completely and frequently emptied. Forty eight per cent of specimens showed pyuria and bacteriuria before the start of intermittent self catheterisation and 42% thereafter. Sixteen patients were followed up for from one to 22 years (mean 3·4 years). Ten remained radiologically and functionally normal. Five showed damage (three with hydronephrosis and two with scarring) that had been present at the start. One woman, an insulin dependent diabetic aged 73, developed slight impairment of renal function.

Discussion

We did not usually recommend intermittent self catheterisation for men because of the increased risk of trauma, false passage, stricture, and epididymo-orchitis. In women, however, if catheterisation proved unhelpful it was stopped without irreversible effects; if it was successful the results were immediate. A severely arthritic woman who had previously had to void six times at night could sleep undisturbed after removing a litre of residual urine. A young girl, recently paraplegic, was delighted to discard her indwelling catheter tubing and bag to wear her usual clothes again. A woman with multiple sclerosis succeeded in self catheterisation despite intention tremor, visual impairment, and instability of her back when balancing on the lavatory.

The remarkable determination of some of these patients arose from the handicap imposed by incontinence, severe urinary infections, and episodes of acute retention. Some had been admitted to hospital frequently and had had numerous investigations and multiple operations. Once self catheterisation was established admissions to hospital stopped. Later problems were mainly iatrogenic from efforts to maintain a sterile urine. Unnecessary administration and frequent changes of antibiotics aroused anxiety, and forcing fluids sometimes caused incontinence. We found that bacteriuria was less common in those patients who inserted the catheter frequently in order to stay dry even when they also restricted their fluids. The long term results of self catheterisation in adults are not known, but the short term results can be rewarding.

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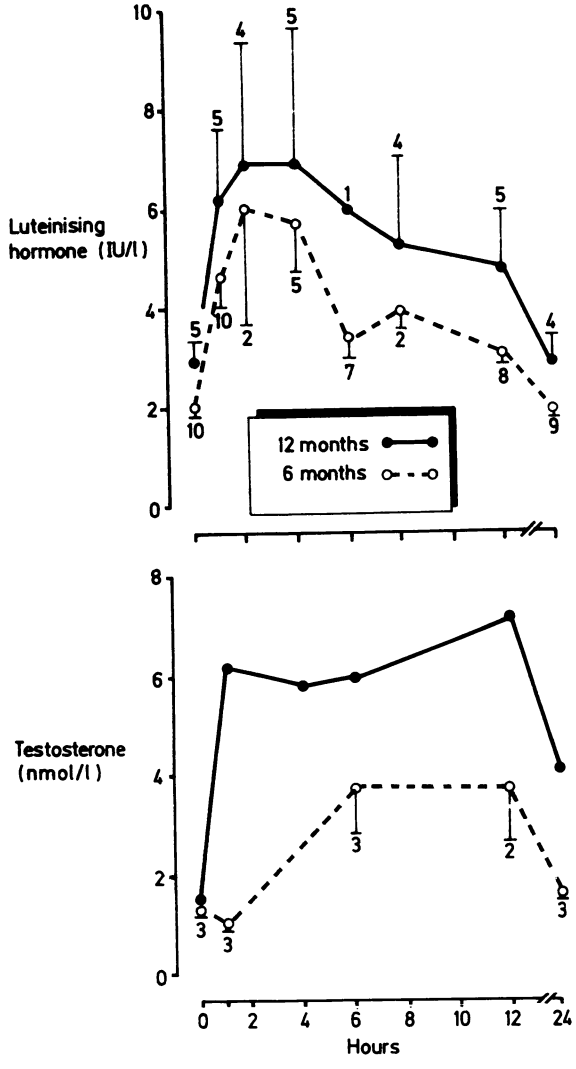
Failure of long term luteinising hormone releasing hormone treatment for prostatic cancer to suppress serum luteinising hormone and testosterone

Administration of luteinising hormone releasing hormone analogues to patients with cancer of the prostate results in stimulation followed by depression of the regulation of pituitary receptors with a fall in serum luteinising hormone and testosterone concentrations. Castrate testosterone concentration is achieved within 21 days. We have previously reported our satisfactory initial experience of using the luteinising hormone releasing hormone analogue ICI 118630 in the treatment of 10 patients with advanced metastatic carcinoma of the prostate.[1] We now report a longer clinical and endocrine follow up of 15 patients.

Case reports

Fifteen patients with prostatic cancer received 250 μg of the luteinising hormone releasing hormone analogue twice daily subcutaneously for one week and thereafter 250 μg daily. They were followed for a mean of 12·7 months (range 1-23 months). Clinical response was assessed according to the criteria of the British Prostate Group.[2] One patient died at one month without responding. At four months responses were complete for three, partial for eight, and stable for three. Six patients subsequently relapsed, two from each response group. These six were free from progression for a mean of 9·5 months. The remaining patients have shown no evidence of progression for a mean of 12·1 months.

Serum samples were obtained before injection and at 1, 2, 4, 6, 8, 12, and 24 hours afterwards, and these were taken from 10 patients after six months of treatment and from the remaining five patients after six and twelve months. All patients showed a rise in serum luteinising hormone concentration after injection, which increased as treatment continued (figure). Three patients showed a rise in testosterone concentration above basal at 6 months and of these, one was also studied at 12 months (figure). Three patients with a rise in testosterone had evidence of disease progression. Of the nine patients with no rise in testosterone, only one showed disease progression.



Mean (SEM) serum luteinising hormone and testosterone concentrations before (0 hour) and after injection with 250 μg of luteinising hormone releasing hormone analogue ICI 118630 at six and 12 months. Each point represents the number of patients from whom samples were taken.

Conversion: SI to traditional units—Testosterone: 1 nmol/l ≈ 0·3 ng/ml.

Comment

The primary response of 14 of the 15 patients compares favourably with the findings of other studies using conventional endocrine treatment with oestrogens or orchidectomy, or both.[3,4] By 15 months, however, six patients had relapsed with progressive disease. Poor patient compliance accounted for one of these cases. The remaining patients had suppressed serum luteinising hormone and testosterone concentrations before their daily injection. The progressive rise in serum luteinising hormone concentration for up to eight hours after

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.

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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.[1-3] 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.[2] 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,[4-5] we decided to investigate the effect of solution tonicity on this paradoxical airway response.

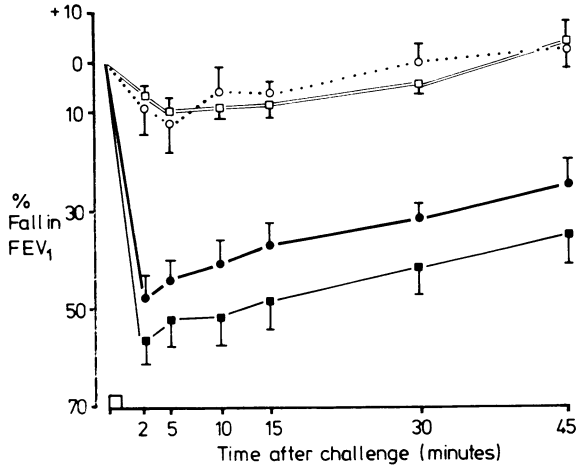
Patients, methods, and results

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_1) 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_1 (PC_{20}).

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

The patients' geometric mean PC_{20} was 0·22 g/l (range 0·10-0·50). There were no significant differences in the mean baseline FEV_1 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_1 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_1 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_1 responses to the hypotonic solutions ($p<0·01$).



Changes in FEV_1 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.[2] 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.[5] 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.

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