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Phosphate nephropathy: an avoidable complication of bowel preparation for colonoscopy

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Abstract

It is known that oral sodium phosphate, used as bowel preparation for colonoscopy, can cause acute phosphate nephropathy, a potentially severe and irreversible form of acute kidney injury. Due to these safety concerns, guidelines have advised against the routine use of this agent for a decade. We present a case report and biopsy series that demonstrate that oral sodium phosphate is still being used and that cases of APN are still occurring, in Australia.

Oral sodium phosphate (OSP) is a hyperosmotic laxative used for bowel cleansing prior to colonoscopy. It is known that OSP can cause acute phosphate nephropathy (APN), a sudden, potentially severe and often permanent kidney injury caused by intra-renal calcium phosphate deposition (nephrocalcinosis).[1] For this reason, endoscopy guidelines advise against routine use of OSP for bowel preparation.[2,3] We present a case and biopsy series, which demonstrate that, in Australia, OSP is still being used by some endoscopists, and cases of APN are still occurring.

A 75-year-old man was noted to have a rise in serum creatinine from 80 to 182 μmol/L (eGFR falling from 83 to 32 mL/min/1.73 m^2) over a 6-month period on routine blood tests arranged by his general practitioner. The patient had undergone a colonoscopy 3 months before the rise in creatinine was first noted, and OSP had been used for bowel preparation. He reported no other new medical problems or medications during this period. Other past medical history was significant for osteoporosis, hypertension, gout, mild interstitial lung disease, diverticular disease and colonic polyps. Medications included ramipril and allopurinol. Urine dipstick and microscopy revealed an inactive urinary sediment. Urine albumin to creatinine ratio was 7 mg/mmol. Ultrasonographic examination of the renal tract was normal. A renal biopsy was performed, which demonstrated nephrocalcinosis with associated tubular injury, mild to moderate intersititial fibrosis and light chronic inflammation (Fig. 1). The calcium deposits were negatively birefringent under polarised light, consistent with calcium phosphate rather than calcium oxalate crystals. The patient was normocalcaemic, and

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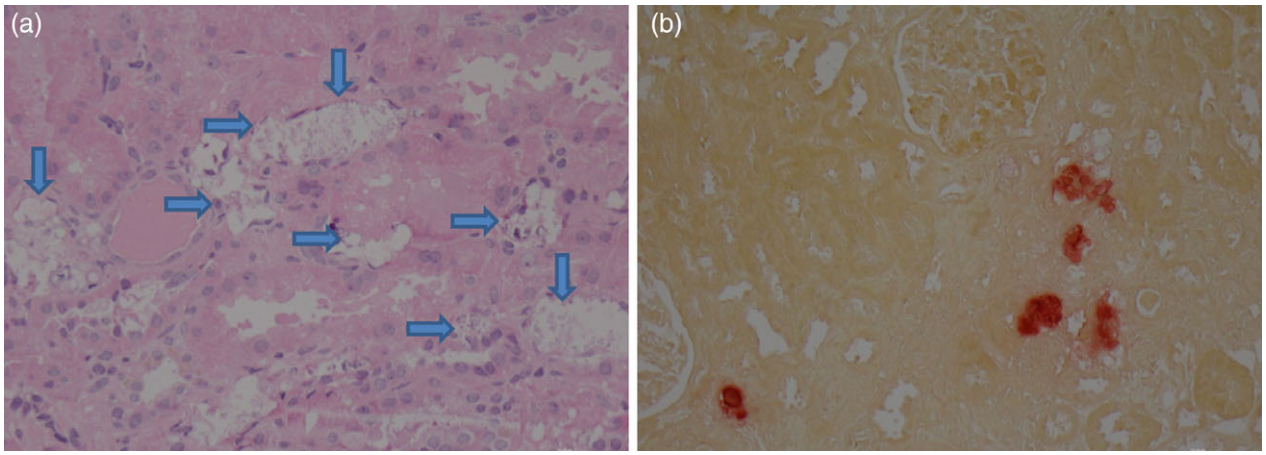

Figure 1 (a) Haematoxylin and eosin staining (400x) reveals numerous deposits consistent with calcium phosphate within the interstitium (arrows) and also within damaged tubules. (b) Alizarin red stain (200x) highlights residual calcium deposits (red).

investigations to identify an alternative cause of nephrocalcinosis were unrevealing. Therefore, the final diagnosis reached was that of APN due to the use of OSP, with resultant chronic kidney disease (CKD). Six months later, creatinine was ~173 μmol/L, with eGFR 33 mL/min/1.73 m^2.

