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Deaths and kidney failures call bowel preparation safety into question

On December 12, 2008, C.B. Fleet issued an immediate product recall and directed US pharmacies to remove the over-the-counter products, Fleet Phospho-soda and Fleet Phospho-soda EZ-Prep Bowel Cleansing System from their shelves. These emergency measures followed an FDA safety alert stating that oral sodium phosphate (NaP) products for use in bowel preparation should be available by prescription only in light of the risk of acute kidney injury.[1,2]

Similar safety concerns were identified by a systematic review published in August 2008 identifying published reports of life-threatening adverse events, including kidney failure and death, for patients given bowel lavage preparations.[3] Approximately 10 million patients in Europe are prescribed bowel lavage preparations (about 7 million PEG [polyethylene glycol] preparations and 3 million NaP [sodium phosphate] preparations) so any concerns over safety are extremely serious.[4] Five times more significant adverse events were reported for NaP when compared with PEG (109 patients using NaP and 22 patients using PEG).[3]*

These safety issues raise potentially life threatening implications for the thousands of healthy people currently undergoing screening as part of a nationwide bowel cancer screening programme in the UK.

In a systematic literature review[3] in *Alimentary Pharmacology & Therapeutics*,[†]
Dr Jonathan Belsey and colleagues investigated the potential safety issues associated with bowel preparation with PEG (polyethylene glycol) and NaP (sodium phosphate) prior to bowel investigation. They found 58 publications that included significant adverse events[‡] in 109 patients using NaP and 22 patients using PEG. Electrolyte disturbances, kidney failure

*As the total number of prescriptions for NaP and PEG were unknown, the rates for these two agents cannot be directly compared.
[†]Supported by an unrestricted grant from Norgine.
[‡]Adverse events included: acute electrolyte disruption, nephrocalcinosis, nephropathy, acute renal failure.

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and colonic ulceration were the most commonly reported adverse events for NaP. Electrolyte disturbances, upper gastrointestinal damage and allergic reactions were reported for PEG.

Bowel cancer affects one in 20 people in the UK and is the second most common cause of cancer deaths, with over 16,000 people dying from it each year.[5] Regular bowel cancer screening aims to detect bowel cancer at an early stage and has been shown to reduce the risk of dying from colon cancer by 15%. Bowel cancer screening programmes are now high on the public agenda, and screening will be offered every two years to all men and women aged 60 to 69 by 2009.[5]

Bowel preparation is crucial for any diagnostic procedure like colonoscopy which requires good visualisation of the bowel mucosa. PEG and NaP are two widely used preparations to cleanse the bowel. Some adverse events are often associated with bowel preparations, such as diarrhoea, nausea and abdominal pain, which can act as a deterrent for many of the patients undergoing screening. The potential for serious adverse events with NaP has also been highlighted by several drug regulatory authorities outside the US.[6-8]

In the cases identified in the systematic review, 25% of the patients with metabolic disturbance died (11 of the 46 cases reported with NaP patients died versus one of the five cases reported with PEG).

Professor Owen Epstein, Professor of Gastroenterology at the Royal Free Hospital, and co-author of the paper commented: "In the UK, 35,000 people are diagnosed each year with colon or rectal cancers. For this reason, bowel screening is increasingly being used in healthy adults. However, the message that may be unappreciated is that although clinically important complications following the use of bowel preparations are uncommon they may be serious. Given that many people who undergo screening are healthy, the risks and benefits should be carefully considered by clinicians when choosing which preparation to use."

In 2001, the US Food and Drug Administration issued guidance relating to the risks associated with the use of NaP.[3] At this stage there were very few reports for cases of

kidney failure associated with calcium or phosphate deposition in the kidney (nephrocalcinosis / acute phosphate nephropathy), which can lead to kidney failure. However, between January 2006 and December 2007 there were 171 cases of kidney injury reported with NaP, but only 10 following the use of PEG. During the same period there were 51 cases of phosphate nephropathy with NaP and none with PEG. These higher numbers are likely to reflect greater awareness of the problematic safety issues associated with NaP as a result of manufacturer warnings.[9]

The Food and Drug Administration have required 'Black Box' warnings regarding the risk of acute kidney injury for two prescription NaP products (Visicol and Osmoprep; Salix Pharmaceuticals Inc.) and that healthcare professionals cease directing patients to use over-the-counter laxative oral liquid NaP for bowel cleansing.[2] In response, C. B. Fleet immediately ceased distribution and initiated a voluntary recall of the over-the-counter NaP products Fleet Phospho-soda and Fleet Phospho-soda EZ-Prep Bowel Cleansing System.[1]

The National Patient Safety Agency in the UK is also in the process of issuing a Rapid Response Report which aims to provide safer practice recommendations for bowel preparations.[10]

Jonathan Belsey, Director of Health Economics at JB Medical Ltd, and lead author of the paper commented: "All case reports of adverse events should be taken seriously. While I strongly support early bowel screening and the use of bowel preparations are important for this, I would urge that all clinicians involved with screening be aware of the safety issues relating to the different bowel preparations available."

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