REVIEW

Medical therapy for the overactive bladder in the elderly

ADRIAN WAGG, MAURICE COHEN

Department of Geriatric Medicine, University College Hospital, Grafton Way, London WC1E 6AU, UK

Address correspondence to: A. Wagg. Fax: (+44) (0) 20 7380 9652. Email: a.wagg@ucl.ac.uk

Abstract

The overactive bladder is the commonest underlying bladder disorder causing urinary incontinence in elderly people. Management of the condition relies upon a holistic assessment of the problem, lifestyle adjustment, behavioural management and drug therapy. The majority of currently available drugs rely on their anti-muscarinic properties for efficacy. Both behavioural techniques and drug therapy are effective in treatment of the elderly and each modality has a particular role to play in successful treatment and maintenance of this condition.

Keywords: *overactive bladder, pharmacotherapy, elderly*

Incidence and epidemiology

A diagnosis of detrusor overactivity, as defined by the International Continence Society, is based upon finding a spontaneous or provoked detrusor contraction whilst filling the bladder during urodynamic testing [1]. Twenty-five percent of people with the classical symptoms of urgency, frequency with or without urge incontinence are not identified by these criteria, as they do not have spontaneous detrusor contractions during urodynamic testing and, in addition, up to 60% of normal, asymptomatic individuals exhibit spontaneous detrusor contractions during such investigations [2]. The clinical syndrome bladder overactivity is used to describe these individuals.

The true incidence of symptomatic bladder overactivity is estimated at between 10–15% of men and women between 10 and 50, rising to 35% of those aged over 75 years old [3]. Although its incidence increases with advancing age, bladder overactivity should not be considered by either the older individual or the healthcare provider to be an expectation of old age.

In the vast majority of cases, the cause of bladder overactivity is unknown. However, it is, as noted above, commonly associated with bladder outflow obstruction, in men and with pelvic surgery in women and neurological injury or disease, such as spinal cord injury, multiple sclerosis, cerebrovascular disease, Parkinson's or Alzheimer's disease.

Overactive bladder can significantly affect quality of life. In a recent survey of 16,776 interviews, 65% of respondents with overactive bladder symptoms reported that the condition adversely affected their daily life [4]. Although 60% of respondents had consulted a doctor about their symptoms, only 27% were receiving treatment. There is thus considerable scope for improving both diagnosis and treatment.

There is growing evidence that the presence of an overactive bladder can adversely affect morbidity. There is an increased incidence of falls [5], depression [6], institutionalization, and social isolation [7]. There is as yet no evidence to suggest that treating the overactive bladder can reduce these.

Making the diagnosis

Patients' symptoms are extremely important in making a diagnosis of bladder overactivity. A relevant focused structured history is therefore an essential component to making the correct diagnosis (Table 1). Not all patients may experience all symptoms and many understandably go to great lengths to avoid experiencing incontinence. Most often this is achieved either by restricting fluid intake or increasing urinary frequency.

In addition to taking a relevant history, a patient-completed voiding diary is a useful aid [8]. The diary

records urinary frequency and volumes passed as well as the number of incontinence episodes experienced. It is often useful to ask the patient to record the timing, volume and types of fluid drunk during the day. In order to get meaningful information the diary needs to be continued for at least 3 days.

A focused physical examination is mandatory (Table 3).

Urinary tract infection and calculi may cause urinary urgency and urge incontinence and should be excluded at an early stage. The simplest method to exclude infection is to use a rapid urinalysis dipstick. The leucocyte esterase and nitrite tests are an accurate method of assessing the absence of infection (combined negative predictive value 98%) and can enable early treatment. If recurrent infections or haematuria in the absence of infection are noted and subsequently confirmed then further investigation is needed.