A review of renal biopsy results over the past decade (2007–2017) at the Austin Hospital identified 12 cases of nephrocalcinosis, of which 3 (25%) were due to APN related to OSP use for colonoscopies. These cases occurred in 2011, 2014 and 2016. In one case, the cause of nephrocalcinosis was not identified at the time but, on review, was felt extremely likely to be OSP used for colonoscopy preparation. All patients had at least one known risk factor for developing APN. All patients sustained permanent renal injury. Mean baseline creatinine was 89 μmol/L, with eGFR 73 mL/min/1.73m^2. Mean follow-up creatinine, at 6–12 months post-OSP, was 200 μmol/L, with eGFR 26 mL/min/1.73m^2. All colonoscopies had been performed in the private system. One endoscopist had performed the colonoscopies for two of the cases (2014, 2016) and was using OSP as first-line bowel preparation. There was no apparent reason why an alternative bowel preparation could not have been used in any of these cases.

Discussion

Acute kidney injury (AKI) related to the use of OSP was first reported in 1975.[4] In 2003, a renal biopsy performed on a patient with AKI following use of OSP identified nephrocalcinosis with tubular deposition of calcium phosphate and associated tubular injury as the mechanism of injury. This led to the term 'phosphate nephropathy'.[5] Shortly after, there followed what remains the largest reported case series (21 cases of APN) of this condition.[1] This retrospective study identified OSP as the most common cause of biopsy-proven nephrocalcinosis at that time, accounting for 68% of cases. All patients with biopsy-proven APN developed CKD. Mean baseline was creatinine 88 μmol/L, and mean follow-up creatinine was 211 μmol/L, at a mean of 16.7 months follow up. Notably, 4 of 21 (19%) cases required permanent renal replacement therapy. This study, along with further reports of the condition, led to an FDA warning about the risk of AKI with OSP in 2006[6] and to a change in endoscopy guidelines to recommend against the routine use of OSP.[2] In response to these safety concerns, the manufacturers of Fleet Phospho-Soda (C.B. Fleet Inc.) withdrew this OSP product from the US market in 2008.[7] However, OSP remains available in Australia as a 'Pharmacist Only' medication (i.e. a prescription is not required but customers must discuss use with a pharmacist prior to it being dispensed).

The incidence of APN after OSP use for colonoscopy is hard to establish. One study reported the rate of biopsy-proven APN after use of OSP to be ~0.1%.[8] The overall incidence of the condition is undoubtedly considerably higher as it is highly likely that many cases of APN remain undiagnosed or do not proceed to biopsy. Even if a biopsy is performed, the causative agent may not be recognised, particularly if some time has elapsed since the colonoscopy took place. Compared with other agents used for bowel preparation, the relative risk of AKI after OSP has been reported to be 2.35, with an adjusted number needed to cause harm of 81.[9]

Identified risk factors for developing APN include advanced age, hypertension, pre-existing renal

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impairment and use of diuretics or blockers of the renin-angiotensin system.[1,7,10,11] APN should be suspected in patients who develop AKI after a colonoscopy if OSP was used for bowel preparation. The main differentials will usually be pre-renal AKI or ischaemic acute tubular necrosis, related to volume depletion and renal hypoperfusion. Indicators that APN is the likely cause include a very high phosphate (e.g. >3 mmol/L), if checked within 48 h of OSP ingestion, or failure of complete renal recovery with volume repletion and time. APN should also be suspected in patients who experience a permanent step down in renal function, first noted some time after a colonoscopy, followed by a period of relative stability, such as described in the case above. The histological hallmark of APN on renal biopsy is the presence of abundant tubular, with less prominent interstitial, calcium phosphate deposits.[7] Calcium phosphate crystals may be removed in the preparation of sections stained with haematoxylin and eosin (due to acidity) leaving only 'ghosts' but, if present, can be distinguished from calcium oxalate by their tinctorial properties and lack of birefringence under polarised light. Alizarin red and von Kossa stains can be used to demonstrate calcium and phosphate in the deposits respectively.[12] Acute tubular degenerative changes can be seen in the first few weeks after development of APN, while tubular atrophy and interstitial fibrosis predominate later.[7]

If APN is recognised early, when phosphate levels are still high, haemodialysis or haemofiltration should be considered to try and reduce further deposition of calcium phosphate in the tubules.

