Age and Ageing 1995;24:287–291

Oxybutynin with Bladder Retraining for Detrusor Instability in Elderly People: A Randomized Controlled Trial

GEORGE SZONYI, DAVID M. COLLAS, YEW Y. DING, JAMES G. MALONE-LEE

Summary

The aim of this study was to examine the efficacy of oxybutynin plus bladder training in the treatment of detrusor instability in frail elderly patients living independently in the community. It was a randomized, double-blind, placebo-controlled parallel-group trial of oxybutynin in 57 elderly patients (mean age 82.2, SD 6.06), with frequency and incontinence due to detrusor instability. After a 2-week run-in period patients received a bladder training and drug or placebo for the next 6 weeks. Outcome measures were changes in frequency and incontinence, recorded throughout on diary charts, and subjective evaluation of symptoms ('better'/'not better', and using a four-point scale 'cure' to 'no change').

Oxybutynin was superior to placebo in reducing daytime frequency [95% confidence interval (CI) of difference in change in frequencies totalled over 14 days was −27.0, −6.0; p = 0.003] and in producing subjective benefit (at day 29 only), when 24/28 (86%) patients on oxybutynin described benefit compared with 16/29 (55%) on placebo (p = 0.02). There was no difference between the groups in reduction of incontinent episodes. The median dose of oxybutynin titrated for therapeutic effect was 5 mg/day, and for placebo 10 mg/day (CI of difference 0.001, 5.001; p = 0.05). Side-effects reported were of similar frequency (50%) in the two groups. We conclude that oxybutynin with bladder training is superior to bladder training alone in reducing frequency due to detrusor instability in very elderly people living at home.

Introduction

Detrusor instability is a common cause of urinary incontinence in late life. Bladder retraining, which takes a variety of forms [1], is an important method of management [2], which can be supplemented with drug therapy. Several agents have been proposed, imipramine [3], propantheline [4], and oxybutynin [5–7]. The latter is the most widely used, and its efficacy in reducing symptoms has been demonstrated in women, both middle-aged (mean age 46) [7] and postmenopausal (mean age 61) [5]. By contrast it has been shown to be ineffective for chronically disabled elderly people in long-term institutions [6, 8], but has not hitherto been studied in frail elderly people living independently. A trial of terodiline with bladder retraining was reported from this centre and failed to show any benefit over placebo [9]. That drug has since been withdrawn because of serious adverse effects.

Oxybutynin is a tertiary amine with unselective antimuscarinic properties, although detrusor effects are mediated through M3 receptors. It is also a local anaesthetic and smooth muscle relaxant [10]. The aim of this study was to test the efficacy of oxybutynin in elderly ambulant patients with detrusor instability.

Methods

This was a randomized, double-blind, parallel-group study with dose titration. After a run-in period of 2 weeks, during which patients kept a diary chart of their frequencies of micturition and episodes of incontinence, patients were reviewed (day 15) and randomized to placebo tablets twice daily or oxybutynin 2.5 mg twice daily. All patients were instructed in bladder retraining which was maintained throughout the treatment period. They were asked to delay micturition for as long as possible whenever they experienced the need to pass urine and to try by this means to reduce their frequency. The patients were reviewed on days 29 and 43 when their dose was adjusted in line with response and side-effects, and their symptoms and the contents of their diary charts noted: patients left the study on day 57.

Outpatients of either sex aged over 70 with symptoms of urinary frequency, urgency and urge incontinence were recruited. Patients had to be mobile, able to attend an outpatient department, able to keep a diary chart and willing to give consent. We excluded patients with urinary infections at the time of recruitment and patients with severe hepatic or

renal disease, glaucoma, or uncontrolled diabetes. Patients on concomitant anticholinergic therapy with imipramine or propantheline were also excluded. The study was approved by the local ethics committee and all patients gave a witnessed written consent.

Before patients were included in the study they underwent a physical examination, with assessment of cognitive function by the Folstein Mini Mental State Evaluation (MMSE) and detrusor instability was diagnosed by water cystometry, filling at 1 ml/s, using the criteria of the International Continence Society [11]. Blood samples were taken for baseline haematology and biochemistry and a catheter specimen of urine was cultured. The randomization was achieved by allocating tablets in random permutations of blocks of four patients at a time.