Behavioural therapy

Bladder retraining was first described in 1966 [9]. This technique involves the simple maxim 'hold on'. This is simple to say but far from simple to perform, requiring much motivation and will power. Even in the most motivated patient, bladder retraining can take months to achieve a lasting change in habit and because of the difficulty and continual attention required there is a high

relapse rate. The regimen involves a gradual increase in the voiding interval, using frequency-volume charts as an objective reinforcement and guide. Data from trials of this method alone are conflicting and there have been few of sufficient methodological quality, to allow firm conclusions to be drawn. Burgio et al., in a recent study of 197 women aged 55–92, showed that behavioural techniques alone may improve patients' experience of their disease to a similar extent to drug therapy when used alone. Both treatments were more effective than placebo. This study was limited by the fact that patients had to be mobile, motivated and without cognitive impairment [10]. There are data to suggest that a combination of pharmacotherapy and behavioural techniques may achieve results, which are superior to either technique in isolation, although the number of patients in this study progressing to combination therapy was small. Where the patient is cognitively impaired or institutionalized, a progressive regular toileting regimen may be employed [11]. There are no data to support the additional use of drugs in this population [12].

Pharmacological treatment

For the bladder, the main drug target has been the muscarinic receptor. In the normal human bladder 100% of motor function is mediated by M3 receptors. However there is some evidence in the abnormal bladder that ATP acting via P2x receptors may be significant [13]. There is as yet, unfortunately, no therapeutic option.

Antimuscarinic drugs are currently the most widely used treatment in the UK. However, data suggesting that such drugs can inhibit contractions of the detrusor are conflicting [14–16] but this does not appear to affect response to treatment. Trials, which have utilized urodynamic studies to assess efficacy, have normally shown that bladder capacity alone is significantly changed following treatment [17]. There are also data, which suggest those patients' symptoms respond as well to antimuscarinic agents regardless of the diagnosis being made by urodynamic or clinical characterisation [18]. The chief drawback of these agents has been their side effect profile, as the target receptor is ubiquitous in the body. Side effects such as dry mouth, constipation, blurred vision and oesophageal reflux, have limited the tolerability of these agents. The elderly are particularly susceptible if side effects are experienced.

Table 1. Focused history for diagnosis of overactive bladder

Frequency of micturition (day-time and night-time)
Presence of urgency (record time patient is able to delay voluntary micturition)
Presence of urge incontinence
Presence of dysuria (exclude infection)
Specific aggravating factors (eg. hearing running water)
Medications affecting continence (Table 2)

Table 2. Medications adversely affecting continence

Depression of detrusor activity
anti-cholinergics
antidepressants
anti-Parkinsonian
antipsychotics
beta-adrenergic agonists
calcium antagonists
Opioid analgesics
prostaglanding inhibitors
sedatives
Increased detrusor activity
beta-blockers
diuretics
Decreased urethral resistance
alpha-blockers
Increased urethral resistance
alpha-adrenergic agonists

Table 3. Focused physical examination for diagnosis of bladder overactivity

Neurological examination of the legs
Abdominal and rectal examination
Pelvic examination
Exclude presence of post voiding residual volume
Exclude presence of urinary tract infection (dipstick or mid stream urine specimen)

The most commonly prescribed treatment for the overactive bladder in the UK is oxybutynin. Oxybutynin is both antimuscarinic, a direct muscle relaxant and a local anaesthetic agent. Its chief metabolite, N-desethyl oxybutynin is also pharmacologically active and occurs in higher concentrations than the parent compound and is thought to be responsible for many of the adverse effects related to this drug. The efficacy of oxybutynin has been shown in both open and controlled trials [19, 20]. The main drawback in trials of high dose oxybutynin (5 mg tds) has been the incidence of side effects; the withdrawal rate has varied between 22–40% with up to 80% suffering significant adverse reactions. More recent work, using lower doses of the drug has also shown efficacy with a concomitant reduction in the adverse effects and an enhanced level of tolerability [21, 22].

