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Potassium and Anticholinergic Drug Interaction

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Old dogs – no new tricks: potassium and anticholinergic medications

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It is not news that potassium chloride (KCl) is irritating to the gastrointestinal (GI) tract. Since the 1970s solid KCl dosage forms have been linked to cases of upper and lower GI bleeding, ulceration, obstruction and perforation. (1,2) Surprisingly, this well-established adverse reaction has recently become one of the most frequent queries to DPIC's drug information service. The source of confusion is an interaction message, which began appearing on PharmaNet in August 2006. The message, assigned the highest severity level, contraindicated the use of solid dosage forms of KCl with anticholinergic medications. (3) Meanwhile, drug interaction texts provided little or no supporting clinical evidence of an interaction. Although the subject was covered in a newsletter from the College of Pharmacists last spring (3), DPIC continues to receive requests for clarification.

In Canada, solid dosage forms of potassium are contraindicated "in any patient in whom there is cause for arrest or delay in tablet passage through the gastrointestinal tract." (4) In approved American monographs this is expanded to pharmacologic causes including "use of anticholinergic agents or other agents with anticholinergic properties at sufficient doses to exert anticholinergic effects." (5,6) Anticholinergics are thought to increase mucosal contact time between solid KCl dosage forms and the GI mucosa. Consequently, First Databank (the company which provides drug interaction information to PharmaNet) introduced an interaction flag when oral potassium and anticholinergic medications are used concurrently. The warning appears on both new prescriptions and on refills. At the request of the College of Pharmacists, First Databank adjusted the message to advise caution rather than contraindicating the combination, although they still maintain the highest severity level for the interaction. (3)

Although KCl is inherently irritating, liquid or effervescent KCl preparations have fewer GI complications than solid forms. Mucosal damage from KCl is caused by high localized potassium ion concentrations in the vicinity of dissolving tablets. (7,8) Before they were removed from the market, enteric-coated KCl products produced GI hemorrhage, perforation, obstruction and death when they dissolved in the small intestine. (9) The rate for small intestinal ulceration is estimated to be 40 – 50 cases per 100,000 patient years with enteric-coated products (9) and about 3 cases per 100,000 patient years with slow-release tablets. (10) There are no corresponding data on the incidence of ulceration when potassium chloride is used in the presence of anticholinergic medications, nor are cases described in drug interaction texts.

The presence of stasis or prolonged GI transit times may increase the risk of potassium-induced GI mucosal damage, as illustrated in an experimental study performed in 1982. (11) This trial involved 48 healthy male volunteers who were randomized to receive microencapsulated KCl (Micro-K®) or KCl in a wax-matrix formulation (Slow K®). Two doses of potassium were examined; 32 mEq three times daily or 8 mEq three times daily. To slow GI transit times, some subjects also received the anticholinergic agent, glycopyrrolate given at 2 mg three times daily. Mucosal damage to the upper GI tract was assessed by endoscopy before treatment and following 7 days of potassium administration. Endoscopists were blinded to the treatment arms. The wax-matrix preparation was associated with a higher incidence of mucosal lesions than the microencapsulated product at both dosages. Concomitant glycopyrrolate worsened the damage with the wax-matrix product, but not with the microencapsulated form. Although erosions, gastric ulcers and bleeding were endoscopically observed, symptoms did not accompany the lesions.

A subsequent study compared the gastrointestinal effects of five different KCl preparations and placebo in 90 healthy volunteers treated with glycopyrrolate. (12) Endoscopic examination of the upper GI tract was performed at baseline, then one week after receiving the KCl or placebo preparation. All subjects also received glycopyrrolate 2 mg three times daily. Potassium doses for four products (wax-matrix KCl, microencapsulated KCl, KCl liquid, experimental extended-release capsules) used were 24 mEq one hour prior to meals. The fifth product (experimental extended-release tablets) was dosed at 30 mEq before breakfast and 20 mEq before lunch and dinner. All KCl doses were taken with 240 mL of water. The principal investigator and endoscopist were blinded to treatment allocation, and the diet of the subjects was controlled. In contrast to the McMahon study (11), after 7 days there were no statistically significant differences found in the number of lesions or symptomatology as compared to placebo in any of the treatment groups. One ulcer was noted in a subject receiving the microencapsulated preparation. There were GI lesions in 4/15 (27%) in subjects receiving placebo plus glycopyrrolate, in comparison to a 9% lesion incidence in subjects screened at entry (those with lesions at entry were excluded from the study). The authors were unable to explain this observation, but considered the possibility that gastric stasis caused by the anticholinergic might predispose to gastric damage. Unfortunately, glycopyrrolate was not compared to placebo, and this hypothesis has not been tested further.

Canadian product monographs and drug information sources provide warnings about the risk of GI damage with solid oral dosage forms of potassium chloride, particularly in patients with delayed GI motility. The potential for GI complications caused by KCl may be increased by any anticholinergic medication, but does not preclude their concurrent use. Experimental evidence of a potential interaction between oral potassium and anticholinergic medications has not been consistent and therefore its clinical importance has not been established. The

one major drug interaction reference, which remarks on the interaction (13) advises that pharmacists should be alert for evidence of the interaction. The presence of a new interaction flag may serve as a reminder of the GI effects of KCl, and of the potential for damage in patients with impaired GI transit.

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