Patients maintained a bladder chart throughout the study, recording with a tick, to the nearest hour, each micturition and each incontinence episode. At each review the charts were collected and the recordings summed over each period of a week. Their subjective response was assessed in two ways, firstly by asking 'Has the treatment been of benefit to you (yes or no)?', and secondly by asking them to grade their improvement on a ranked ordinal scale; 'No change', 'Marginal improvement', 'Significant improvement', 'Cure'. Patients were also questioned about side-effects; specifically they were asked whether they had experienced dryness in the mouth, about its timing and severity, and whether it interfered with swallowing or speech, or prompted them to drink more. Other anticholinergic side-effects specifically asked after included hesitancy, constipation and blurred vision, with severity being graded on a five-point scale from nil (0) to unbearable (4). Their tablets were counted in order to check compliance. If there had been no objective or subjective improvement the dose of the drug was increased, in a stepwise manner, until either a response was obtained, side-effects became intolerable, or a dose of 5 mg three times daily had been reached. Blood samples were taken in order to check haemoglobin, blood cell counts, urea, electrolytes and hepatic function.

Statistical analysis. The sample numbers were estimated from an expected placebo response of 35% and an expected drug response of 75% [4, 6, 7]. With a probability of a type I error of 0.05 and probability of type II error of 0.10, a sample of 30 patients in each group was calculated as achieving sufficient power (85%–95%). The classification data were analysed for differences between groups using Fisher's exact probability test. Comparisons of frequency data were achieved with the Mann–Whitney U test applied to the median changes in variables, quoting the test statistic W.

Results

Sixty patients (mean age 82.19, SD 6.06, range 72–98 years) were entered into the study, 30 randomized to each group. The groups were well matched for age, sex (with women predominating at 14 : 1 in both groups), weight (mean weight 67.4 kg, SD 14.92) and MMSE score (mean 28.9, SD 7.6). The urodynamic characteristics are given in Table I, and are also well matched, with only the mean maximal flow rate differing significantly between groups, being higher in the treatment group ($p = 0.03$).

One patient in the placebo group and two randomized to active treatment failed to attend the first review and so no data were available for analysis. All other patients provided data which could be analysed on an intention-to-treat basis. Not all patients kept the diary charts as requested, but diary data were available for analysis from 28 patients on

Table I. Principle urodynamic characteristics of patients

	Oxybutynin		Placebo	
Variable	Mean	SD	Mean	SD
Free flow rate (ml/s)	4.5	6.6	7.5	8.8
Free flow volume (ml)	82.4	88.1	92.2	82.1
First residual volume (ml)	45.3	70.2	43.5	50.9
Bladder capacity at first sensation (ml)	156.3	111.5	191	106
Detrusor pressure at first sensation (cmH_2O)	14.7	10.4	14.2	9.2
Maximum filling detrusor pressure (cmH_2O)	31.9	14.9	30.9	13.5
End filling pressure (cmH_2O)	21	13.1	18.4	12.1
Bladder capacity (ml)	305.1	140.7	370	176
Maximum flow rate (ml/s)*	8.7	7	7.5	8.5
Voided volume (ml)	278.9	141.3	338	150
Second residual volume (ml)	42	98.9	30	81.6

*Mean maximal flow rate was significantly higher in the treatment group ($p = 0.03$).