However, only 10–30% of patients will still be taking the drug one-year after initiation [23]. Oxybutynin has been found to add little to the clinical effectiveness of a prompted voiding regimen in a nursing home population [24]. The modified release preparation, Oxybutynin XL retains the efficacy of the standard release form but with up to 40% fewer reported side effects [25]. Recent studies have concentrated upon comparing this compound to immediate release oxybutynin and have resulted in an equivalent efficacy in controlling urge incontinence. The incidence of dry mouth was similar, but with a reduced severity in one study [26] and was reduced in incidence in a second [27]. In this study approximately two thirds of the patients prescribed extended-release oxybutynin for detrusor instability were still taking the medication 6 months later. These studies have included men and women up to the eighth decade of life. From available data there appears to be no gender specificity.

Tolterodine is a newer, non-selective anti-muscarinic competitive antagonist, which, in the anaesthetized cat model, appears to have some functional selectivity for bladder muscarinic receptors over those in the salivary glands [28]. This appears to explain the lower incidence of dry mouth and the reduction in withdrawals due to severe dry mouth seen with use of the drug. Like oxybutynin it too has an active metabolite which appears to be responsible for some of the observed therapeutic effect [29]. Several randomized, double blind placebo controlled studies in patients with detrusor instability, detrusor hyperreflexia, overactive bladder and specifically in the elderly have been performed [31, 32]. In doses of 2 mg twice daily, tolterodine has consistently resulted in a reduction in urinary frequency and, in some trials, a reduction in the number of incontinence episodes. Where tolterodine has been compared to oxybutynin, the drug has been found equally efficacious in the elderly [30, 33] and has the advantage of greater tolerability and fewer withdrawals due to adverse effects. There has been no direct comparison with the lower doses of oxybutynin used widely in UK practice. The

proportion of patients continuing therapy for 6 months in one study comparing approximately 500 patients taking either tolterodine or oxybutynin was statistically superior for tolterodine (32%) compared with IR (immediate release) oxybutynin (5 mg tds) (22%, $P < 0.001$). For those discontinuing either drug, oxybutynin was stopped significantly earlier [34]. In one open label study, including patients over 65, 70% of 854 patients remained on treatment for 9 months. Dry mouth was the most frequently reported adverse event, occurring in 28% of patients (intensity: 19% mild, 7% moderate, 2% severe). 9% of patients withdrew due to adverse events [35].

Although tolterodine is more costly than oxybutynin (£30.56 compared to £8.48), its use may allow treatment of a greater number of patients. What is not known, and not yet tested, is whether tolterodine has any other advantages, such as its effect upon cognitive impairment. The effect of bladder retraining with or without the drug has not been assessed other than in a relatively small study [36].

Tolterodine is also available in an extended release once daily preparation. In a recent study involving 1500 patients comparing IR tolterodine with once daily dose and placebo, both treatments significantly reduced incontinence episodes though the extended release (ER) formulation was 18% more effective than IR ($P < 0.05$). Dry mouth was 23% lower in ER. This may therefore be a useful progression as once daily regimen is easier to take and in this study had a better side effect profile. (It has also been shown that there is no consideration as to relation to food [37]).

The older antimuscarinic drug imipramine, although not licensed for treatment of detrusor instability or overactive bladder, is commonly used for this indication. It is both a centrally and peripherally acting antimuscarinic agent, it blocks reuptake of 5-hydroxytryptamine and norepinephrine and has alpha adrenergic agonist properties. There is no evidence that imipramine can suppress unstable detrusor contractions but several small trials have shown the drug efficacious in the treatment of detrusor instability [38] although a recent Drug & Therapeutics bulletin [39] felt that the data available does not justify its use. In the treatment of 10 elderly patients with detrusor instability the use of imipramine was efficacious in achieving continence (6/10 patients) in doses between 25–150 mg [40, 41].

