**Propantheline**

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**Introduction**

Sweating, or diaphoresis, is an essential mechanism of thermoregulation. Aberrant diaphoresis is a recognised complication of diabetic autonomic neuropathy which is manifest at the time of eating (gustatory sweating). This has potentially debilitating physiological, social and psychological effects and is difficult to treat. If avoidance of triggering foods does not improve symptoms, a trial of drug therapy may be indicated. Propantheline has been used for many years to treat gustatory sweating, but its effectiveness compared to more novel agents and multi-modal therapies is uncertain.

**Pharmacology**

Propantheline bromide (Pro-Banthine) is a synthetic analogue of methantheline bromide (Banthine), which was used in the past for the treatment of peptic ulcer disease. It is a synthetic quaternary ammonium compound which acts via two distinct pathways. It is a non-specific acetylcholine antagonist at the muscarinic M1–3 receptors (Figure 1), but it also has a direct musculotropic effect causing relaxation of smooth muscle. Propantheline is the isopropyl analogue of methantheline and has up to five times the antimuscarinic activity, a longer duration of action and a smaller side effect profile.

Propantheline undergoes extensive first pass metabolism, reducing bioavailability significantly to between 10–25%. Metabolism is mainly via hydrolysis with studies demonstrating peak plasma levels at 2 hours and elimination half-life between 2–3 hours post single-dose administration. The pharmacological effect is seen at 1 hour and persists until 6 hours post dose. Elimination is mainly via renal excretion as inactive metabolites (70%) with up to 10% remaining as intact propantheline.

The dual mechanism of action produces an array of effects with possible clinical benefits, including decreased secretions (anaesthesia), decreased gastric acid production (peptic ulcer disease) and smooth muscle relaxation (enuresis/gastro-intestinal spasm disorders). Specific benefits for hyperhidrosis (excessive...
sweating) and gustatory sweating are attributed to its antagonism of acetylcholine at M3 receptors of glandular tissue.

Tolerability of anticholinergic side effects is widely reported as a limiting factor. These include dry mouth, bradycardia, constipation and urinary retention among others. The elderly population are particularly susceptible to intensified symptoms due to polypharmacy and comorbidities. Awareness of precautions and contraindications including gastrointestinal obstructive diseases and closed-angle glaucoma is necessary.

Toxicity due to delayed gastroparesis is reported with digoxin. Propantheline overdose will result in intensification of usual side effects, but at extreme doses propantheline exhibits nicotinic action that may result in paralysis through neuromuscular blocking.

Propantheline is the only antimuscarinic and oral therapy licensed for the treatment of hyperhidrosis in the UK.

Trials of safety and efficacy
The use of antimuscarinic drugs for excessive sweating developed from a case report in 1950 where dry hands were observed as a side effect when methantheline was prescribed for the treatment of peptic ulcer disease. In a mechanistic study, both methantheline and propantheline reduced the production of sweat in response to galvanic skin stimulation compared to placebo. Case reports of generalised hyperhidrosis in two patients following spinal cord injury, and of one patient with gustatory sweating post thyroidec- tomy, reported propantheline as effective in reducing symptoms.

In a multi-centre, randomised, placebo-controlled trial of methantheline bromide, 339 patients were randomised. On day 28±1, the mean axillary sweat production was 99mg for methantheline bromide and 130mg for placebo compared with 168mg and 161mg respectively at baseline (p=0.004). Quality of life scores were also improved. Tolerability was good for both groups. The most frequent adverse event was dry mouth. No such study has been performed for propantheline.

Oxybutynin and glycopyrrolate are anticholinergic drugs that may also be used to treat hyperhidrosis although not licensed for this indication. In a head-to-head study of patients with enuresis, propantheline was described as a less effective but more tolerable therapy than oxybutynin. Both symptom improvement and adverse events were significantly greater for oxybutynin than propantheline; 58.2% versus 44.7%, and 63% versus 44%, respectively.

Specific evidence for use in diabetes
No evidence of trials supporting the use of propantheline in gustatory sweating could be found although it is referred to as a possible treatment within review articles of diabetes and diabetic autonomic neuropathy. A single metabolic study was found investigating growth hormone suppression with atropine and propantheline in people with diabetes and concluded that propantheline was ineffective with a high incidence of adverse events.

Discussion
Gustatory sweating is an increasingly recognised complication of diabetic autonomic neuropathy. Currently, it is thought to be irreversible and treatment consists of symptom control. Propantheline may be an effective treatment for some patients if avoidance of triggering food does not reduce symptoms. Although the only licensed oral treatment, propantheline is one of several drug therapies which may be used to reduce symptoms. Its use is historically based and evidence of its efficacy, safety and superiority over other treatment modalities is lacking.

As a result of the high prevalence of side effects with oral therapies, other treatment modalities have been explored. These include topical glycopyrrolate, topical antiperspirants, botulinum injections, and in patients with severe and disabling symptoms surgery may be considered. Comparative studies of oral and topical antimuscarinic medication and other treatment modalities in gustatory sweating and hyperhidrosis are required.

Declaration of interests
There are no conflicts of interest declared.

References