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drug and therapeutics bulletin

▼PIRENZEPINE: A SELECTIVE ANTICHOLINERGIC FOR PEPTIC ULCER

Anticholinergic drugs reduce gastric acid secretion and have been used in the treatment of peptic ulcer, but their use is limited by unwanted effects - dry mouth, blurred vision, constipation, difficulty in micturition in men and exacerbation of glaucoma. Pirenzepine (Gastrozepin - Boots) is an anticholinergic drug claimed to act selectively on the stomach, and therefore to promote healing of peptic ulcers whilst being well tolerated. It has been the subject of five sponsored supplements in the Scandinavian Journal of Gastroenterology,[1-5] several reports at the XI and XIIth International Congresses of Gastroenterology (1980 and 1984), and at least two other international sponsored symposia.[6,7] Our assessment is therefore based to a considerable extent upon papers in sponsored publications rather than on studies submitted to the full refereeing procedures of the specialist journals.

PHARMACOLOGY - Pirenzepine has structural similarities to other anticholinergic drugs such as propantheline, and to the benzodiazepines, but being hydrophilic, little enters the brain. Like other anticholinergics it is poorly absorbed from the gut. It is excreted mainly unchanged both in urine and in bile. Repeated doses give steady state concentrations in the plasma within two to three days.[8] Unlike other anticholinergic drugs, it binds with varying affinity in different organs[9] and has therefore led to the definition of two subtypes of muscarinic cholinergic receptors M_1 and M_2; pirenzepine blocks principally the M_1 type. Pirenzepine probably acts on the stomach mainly at the level of the parasympathetic enteric ganglia.[10]

Antisecretory effect - Intravenous pirenzepine reduces peptone-stimulated gastric acid secretion in normal subjects and in patients with duodenal ulcer, but less effectively than cimetidine or ranitidine.[11,12] In healthy volunteers pirenzepine 100-150 mg daily for 2-4 days lowered basal and stimulated acid secretion in response to pentagastrin (by about 30%), insulin (about 40%) and sham feeding (about 50%)[3] - reductions similar to those achieved with other anticholinergics such as atropine and l-hyoscyamine, but less than those usually observed with histamine H_2-receptor blockers. In patients with peptic ulcer, measurements of acid secretion during clinical trials lasting several weeks suggest that pirenzepine reduces maximal acid output much less than the H_2 blockers.[13-16] It may promote ulcer healing by other mechanisms in addition to its weak antisecretory effect.

CLINICAL TRIALS are cited only if ulcer healing was assessed endoscopically. Pirenzepine is usually given twice daily; total daily dosage is cited below.

Duodenal Ulcer - Pirenzepine 100 mg daily healed more ulcers than placebo in most trials,[17-19] and 150 mg daily did so in all trials.[13,20-23] Lower doses were ineffective.[24,25] In comparative trials pirenzepine 100 mg[5,26-30] or 150 mg daily[20,31,32] was as effective as cimetidine 1000 or 1200 mg daily over 4-6 weeks, but in some trials symptoms disappeared much sooner with H_2-blockers - for example[16] ranitidine (3 days) or cimetidine (4 days) compared with pirenzepine (13 days) or placebo (18 days).

Duodenal ulcer maintenance - In small trials pirenzepine 50 mg once[33,34] or twice[35] daily reduced the recurrence of healed duodenal ulcers more than placebo over one year. In comparative trials nightly maintenance treatment with pirenzepine 30 mg was less effective than cimetidine 400 mg[25] and 50 mg was less effective than ranitidine 150 mg.[33] The suggestion that ulcers healed with pirenzepine remain healed after stopping treatment for longer than those healed with an H_2-receptor blocker[36] is not supported by most trials.

Gastric Ulcer - Pirenzepine 100 mg daily healed more ulcers than placebo[19,22] and in a large Italian multicentre trial (437 patients)[5] 100-150 mg was as effective as cimetidine, but there was no placebo group and the healing rate with cimetidine (48%) was below that usually observed. This trial was large enough to detect a 20% difference in healing rates.[37]

Combination Therapy - Well designed studies have shown that the combination of pirenzepine with an H_2-receptor blocker inhibits peptone-stimulated gastric acid secretion more than either drug alone in usual doses.[11,12] This can be useful in patients with Zollinger-Ellison syndrome,[38] and might prove so in treating the rare "resistant" duodenal ulcer.

UNWANTED EFFECTS - No specific adverse biochemical or haematological effects of pirenzepine have yet been reported. Its claimed selectivity for the stomach is only partial and a few patients suffer typical anti-cholinergic symptoms such as dry mouth and eyes, blurred vision and difficulty of accommodation - fewer than with propantheline.[39] At doses of 100 and 150 mg daily, 13% and 17% of 3329 patients had a dry mouth and 0.5% and 0.7% stopped treatment because of this symptom; 1% and 6% had blurred vision which led 0.2% and 1% to stop treatment; urinary delay was rare.[5] Two studies[28,32] suggest that pirenzepine causes more unwanted effects than cimetidine, but other studies have not confirmed this.[27] In one large multicentre study[5] cimetidine caused more headache, skin allergy and endocrine unwanted effects than pirenzepine but withdrawal rates were similar. Some of the trials, however, excluded patients with glaucoma or a tendency to urinary retention, so that these comparisons are difficult to interpret. The data sheet does not, but should, suggest caution in such patients until more is known about this aspect.

CONCLUSION - Pirenzepine is the first anticholinergic claimed to act selectively on the stomach to be marketed, for the treatment of peptic ulcer. Although it is a weaker inhibitor of gastric acid secretion than the H_2-receptor blockers, many trials suggest that it is as effective in healing peptic ulcers. Dry mouth, blurred vision and difficulty in accommodation may occur, but treatment seldom needs to be stopped; more experience is needed of its use in patients with glaucoma or at risk of urinary retention. Pirenzepine relieves symptoms more slowly than the H_2-blockers, and has no advantage over these well-tried drugs. It is certainly effective, and should prove a useful second-line treatment.

Approximate costs of 28 days' treatment -

▼pirenzepine	50 mg b.d.	£19.15
cimetidine	400 mg b.d.	£16.60
ranitidine	150 mg b.d.	£25.60

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'S' identifies papers from proceedings of a manufacturer-sponsored symposium.

SPIROPROP (SPIRONOLACTONE + PROPRANOLOL) FOR HYPERTENSION

Spiroprop (Searle) is a combination of spironolactone 50 mg and propranolol 80 mg marketed for the treatment of hypertension. The manufacturer claims that it is effective when given once daily, and that its two constituent drugs are synergistic in lowering blood pressure. Our criticism of the inflexibility of β-blocker + thiazide combinations[1] applies to this combination too. Spironolactone avoids the unwanted effects of the thiazides such as hypokalaemia, impaired glucose tolerance and hyperuricaemia,[2] but has its own unwanted effects. We recently concluded, however, that thiazide-induced hypokalaemia is not a problem in patients with uncomplicated hypertension;[3] and in any case it can be offset by concurrent use of a β-blocker.[2]

Duration of action - Spironolactone's active metabolite canrenone has a long half-life, making it effective when given once daily.[4] Propranolol has a slow terminal elimination rate during chronic use;[5] once daily dosage reduces blood pressure for 24 hours,[6] and is as effective as thrice daily dosage.[7] In a small study of chronic usage Spiroprop was effective for up to 18 hours after administration.[8]