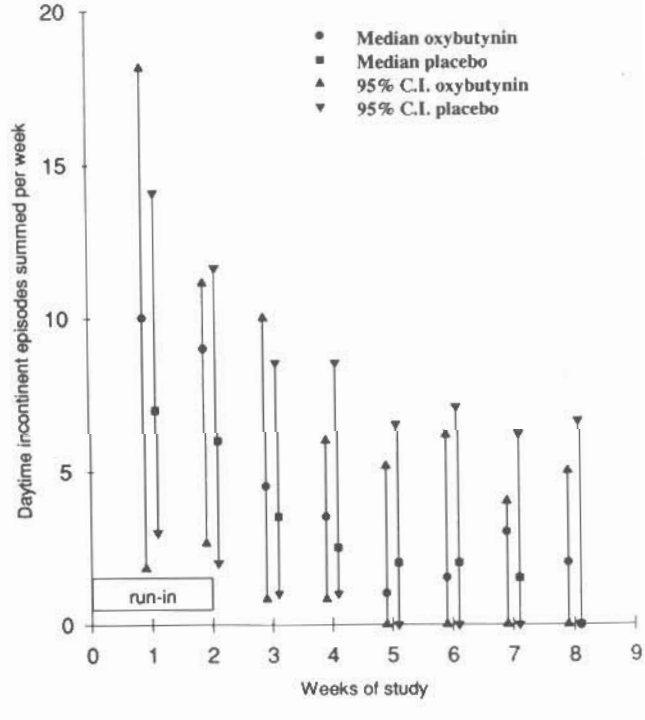

Figure 1. Median daytime incontinent episodes summed per week with 95% confidence intervals.

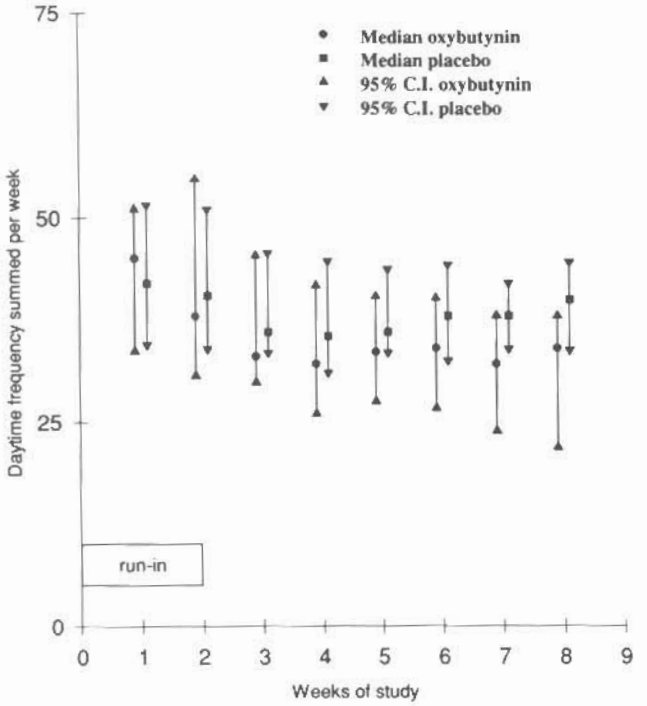

Figure 2. Median daytime frequency summed per week with 95% confidence intervals.

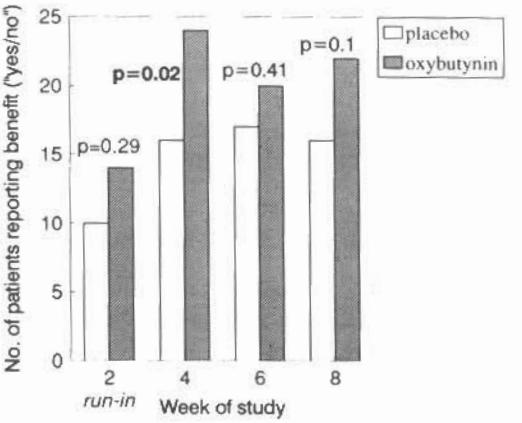

Figure 3. Subjective benefit during study.

active treatment. Five patients on placebo withdrew early (four provided analysable data); one because of heartburn, one because of vertigo and three because they did not wish to persist with the protocol. Eight patients on oxybutynin withdrew early (six provided analysable data); three because of oesophageal reflux, one because of falls, three because they did not wish to persist with the protocol and one died from a stroke.

The bladder charts showed that 22/28 (79%) of patients randomized to placebo were incontinent during the run-in period, and 20/24 (83%) of those randomized to oxybutynin (Figure 1). The reduction in urinary frequencies and episodes of incontinence over the study period was calculated by subtracting the total episodes over the last 14 days from the total over the first 14 days (the run-in period). There was a greater reduction in daytime frequencies in patients taking oxybutynin compared with those on placebo ($W = 577$; 95% CI difference in change −27.0, −6.0; $p = 0.0025$). There were no differences in the median changes, totalled over 14 days, in nocturia (median change −6; 95% CI of difference in change −5, 7.0), daytime incontinence episodes (median change −9.5; 95% CI of difference in change −11.0, 3.0) and episodes of nocturnal enuresis (median change −1; 95% CI of difference in change −3.0, 2.0) between the two groups. A week-by-week analysis of the trial is shown in Figures 1 and 2. Comparison between the treatment and the control groups shows (Figure 2) a gradually increasing separation in the median daytime frequencies (totalled for each week of the study), but no such separation is seen in the number of episodes of incontinence (Figure 1).

