Renal aspects of peptic ulcer pharmacology

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D MURUVE, E BURGESS. Renal aspects of peptic ulcer pharmacology. *Can J Gastroenterol* 1992;6(1):29-34. Medications to treat peptic ulcer disease are used widely and may have adverse effects on renal function. Similarly, renal dysfunction may alter the pharmacokinetics of this diverse group of medications resulting in dosage adjustments. The older agents, antacids and sucralfate, allow absorption of cations (calcium, magnesium and aluminum) which may result in toxicity. Newer medications (H₂ blockers and omeprazole) appear to have fewer side effects and be better tolerated with appropriate dosage adjustments.

Key Words: Duodenal ulcer, Peptic ulcer, Renal pharmacology

Aspect rénal de la pharmacologie de l'ulcère gastroduodénal

RESUME: Les antiulcéreux sont largement prescrits et peuvent avoir des effets indésirables sur la fonction rénale. Pareillement, le dysfonctionnement rénal peut altérer la pharmacocinétique de ce groupe de médicaments divers et nécessiter l'ajustement de la posologie. Les médicaments plus anciens tels que les antiacides et le sucralfate permettent l'absorption des cations (calcium, magnésium et aluminium) et comportent des risques de toxicité. Administrés à des doses appropriées, les médicaments plus récents (antihistaminiques H₂ et oméprazole) semblent causer des effets secondaires moindres et être mieux tolérés.

THERE HAS BEEN AN INCREASE IN the number and classes of medications used to treat peptic ulcer and related diseases over the past 15 years. Most of these medications are relatively free from significant adverse effects and widely prescribed in clinical practice.

Patients with chronic renal failure have an increased incidence of upper

gastrointestinal bleeding which may be related to acid hypersecretion (1,2) or disturbances in serum gastric concentration or the mucosal barrier (3). Patients undergoing renal transplantation have a high incidence of postoperative gastrointestinal complications including gastritis and peptic ulceration due to factors including underlying

chronic renal failure, stress and steroid therapy (4,5). Certain medications designed to treat peptic ulcer disease have different applications in the renal patient, eg, using antacids as phosphate binders and prostaglandin analogues in renal transplantation.

This article reviews the nephrological aspects of peptic ulcer pharmacology, focusing on adverse effects on the kidneys and pharmacokinetic changes produced by renal insufficiency.

H₂ BLOCKERS

There are four H₂ blockers available in Canada: cimetidine, ranitidine, famotidine and nizatidine – all equally effective in treating peptic ulcer disease (6). All of the H₂ blockers are cleared primarily by the kidneys as unchanged drug. Following intravenous administration, 50 to 80% of the dose of cimetidine (7), 70% of ranitidine (8) and famotidine (9) and 75% of nizatidine (10,11) is eliminated unchanged in the urine. Renal clearance of H₂ blockers greatly exceeds the glomerular filtration rate consistent with active tubular secretion of the drugs which are all weak bases at physiological pH; this tubular secretion may be via an organic cation secretory mechanism in the proximal tubule (12).

Renal insufficiency, therefore, results in decreased plasma clearance

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TABLE 1

Dose reduction recommended for peptic ulcer drugs in patients with renal insufficiency

Drug	Elimination metabolism	Recommended dose	Adjustment in renal failure (GFR mL/min)			
			>75	30-75	15-30	<15
Cimetidine	Renal: 50-80% Hepatic: 20-40%	PO: 800-1200 mg/day IV: 300 mg q8h	No change	800 mg/day 300 mg/day	600 mg/day 150 mg q12h	400 mg/day 150 mg q24h
Ranitidine	Renal: 70% Hepatic: 30%	PO: 300 mg/day IV: 50 mg q8h	No change	225 mg/day 50 mg q12h	150 mg/day 50 mg q24h	75 mg/day 25 mg q24h
Famotidine	Renal: 70% Hepatic: 30%	PO: 40 mg/day IV: 10 mg/q8h	No change	30 mg/day 10 mg q12h	20 mg/day 10 mg q24h	10 mg/day 10 mg q24h
Nizatidine	Renal: 75% Hepatic: 25%	PO: 300 mg/day	No change	225mg/day	150 mg/day	75 mg/day
Omeprazole	Hepatic: 95-100%	PO: 20-40 mg/day	No adjustment required			
Misoprostol	Hepatic: 95-100%	PO: 100-200 mg qid	No adjustment required			
Sucralfate	Renal (aluminum absorbed)	PO: 1 g qid	Should be avoided			