Alternative bowel preparations, such as polyethylene glycol (PEG) and sodium picosulfate, have been shown to be as efficacious as OSP for bowel cleansing and do not cause APN.[13] Current endoscopy guidelines recommend the use of these safer agents in preference to OSP. The European Society of Gastrointestinal Endoscopy Guidelines 'advise against the routine use of OSP for bowel preparation' and 'suggest that OSP can only be advised in selected cases of specific needs (e.g. patient unable to tolerate other agents)'.[3] The American Gastroenterology Association recommendations on bowel cleansing prior to colonoscopy comment that OSP is 'unsuitable as a first line agent', is 'not recommended in patients with renal insufficiency' and should be used with caution in patients with any risk factors for APN.[13]

This biopsy series, along with another recent case report,[14] demonstrates that OSP is still being used by some endoscopists in Australia, and cases of APN are still occurring, some 10 years after guidelines have advocated for the use of safer agents for bowel preparation. Increasing awareness of this condition is important to help prevent further cases occurring. Available Australian OSP products include Fleet Phospho-Soda (Ferring Pharmaceuticals), a saline-based liquid preparation, and Diacol (Fresenius) tablets. Diacol tablets are the only tablet-based colonoscopy bowel preparation available in Australia and may be requested by some patients in preference to liquid-based preparations. Before considering the use of Fleet Phospho-Soda or Diacol, it would be crucial to exclude any risk factors for APN and to obtain informed consent from the patient after explaining the additional risk of APN with these agents.

While the incidence of APN after OSP for colonoscopy is low, this condition is both serious – commonly causing CKD and potentially resulting in dialysis-dependent renal failure – and completely avoidable. Given the availability of safer agents, and in line with endoscopy guidelines, OSP should only be used in exceptional circumstances and only in patients with no risk factors for APN.

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Australian driving restrictions: how well do neurologists know them?

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Abstract

Driving regulations are complex, particularly for neurological conditions, but accurate application of restrictions is important. This study was designed to investigate knowledge of the Austroads guidelines in medical students, neurological trainees and consultant neurologists using a questionnaire addressing both private and commercial licence restrictions related to five common neurological conditions, namely transient ischaemic attack (TIA), vasovagal episode, unwitnessed blackout, first epileptic seizure and benign paroxysmal positional vertigo. In total, 118 of the 120 returned responses could be analysed. Overall, 50% of all responses were correct. Respondents performed better for private than commercial licences, and consultants performed better than trainees and students. The highest proportion of correct answers was seen for vasovagal attack, and the lowest for TIA. In summary, knowledge of driving restrictions was relatively poor, and regular consultation of the guidelines is recommended. A larger study is warranted and increased education at both medical school and postgraduate levels should be considered.

In 2015, the Australian population was almost 24 million, and there were approximately 18 million cars on the roads. At that time, 5.25 million driving licences were held in New South Wales (population 7.62 million). Of these, the vast majority were private licences, with approximately 10% being commercial.[1] In view of these numbers, driving regulations are essential to minimise the risk of accidents and injury. In particular, it is incumbent on medical practitioners to advise their patients accurately. However, the driving regulations in Australia are complex, particularly in relation to neurological conditions.[2]

To be effective, any restrictions must be observed by the individuals to whom they apply. It is obvious that many individuals do not observe the restrictions[3] and, in the USA, it has been estimated that fatalities are three times more common in individuals who drive while disqualified compared to licensed drivers.[4] A recent article in this journal described an individual who was inappropriately certified as fit to drive but then had an accident, striking and killing a pedestrian.[5]

For the appropriate driving restriction to be recommended to the Driver Licence Authority (DLA), physicians must be aware of the various conditions which can impair fitness to drive. Ideally, they either need to know

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