The patients' assessments of response on the binomial scale are shown in Figure 3. At day 29, 24/28 (86%) of patients on oxybutynin and 16/29 (55%) on placebo described a benefit ($p = 0.02$). At day 43, 20/28 (71%) of patients on oxybutynin described a benefit, and 17/29 (59%) on placebo described a benefit ($p = 0.41$). At the end of the study, 22/28 (79%) of patients on oxybutynin described a benefit, and 16/29 (55%) on placebo described a benefit ($p = 0.09$).

The subjective data collected on the four-point ranked ordinal scale are illustrated for days 29 and 57 in Table II. A statistically significant difference between groups in favour of active treatment was identified on day 29 but not at any other stage.

Table II. Patient's subjective response

	Day 29		Day 57	
Four-point ordinal scale	Treatment	Placebo	Treatment	Placebo
No change	5	13	7	14
Marginal improvement	7	8	3	4
Significant improvement	15	8	14	8
Cure	1	0	4	3

Table III. Side-effects and compliance

Side-effect	Treatment (%)	Placebo (%)
Dry mouth	93	86
Blurred vision	50	59
Heartburn	57	45
Constipation	50	45
Dry skin	50	59
Poor compliance	20	20

At the end of the study the median dose of oxybutynin being taken by those on active treatment was 5 mg per day and for those on placebo the median dose was 10 mg per day ($W = 1041$; 95% CI of difference 0.001, 5.001; $p = 0.05$). Poor compliance was identified in those patients who took less than 75% of their tablets. Six (20%) of patients randomized to placebo showed poor compliance as did six (20%) of those randomized to active drug (Table III). Side-effect profiles were obtained on direct questioning. The incidences in the two groups were very similar and are illustrated in Table III. No alterations in biochemistry or haematology were noted.

Discussion

Most previous studies have used visual analogue scales to assess response of symptoms to treatment, two also used frequency charts kept for 3-day periods only [6, 12], and two others an incontinence record kept by nursing-home staff [5, 11]. This study is the first to combine subjective assessment with recording of both frequency and incontinence throughout the trial, and the first to study elderly patients living in the community. It demonstrates the efficacy of oxybutynin in this age group in reducing frequency and producing subjective benefit when used in conjunction with bladder retraining. A previous study, using a similar protocol to test the drug terodiline, failed to demonstrate such benefit.

The results of this study also underline some important points in relation to the treatment of detrusor instability. The median dose of oxybutnin remained at or returned to 2.5 mg bd, the starting level, at the end of the study, although the protocol allowed upward titration of dose at each assessment until a satisfactory therapeutic response had been achieved, or until side-effects required a reduction or limited further increase. As the incidence of side-effects was similar in the two groups, the difference between the median daily dose of 5 mg in the oxybutynin group and 10 mg in the placebo group supports the view that the drug is efficacious. The dose of the drug which was used (mode = 2.5 mg bd) was lower than that recommended in the formulary but in line with previous observations [12].

The subjective assessment favoured oxybutynin but this was statistically significant at the first visit (Day 29) only. This may reflect the difficulty patients have at later visits in comparing current status with the baseline situation (the run-in period) rather than with that at their previous visit. Though subjective benefit was perceived after 2 weeks it was 5–6 weeks on therapy before maximum reduction in frequency was recorded (Figure 2). This lag may reflect a reluctance of patients to alter established micturition behaviour for fear of incontinence. Eventually the reduction in urgency gives them the confidence to reduce frequency of micturition. These data suggest that it is inadvisable to increase the dose or assume a failure of response before 6 weeks have elapsed.

