January 2005 and December 2014 in our institute were reviewed. Patients with a pre-existing history of renal stones; long-standing or intermittent urinary catheterisation; history of recurrent urinary tract infection; chronic diarrhoea; or concomitant use of other carbonic anhydrase inhibitors, antacids, or diuretics were excluded. Their demographic data including age, sex, ambulatory status, age at initiation of treatment, duration and dosage of TPM treatment, and concurrent use of a ketogenic diet were recorded. Urinary symptoms reported by patients or carers including stone passage, haematuria, and dysuria were noted. The occurrence of nephrolithiasis was assessed by USG screening that was arranged at around 1 year after initiation of TPM treatment or when any urinary symptoms were reported. The study was approved by the local institutional ethics review board and conducted in accordance with good clinical practice guidelines and the Declaration of Helsinki.

During the study period, 81 patients were prescribed TPM. The study group comprised 48 patients who had been on TPM treatment for at least 12 months of whom 16 (33.3%) were female and 35 (72.9%) were ambulatory; TPM was initiated at the age of 1.1-15.4 years with dose range of 1.2-12.0 mg/kg/day (mean, 6 mg/kg/day). Length of time on treatment was 1.3-12.0 years (mean, 8.3 years) and at least one renal USG examination had been performed in 29 (60.4%) patients. In this group of patients, 21 (72.4%) were ambulatory. The group without USG (n=19) were older at commencement of TPM treatment and were on TPM for a shorter duration compared with the group who had USG performed (n=29); the difference was statistically significant (both $P<0.05$). Nonetheless, there was no difference in sex, mean TPM dosage, or ambulatory status.

Overall two patients developed nephrolithiasis while they were on TPM. Both were non-ambulatory. One boy was on a concomitant ketogenic diet and reported a history of passing sand-like material in his nappies. His renal USG showed possible soft stone formation that resolved on subsequent imaging. Another girl had a 3-mm stone noted on routine USG screening but remained asymptomatic; TPM was stopped and she was managed conservatively. No renal stone was noted on follow-up scan 11 months later. Both patients had normal renal function tests and no active intervention was required for the nephrolithiasis. No other patients in the cohort reported symptoms attributable to nephrolithiasis and all other USG scans were normal.

Our results are comparable to patients prescribed TPM in other countries. In children, there are limited published data and no reports from the Chinese population. It is known that prevalence and incidence of nephrolithiasis vary with race, climate, and diet.[2] In children, the Texas group reported a 4.9% (2/41 patients) of incidence of stone in children prescribed TPM compared to 5.2% (5/96 patients) in a Saudi Arabia population.[3,4] In Asia, there have been some case reports of nephrolithiasis in association with TPM use in children in Japan and Korea.[5,6] The true incidence of nephrolithiasis in the general paediatric population was unclear. Dwyer et al[7] reported an incidence of stone disease of 36 per 100 000 person-years between 2003 and 2008 in Rochester, US. In Hong Kong, a 2008 community screening programme in children exposed to melamine-tainted milk products revealed a kidney stone prevalence of 0.03% to 0.27% although these children were otherwise healthy.[8,9] Our study is the first report in a Chinese population of screening for asymptomatic nephrolithiasis in children with

epilepsy managed with TPM. The development of nephrolithiasis in our TPM users was much more common compared with the local general paediatric population.

The clinical significance of these stones is uncertain. Both affected patients were asymptomatic, similar to previous reports. The patients reported by Bush et al[3] were asymptomatic, one had a 7-mm stone that was treated with extracorporeal shock wave lithotripsy and the other with two 3-mm stones was treated with ureteroscopy because of increasing stone size. The five patients with kidney stones reported by Mahmoud et al[2] were also asymptomatic. A recent observational cohort study by Shen et al[10] in Taiwan found that TPM may not increase the risk of urolithiasis. They analysed 1377 patients prescribed TPM and 1377 age- and sex-matched controls. Urolithiasis was identified by ICD (International Classification of Diseases) code in National Health Insurance Research Dataset. There was no difference in the proportion of patients who developed urolithiasis between the two groups. The prevalence of urolithiasis, however, may have been underestimated since only symptomatic stones would have been reported.[10] This further supports that most stones that develop in association with TPM use are likely to be asymptomatic clinically.

Some groups have proposed routine baseline and follow-up USG of the urinary system for children prescribed TPM.[2] In an open-label extension study of 284 paediatric patients aged 1 to 24 months with epilepsy and TPM prescription for up to 1 year, 7% developed kidney stone or bladder stone diagnosed clinically or by sonogram.[11] Mahmoud et al[2] also reported five asymptomatic stone formers in 96 children on TPM. The median time between initiation of TPM treatment and stone detection by USG was 21.2 months. On this basis, we also arrange USG screening of the urinary system in patients prescribed TPM for longer than 1 year or when urinary symptoms related to nephrolithiasis are reported. Patients who underwent USG were younger and on TPM for a longer duration than those without. Parents might be more concerned about long-term side-effects, especially in younger patients. We could also arrange appointment easier if they were on treatment for longer duration, taking into consideration of the waiting time for routine USG.

In clinical practice, it may be difficult to perform surveillance screening for stones in patients prescribed TPM. First, the minimal time and dosage exposure required to develop nephrolithiasis is uncertain. Stone formation has been noted within days to weeks of TPM treatment.[12] There is also evidence that TPM dose and duration might not directly correlate with stone formation.[4] Second, although USG is non-invasive and relatively accessible, parents/carers may be unwilling to perform investigations for screening purposes (ie when patients are asymptomatic). This is consistent with the experience reported by Bush et al.[3] In their Texas study, a significant number of patients prescribed TPM did not wish to be enrolled in a screening study.[3] Up to 39 (44.8%) of 87 patients with surveys obtained did not undergo USG screening and/or urinalysis screening.[3]

Our survey found that children on TPM are at a higher risk of nephrolithiasis than the general paediatric population in Hong Kong. The clinical significance of these stones, however, is still uncertain and asymptomatic stones are common.[3,4,10] All TPM users should be considered universally at risk of nephrolithiasis.[2-4] A high index of suspicion and general education of carers are essential.

Declaration

No author has disclosed any conflicts of interest.

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