None of the drugs is removed by dialysis. IV Intravenously; PO Orally

and increased elimination half-life of all four medications (7,13-18). Drug accumulation can occur, leading to adverse effects – particularly central nervous system toxicity and mental confusion (19-21). Dose reduction is recommended for H₂ blockers based on creatinine clearance (Table 1). All medications are minimally cleared by dialysis (both hemodialysis and peritoneal dialysis) and do not need to be supplemented post dialysis (7,15,22,23).

Cimetidine, the first and prototypical H₂ blocker, has several direct and indirect renal effects; it has been shown to inhibit competitively the tubular secretion of cations such as creatinine (thereby affecting creatinine-dependent measurements of renal function) and numerous basic drugs in the proximal tubule. It was first demonstrated by Burgess et al (24) to decrease renal creatinine clearance without affecting renal function as measured by inulin clearance. Cimetidine was also shown to decrease renal clearance of procainamide and its active metabolite, N-acetylprocainamide (25); this inhibition of cationic tubular transport was confirmed in the isolated rabbit proximal tubule model by McKinney and Speeg (26). Cimetidine has also been shown to reduce the renal clearance of triamterene (27), metformin (28) and flecainide (29), presumably via the same mechanism.

These interactions with cimetidine are clinically significant because a decrease in drug clearance may lead to an increase in adverse effects, especially

in the elderly and those with impaired renal function.

Numerous cases of acute interstitial nephritis have been reported with cimetidine therapy (30-34). Renal biopsies of such cases showed typical features of interstitial nephritis with infiltrates consisting of plasma cells, lymphocytes and eosinophils. Renal function in all patients improved over two to four weeks upon stopping the drug. Prednisone was used in several cases with apparent benefit.

Concerning the safety of cimetidine in renal transplantation, there were early reports of increased allograft rejection with cimetidine use (35); a study by Gifford and Tilberg (36) demonstrated that cimetidine reduced cyclosporine-mediated inhibition of interleukin-2 and therefore affected immunosuppression. However, the majority of studies using cimetidine as gastrointestinal prophylaxis in renal transplant recipients have shown no increase in rejection (37-41) or decrease in graft survival (39,40). Therefore cimetidine appears to be safe for use in renal transplantation.

Like cimetidine, ranitidine is secreted by the proximal tubule and competitively inhibits the cationic secretory mechanism, but is five to eight times more potent than cimetidine with no known direct renal side effects or reports it causes acute interstitial nephritis (unlike cimetidine). Procainamide and N-acetylprocainamide renal clearance is reduced by ranitidine, especially at high doses (42). However,

the effect is minimal at therapeutic doses. In a select group of patients, such as the elderly and those with renal insufficiency, a reduction in procainamide dosage may be necessary when given concomitantly with ranitidine. Ranitidine has no influence on plasma (or serum) creatinine levels (42).

Famotidine is at least twenty times more potent than cimetidine and does not appear to inhibit the proximal tubule's cationic transport system at therapeutic doses. Famotidine has no effect on the renal clearance of procainamide (43) or tubular secretion of creatinine (44) and thus does not affect creatinine-dependent measurements of renal function. There are no reported cases of acute interstitial nephritis with famotidine.

Nizatidine is similar to ranitidine in potency. It has no known direct adverse effects on kidneys and is secreted in the proximal tubule. No studies regarding its effect on cationic secretion have been performed. Its metabolite N₂-monodesmethyl-nizatidine is 60% as active as the parent drug and is excreted primarily by the kidneys (45).

OMEPRAZOLE

Omeprazole, a substituted benzimidazole, is the most potent inhibitor of gastric acid secretion available. Its mechanism of action is direct irreversible inhibition of H⁺,K⁺-ATPase, the gastric proton pump, in the parietal cell. Omeprazole is the most effective peptic ulcer therapy when evaluated at two and four weeks of treatment (6) with

healing rates equivalent to other peptic ulcer medications at six weeks.

