

the injection of luteinising hormone releasing hormone is of considerable interest. At three months this rise was absent in samples taken one hour after injection but it was seen in all patients at six months and was more appreciable at 12 months. The mechanism for the rise is unclear but it may arise from either a change in the receptors that makes them unable to accept the analogue or an acceleration in regulation by the receptors. Further studies are needed to explain the mechanism. Rises in testosterone concentration were seen in only three patients, all of whom developed disease progression. The reason why testosterone concentration failed to rise in all patients may relate to prolonged suppression of testicular activity by the analogue.

Daily administration of luteinising hormone releasing hormone analogues is not recommended as a long term treatment for carcinoma of the prostate because of its failure to suppress luteinising hormone and testosterone concentrations. The mechanism for this failure has considerable implications in the long term use of peptide analogues.

<sup>1</sup> Allen JM, O'Shea JP, Mashiter K, Williams G, Bloom SR. Advanced carcinoma of the prostate: treatment with a gonadotropin releasing hormone agonist. *Br Med J* 1983;286:1607-9.

<sup>2</sup> Chisholm GD, Beynon LL. The response of the malignant prostate to endocrine treatment. In: R Ghanadian, ed. *The endocrinology of prostate tumours*. Lancaster: MTP Press, 1983;241-62.

<sup>3</sup> Emmett JL, Greene LF, Papanitiou A. Endocrine therapy in carcinoma of the prostate gland: 10 year survival studies. *J Urol* 1960;83:471-84.

<sup>4</sup> Mellinger GT, Bailar III JC, Arduino LJ, et al. The Veterans Administration cooperative urological research group. Treatment and survival of patients with cancer of the prostate. *Surg Gynecol Obstet* 1967;124:1011-7.

Accepted 4 June 1984

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## Bronchoconstriction induced by ipratropium bromide in asthma: relation to hypotonicity

The antimuscarinic agent ipratropium bromide has been reported to cause paradoxical bronchoconstriction when administered by nebuliser to patients with asthma.<sup>1-3</sup> The mechanism of this bronchoconstriction has not been clearly defined, although an idiosyncratic response to the bromide moiety was suggested from a study of one patient.<sup>2</sup> The importance of solution tonicity with respect to this bronchoconstriction, however, has not been investigated. As commercially available ipratropium bromide solution is hypotonic, and inhalation of nebulised hypotonic solutions may produce bronchoconstriction in asthma,<sup>4-5</sup> we decided to investigate the effect of solution tonicity on this paradoxical airway response.

### Patients, methods, and results

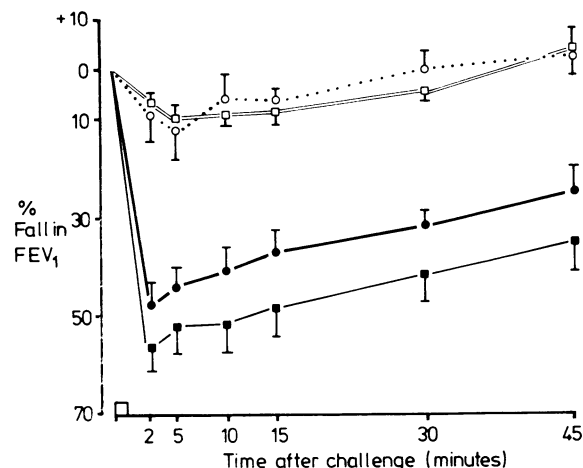
Eight asthmatic subjects with marked non-specific airway reactivity were selected for study, and all were found to bronchoconstrict with nebulised ipratropium bromide. They subsequently participated in a double blind, placebo controlled, randomised study. On four separate days, after omitting their usual medication for at least six hours, each subject received one of four nebulised solutions: commercially available ipratropium bromide (0.025%) in hypotonic vehicle (osmolality 7.5 mmol (mosmol)/kg); the hypotonic vehicle alone (7.5 mmol/kg); ipratropium bromide in isotonic vehicle (296 mmol/kg); and nebulised isotonic 0.9% sodium chloride alone (296 mmol/kg). All solutions were nebulised using an Inspiron minijet nebuliser (Bard, Pennywell, Sunderland) at a flow of 8 l/min with a 4 ml starting volume. Patients inhaled the aerosols through a mouthpiece during tidal breathing for three minutes. Under these conditions approximately 1 ml of the test solution was delivered, on inspiration, by the nebuliser. Measurements were made of the forced expiratory volume in one second (FEV<sub>1</sub>) before and 2, 5, 10, 15, 30, and 45 minutes after nebulisation.

On a separate occasion each subject's non-specific bronchial reactivity was measured as the provocative concentration of methacholine required to produce a 20% fall in the FEV<sub>1</sub> (PC<sub>20</sub>).

Statistical analysis was by Student's *t* test and Duncan's multiple range test.

The patients' geometric mean PC<sub>20</sub> was 0.22 g/l (range 0.10-0.50). There were no significant differences in the mean baseline FEV<sub>1</sub> values (litres) on

any of the four separate days when the patients received either hypotonic ipratropium bromide (3.01 (SEM 0.26)), isotonic ipratropium bromide (2.95 (0.25)), hypotonic placebo (2.96 (0.23)), or isotonic saline (3.13 (0.30)). Both hypotonic solutions caused bronchoconstriction, with maximum falls in FEV<sub>1</sub> two minutes after nebulisation of 55.5 (SEM 5.5)% with hypotonic placebo and 48.0 (5.2)% with hypotonic ipratropium bromide (*p* < 0.01; figure). The bronchoconstriction with the hypotonic placebo was significantly greater than with the hypotonic ipratropium bromide at all time points (*p* < 0.05). In these patients with pronounced airway reactivity both isotonic ipratropium bromide and saline solutions caused small falls in FEV<sub>1</sub> of 12.5 (SEM 6.1)% and 8.4 (3.4)% respectively (figure). These falls were significantly less at all time points when compared with the FEV<sub>1</sub> responses to the hypotonic solutions (*p* < 0.01).



Changes in FEV<sub>1</sub> after nebulisation of hypotonic placebo (■), hypotonic ipratropium bromide (●), isotonic ipratropium bromide (○), and isotonic saline (□). Points are means. Bars are SEM.

### Comment

This study clearly shows that nebulised ipratropium bromide, as now marketed, causes bronchoconstriction in a group of asthmatic patients with pronounced non-specific airway reactivity. The bronchoconstriction was reproduced by the vehicle alone and could be largely attenuated by adding sodium chloride to render the solution isotonic. We therefore believe that the paradoxical airway response produced by commercially available ipratropium bromide nebuliser solution is due to its hypotonicity. These results are not consistent with an idiosyncratic response to the bromide moiety of this compound as suggested by Patel and Tullett.<sup>2</sup> In their study no details of the tonicity of the nebulised solutions were given. The recognised association between tonicity of nebulised solutions and bronchoconstriction in asthma suggests that hypotonicity is a more widely applicable mechanism to account for bronchoconstriction induced by nebulised ipratropium bromide.<sup>5</sup> Thus while nebulisation of the currently available ipratropium bromide nebuliser solution may cause bronchoconstriction in asthma, reformulation as an isotonic solution would prevent this risk.

JSM was supported by an MRC project grant, and PHH is in receipt of a BMA TV James fellowship.

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(Accepted 8 June 1984)

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