Ipratropium bromide delivered orally by metered dose inhaler does not decrease salivary flow in normal subjects

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A randomised placebo-controlled cross-over group study was conducted to ascertain the occurrence and duration of xerostomia induced by 240 µg (high dose) and 120 µg (low dose) of ipratropium bromide (IPB) delivered by metered dose inhaler (MDI) into the mouth in normal subjects. Salivary output was higher with both doses of IPB than with placebo though the differences were not statistically significant. IPB was less palatable than placebo as indicated on visual analogue scale (VAS) and the taste of the drug may have caused a reflex increase in salivary output from the major salivary glands which would have masked any possible local effect of the drug on the smaller submucosal glands of the mouth. IPB delivered into the oral cavity by MDI is therefore not a suitable treatment for hypersalivation.

Keywords ipratropium bromide antimuscarinics drug side effects
salivary flow

Introduction

IPB is an anticholinergic agent widely used in the treatment of asthma and obstructive airways disease. Xerostomia has been reported with inhaled and nasal IPB (Groth *et al.*, 1983) suggesting that IPB delivered into the oral cavity might be a simple and effective treatment for hypersalivation. In this study we wished to assess the effect of IPB delivered into the oral cavity by MDI on salivary output in normal healthy subjects.

Methods

Twelve volunteers (nine female, age range 22–33 years) took part, all of whom were healthy, free from oral pathology, salivary gland disease or other significant disease. The study was approved by the Queen Charlotte's and Hammersmith Hospital Ethics Committee and all subject gave their written consent.

A randomised placebo controlled cross-over study was performed. Subjects attended fasting on 3 separate days within a 14 day period, with at least 24 h between attendances. IPB 120 µg, 240 µg or placebo was given on each test day. A single puff of the inhaler was actuated into the subject's mouth by the investigator every 5 s to a total of 6 puffs. The nose was occluded and the breath held during discharge of the inhaler but normal nasal breathing continued between discharges.

Subjects were asked not to swallow until 10 s after the last puff.

Salivary output was measured by inserting a dental roll (cotton wool cylinder) into each buccal and lingual sulcus. These were left in place for 1 min, then discarded. Four pre-weighed rolls were then inserted for 1 min, removed and re-weighed. The difference in weight was taken as the salivary output in g min⁻¹. A further four pre-weighed rolls were inserted to give duplicate readings. The mean of these readings was taken as the salivary output.

Following a 30 min acclimatization period in a quiet temperature controlled environment the test measurement procedure was carried out 30 and 15 min prior to and 15, 30, 60, 90 and 180 min after drug administration. Thirty minutes before, and 15, 60 and 180 min after drug administration, subjects recorded on a 10 cm VAS the degree of dry mouth which they had experienced from 'completely dry' to 'very much wetter than normal'. This was carried out immediately before insertion of the dental rolls. Palatability of the drug was recorded 180 min after drug administration using a 10 cm VAS from 'very pleasant' to 'very unpleasant'. The mean of the salivary outputs 30 and 15 min prior to drug administration was taken as the baseline salivary output on each study day. The change from baseline was calculated at each time point after drug administration and treatments were then compared by two way analysis of variance

(ANOVA). Area under the curve for each treatment was calculated by the trapezoidal rule and these were also compared by ANOVA. Visual analogue scores for dryness of mouth and palatability of the drug were compared by Kruskal-Wallis ANOVA for non-parametric data.

Results

There was no significant difference between baseline salivary outputs on the 3 study days ($PI = 0.74 \pm 0.11$, low dose IPB = 0.84 ± 0.11 , high dose IPB = 0.82 ± 0.11). Change in salivary output from baseline was higher with both doses of IPB than with placebo but the differences were not statistically significant (area under the curve with $PI = -1.51 \pm 10.62$, low dose IPB = 4.84 ± 15.9 , high dose IPB = 22.25 ± 12.42 , $P = 0.43$), (Figure 1).

There was no significant difference between the VAS scores for dryness of mouth on any day either before or after drug administration (Figure 2). VAS scores for

Figure 1 Effect of ipratropium bromide on salivary output in normal healthy volunteers. ▲ IPB 240 µg, ▼ IPB 120 µg, ○ placebo.

Figure 2 Effect of ipratropium bromide on VAS for dryness of mouth in normal healthy volunteers. ▲ IPB 240 µg, ▼ IPB 120 µg, ○ placebo.

Figure 3 Palatability of ipratropium bromide in normal healthy volunteers. * $P < 0.05$ vs placebo.

palatability showed that both low dose and high dose IPB were more unpleasant than placebo ($PI = 49.3 \pm 4.00$, low dose IPB = 69.4 ± 4.19 , high dose IPB = 71.9 ± 4.23 , $P = 0.003$) (Figure 3).

Discussion

There are several small but important groups of patients for whom hypersalivation or drooling may be a problem, including Parkinsonism, mental handicap, post-operative patients, and conditions affecting pharyngeal motility. Various treatments are available for drooling but those which are effective have unpleasant and often unacceptable side effects (Brodtkorbe *et al.*, 1988; Bruno *et al.*, 1989). Dry mouth has been reported with inhaled IPB, and as 90% of the inhaled drug remains in the oropharynx (Newman *et al.*, 1980), this suggests that IPB might be a simple, effective treatment for hypersalivation and drooling. In this study however salivary output was in fact higher with both doses of IPB than placebo though the differences were not statistically significant.

Only minute quantities of IPB are detectable in plasma after inhaled or oral administration (Deckers, 1975). It is not surprising therefore that there are no reports of significant systemic side effects with inhaled IPB therapy. Systemic absorption may occur with nasal IPB, particularly in rhinitis (Kaila *et al.*, 1990), but systemic side effects occur only with very large nasal doses (Kirkegaard *et al.*, 1987). Xerostomia however, is a relatively common complaint in patients on high dose inhaled or nasal IPB therapy, and in view of the poor absorption of the drug, any true decrease in salivary output must be due to a local effect of the drug on the submucosal salivary glands of the mouth. IPB was significantly less palatable than placebo in this study as indicated on VAS and the taste of the drug may have caused a reflex increase in salivary output from the major salivary glands which would have masked any possible local effect of the drug on the smaller submucosal glands of the mouth. It is possible that patients on long-term inhaled IPB may become used to the taste of the drug such that reflex increase in salivation no longer occurs and true xerostomia may

become manifest through a local effect of the drug in the mouth. There are no reports of actual measures of salivary output in patients on long-term inhaled IPB however.

We conclude that IPB administered directly into the

oral cavity is not a suitable treatment for hypersalivation. Further studies may determine whether a true decrease in salivary output occurs in patients on long-term inhaled IPB who complain of dry mouth.

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(Received 15 January 1992,
accepted 8 April 1992)