The study failed to demonstrate efficacy of oxybutynin in reducing the number of episodes of incontinence. This is in line with the findings of the only two other studies in which incontinence was measured, both in nursing homes, in one case with bladder training [8] and in the other without [6]. In the current study the number of incontinent episodes fell in both groups, probably owing to the effect of bladder training, though the fall did not reach the level of statistical significance, as it had done in the similarly designed study of terodiline. Here the range varied widely between patients and confidence limits were correspondingly wide. This accords with an examination of outcome measures in detrusor instability (in 350 adults) which found that levels of incontinence may be too low and variable for changes in comparative studies to reach statistical significance unless numbers are very large [13]. Patients with detrusor instability will avoid incontinence by increasing frequency of micturition and therapeutic response should be assessed by measuring reduction of this frequency.

The subjective response to the therapy was measured on a binomial scale as well as a four-point ranked ordinal scale. As the sample numbers were calculated on the assumption of a binomial measure rather than a four-point scale the interpretation of Table II requires some caution. The data were obtained from elderly people who were ambulant and independent: there must remain doubt over the efficacy of oxybutynin for elderly patients in long-term institutions [6]. The sample was predominantly female and differences in the patterns of detrusor instability have been identified between the sexes [14]. Lastly, the study design does not allow conclusions to be drawn on the efficacy of bladder training.

These reservations apart, this study supports the use of oxybutynin in elderly outpatients with detrusor instability, in whom it was found to reduce frequency and produce subjective benefit.

Acknowledgement

This study was funded by Smith & Nephew Pharmaceuticals Ltd. who also supplied the oxybutynin and placebo tablets.

References

1. Hadley EC. Bladder training and related therapies for urinary incontinence in older people. *JAMA* 1986;**256:**372–7.
2. Frewen WK. A reassessment of bladder training in detrusor dysfunction in the female. *Br J Urol* 1982;**54:**372–3.
3. Castleden CM, George CF, Renwick AG, Asher MJ. Imipramine a possible alternative to current therapy for urinary incontinence in the elderly. *J Urol* 1981;**125:**318–20.
4. Holmes DM, Montz FJ, Stanton SL. Oxybutynin versus propantheline in the management of detrusor instability: a patient-regulated variable dose trial. *Br J Obstet Gynaecol* 1989;**96:**607–12.
5. Tapp AJ, Cardozo LD, Versi E, Cooper D. The treatment of detrusor instability in post-menopausal women with oxybutynin chloride: a double blind placebo controlled study [see comments]. *Br J Obstet Gynaecol* 1990;**97:**521–6.
6. Zorzitto ML, Holliday PJ, Jewett MAS, Herschorn S, Fernie GR. Oxybutynin chloride for geriatric urinary dysfunction: a double-blind placebo-controlled study [see comments]. *Age Ageing* 1989;**18:**195–200.
7. Moore KH, Hay DM, Imrie AE, Watson A, Goldstein M. Oxybutynin hydrochloride (3 mg) in the treatment of women with idiopathic detrusor instability. *Br J Urol* 1990;**66:**479–85.
8. Ouslander JG, Blaustein J, Connor A, Pitt A. Habit training and oxybutynin for incontinence in nursing home patients: a placebo controlled trial. *J Am Geriatr Soc* 1988;**36:**40–6.
9. Wiseman PA, Malone Lee J, Rai GS. Terodiline with bladder retraining for treating detrusor instability in elderly people. *Br Med J* 1991;**302:**994–6.
10. Geraint M. The pharmacology and pharmacotherapy of oxybutynin. *Rev Contemp Pharmacol* 1994;**5:**189–94.
11. Abrams P, Blaivas JG, Stanton SL, Andersen JT. The standardisation of terminology of lower urinary tract function. *Scand J Urol Nephrol [Suppl]* 1988;**114:**5–19.
12. Malone-Lee JG, Lubel D, Szonyi G. Low dose oxybutynin for the unstable bladder. *Br Med J* 1992;**304:**1053.
13. Ng KJ, Lieu PK, Orugun EO, Malone-Lee JG. Outcome measures in clinical trials of therapies for detrusor instability. *Proc Int Cont Soc* 1993;**233:**1–2.
14. Malone-Lee JG, Orugun EO. A data reduction technique for describing detrusor instability. *Int Urogyn J* 1993;**4:**203–11.

Authors' address

Division of Geriatrics, Department of Medicine,
University College London Medical School,
St Pancras Hospital, London NW1 0PE

Address correspondence to Professor J. G. Malone-Lee

Received in revised form 15 December 1994