Omeprazole is rapidly and completely metabolized by the liver with insignificant amounts of unchanged drug present in the urine. However, approximately 80% of an intravenous and oral dose is excreted as metabolites via the kidney while the remainder is excreted in the stool (11). These metabolites, of which there are at least six, are not known to have any pharmacological activity.

Renal impairment has no effect on the pharmacokinetic profile of omeprazole because of its metabolism by the liver. However, the elimination of metabolites is significantly decreased during renal insufficiency and the percentage recovered in the urine is correlated with creatinine clearance (46). In the presence of renal impairment, total body clearance is complete approximately four days after a single dose, suggesting that metabolites are excreted by alternative methods. No alterations in dose or interval are required in renal failure.

Omeprazole is not known to affect the kidney directly. It has been shown not to affect urinary acidification or renal handling of electrolytes (47) consistent with a specific effect of omeprazole on parietal cells.

SUCRALFATE

Sucralfate is a basic aluminum salt of sucrose octasulfate effective in the treatment of peptic ulcer disease (48) with very few adverse effects; however, special consideration is needed in patients with renal failure.

Sucralfate contains significant amounts of aluminum which is absorbed and results in raised serum aluminum levels in subjects with normal renal function (49,50). Aluminum is rapidly cleared by the kidneys and serum levels quickly return to baseline once therapy is stopped. Daily urinary excretion remains elevated for at least 10 days after discontinuation of a short course of therapy (49).

In patients with impaired renal function, significant increases in serum aluminum concentration and urinary aluminum excretion occur in patients

receiving therapeutic doses of sucralfate (51). Elimination half-life of aluminum is prolonged in renal insufficiency (51) and aluminum accumulation may occur in patients who receive long term sucralfate therapy. Sucralfate has been demonstrated to reduce effectively phosphate levels in chronic renal failure compared to aluminum hydroxide (52,53). However, similar aluminum absorption occurs with both medications, precluding the use of sucralfate as an alternative phosphate binder in chronic renal failure. Aluminum toxicity from sucralfate therapy manifested by dementia, renal osteodystrophy and anemia has been reported (54-56). Sucralfate should be used with caution or avoided in patients with renal insufficiency.

PROSTAGLANDINS

Prostaglandins have numerous effects on the gastrointestinal tract, inhibiting basal gastric acid secretion and secretion stimulated by food and histamine in the stomach (57), they exert a trophic action on the gastric mucosa (58) and increase bicarbonate secretion (59), mucus production and mucosal bloodflow (60,61). Prostaglandin E₂ has been shown to inhibit histamine stimulated acid secretion by inhibiting adenylate cyclase via the inhibitory GTP binding protein and decreasing cyclic AMP production (62). In the kidney, prostaglandins E, D and I reportedly increase renal bloodflow and redistribute flow to the inner cortex (63).

Misoprostol is a synthetic prostaglandin E₁ analogue that has been demonstrated to reduce the volume and concentration of stomach acid (64). Its short half-life, frequent side effects and diarrhea have limited its use in clinical practice, although it has been proven effective in treating peptic ulcer disease (65) and is probably the most effective agent for preventing gastropathy caused by nonsteroidal anti-inflammatory drugs (66). Enprostil is a synthetic prostaglandin E₂ analogue with similar properties to misoprostol (67). Misoprostol is well absorbed and undergoes extremely rapid de-esterification to the biologically active metabolite, misoprostol acid, prior to or during absorp-

tion. No unchanged drug is found in the urine. Misoprostol acid has a very short half-life and is rapidly metabolized to a number of metabolites which are excreted primarily by the kidneys (68). Only 1 to 4% of misoprostol acid is found intact in the urine. Renal insufficiency does not change the pharmacokinetic profile of misoprostol to any great extent and thus dosage change is not required in renal failure (69).

Several studies in rats, evaluating the use of misoprostol in renal transplantation, have demonstrated that it reverses or reduces acute cyclosporine toxicity in the kidney (70,71), with reversal of the cyclosporine-induced acute renal vasoconstriction and decreased glomerular filtration rate. Ryffel et al (72) demonstrated a protective effect of misoprostol against cyclosporine nephrotoxicity, but also found that misoprostol reduced the bioavailability of cyclosporine (and thus decreased serum levels) and possibly interfered with the immunosuppressive effect of cyclosporine. However, prostaglandin E has been shown to prevent rejection in rat renal allograft recipients (73).

A recent double-blind placebo controlled study by Moran et al (74) evaluated the effect of misoprostol in renal transplant recipients treated with cyclosporine and prednisone; they concluded misoprostol reduced the acute rejection incidence in renal transplant patients. There was no statistically significant difference in acute cyclosporine nephrotoxicity between the treated and placebo groups, although nephrotoxicity tended to be higher in the misoprostol-treated patients.

The results of these studies demonstrate a possible role for misoprostol and other prostaglandin analogues in renal transplantation, but further studies are required before regular use can be advocated.

ANTACIDS

Prior to the development of newer drugs to treat peptic ulcer disease, antacids were the drug of choice. Their mode of action primarily is by neutralizing acid and increasing intragastric pH (although aluminum containing antacids may also be cytoprotective) (75).

When used properly, antacids are effective in healing peptic ulcers.

There are several kinds of antacids; the majority are composed of aluminum, magnesium, calcium and/or sodium bicarbonate. In general, the major side effects are related to intestinal absorption of their constituents. Calcium, magnesium and aluminum containing antacids all undergo significant gastrointestinal absorption and are excreted mainly by the kidneys. In patients with impaired renal function, elimination of these cations is reduced; with protracted antacid use accumulation occurs, leading to hypercalcemia (76,77), hypermagnesemia (78,79) and hyperaluminumemia (80,81).

Many other adverse effects can result from excessive antacid use such as nephrolithiasis (82), metabolic alkalosis (83) and the 'milk-alkali syndrome' (82-84). The milk-alkali syndrome consists of hypercalcemia, metabolic alkalosis and renal failure, and is associated with ingestion of large quantities of calcium (as milk or calcium containing antacids) and alkali (antacids). Symptoms include nausea, vomiting, anorexia, polyuria and polydipsia. The condition has become quite

uncommon with the advent of modern therapy for peptic ulcer disease. Patients with underlying renal disease are more susceptible to the milk-alkali syndrome; its pathogenesis is unclear, but it is thought to be due to prolonged hypercalcemia, secondary to increased absorption and decreased renal excretion of calcium with subsequent compromised tubular dysfunction and nephrocalcinosis (85). The alkalosis is due to excessive alkali absorption and vomiting, leading to volume contraction which further exacerbates hypercalcemia and renal failure. Soft tissue calcification can also occur. Treatment with intravenous fluids, furosemide and a low-calcium diet is directed at hypercalcemia.

Aluminum hydroxide was the phosphate binder of choice for many years in hyperphosphatemia treatment in chronic renal failure. After it was demonstrated that aluminum absorption and toxicity occurred (80,81), causing encephalopathy and bone disease, alternative phosphate binders were sought. Calcium carbonate has emerged as the new agent to control hyperphosphatemia. Several studies have demonstrated the efficacy of lowering serum

phosphate levels using oral calcium carbonate without the risk of aluminum toxicity (76,77,86). One-quarter of patients receiving calcium carbonate develop mild hypercalcemia which resolves upon stopping the drug or with use of low-calcium dialysate. Risk concerning metastatic calcinosis (such as corneal, conjunctival, subcutaneous, periarticular) with long term calcium carbonate therapy has never been fully evaluated and thus serum calcium levels should be followed.

Antacids are readily available and may produce a variety of adverse effects especially in the patient with diminished renal function. Aluminum containing antacids should be avoided in patients with renal failure due to the risk of developing aluminum accumulation and toxicity.

Peptic ulcer medications are widely used in clinical practice and have many gastrointestinal and nongastrointestinal applications in patients with renal disease. Generally, antacids are safe with very few renal side effects. However, certain precautions do exist and some medications should be used with caution or avoided in patients with renal failure.

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