Propiverine hydrochloride has combined antimuscarinic and calcium channel blocking activity. It has several active metabolites and is rapidly absorbed orally where it undergoes significant first pass metabolism. There has been no cardiac toxicity associated with use of the drug to date. Placebo controlled clinical trials have demonstrated superiority to placebo in the treatment of detrusor hyperreflexia in a two week double blind placebo controlled trial of oral treatment [42]. Comparative trials, have demonstrated that propiverine has a similar efficacy to oxybutynin [43, 44]. Madersbacher,

in a recent four-week study comparing the use of propiverine against oxybutynin 5 mg b.d. and placebo [43], reported a similar efficacy in treatment of symptoms to oxybutynin, but with statistically significantly milder, and less common incidence of dry mouth. Up to 20% of patients do however, experience adverse effects which are mainly anticholinergic in nature. There are as yet no longer term data from European trials of the drug and its use has been confined to patients with urodynamically confirmed detrusor instability. In addition, there is no evidence regarding use of the drug in relation to behavioural intervention. The place of propiverine in the treatment of overactive bladder in the UK remains to be resolved but given its equal efficacy and apparent milder incidence of side effects it is likely to remain as an alternative second line treatment.

Trospium chloride, an antimuscarinic agent derived from atropine, has also recently been approved for use in Europe. This drug has been shown to be effective in the treatment of detrusor instability in several randomized controlled trials using urodynamic measures of diagnosis and extent of disease as well as clinical and quality of life outcomes [45, 46].

The drug has been assessed in short-term studies versus placebo and standard release oxybutynin and has been found to be superior in effect to placebo and equivalent in efficacy to oxybutynin, when treating detrusor hyperreflexia, at doses of 5 mg three times daily. The number of withdrawals due to side effects in the trospium group was lower than the oxybutynin group [47].

The potential for antimuscarinic agents to cause deterioration in cognition, especially in the elderly, has been well recognized in association with oxybutynin [48, 49]. The effect of trospium chloride on EEG activity has been assessed compared to oxybutynin administration in two studies in healthy volunteers. When comparing EEG tracings after administration of oxybutynin, tolterodine and trospium, only oxybutynin was shown to result in power reductions in EEG frequency bands [50]. This difference is due to the fact that oxybutynin is most lipophilic and thus able to cross the blood brain barrier. A similar minimal reduction in quantitative EEG activity has also been reported for tolterodine [50]. How the EEG tracings correspond to cognitive ability has not yet been shown; this would be particularly important in the elderly with mild cognitive impairment to determine the safety of these treatments.

Summary

Overactive bladder is a common condition, seen commonly in the elderly but it is probably not an effect of ageing as is often thought by patients, carers and unfortunately, by many physicians. Urge incontinence has significant effect on morbidity and quality of life, yet is rarely treated despite a growing evidence base.

For institutionalized patients who are cognitively impaired a structured toileting programme has proven beneficial but difficult to maintain in terms of physical resources. Behavioural therapy alone is efficacious, even in housebound older adults.

The choice of which drug to use should, like all practice of medicine in the elderly, incorporate patient characteristics, side effect profile, cost and compliance. There is good evidence that the once daily formulations of oxybutynin and tolterodine are as effective as currently available formulations and this would assist in compliance in the non-clinical trial situation.

Key points:

- Bladder overactivity is the commonest underlying cause for bladder problems in the elderly.
- Bladder problems are associated with considerable morbidity in older individuals.
- An holistic assessment of the problem may add to the efficacy of drug and behavioural techniques to manage the bladder.
- The majority of individuals do not need invasive testing prior to treatment of their bladder problem.
- Drug and behavioural therapy is effective, even in the frail elderly.

References

1. Abrams PH, Cardozo L, Fall M *et al.* The standardization of terminology of lower urinary tract function: Report from the standardization sub-committee of the International Continence Society. Neurourol Urodyn 2002; 21: 167–78.

2. Robertson AS, Griffiths CJ, Ramsden PD, Neal DE. Bladder function in healthy volunteers: ambulatory monitoring and conventional urodynamic studies. Br J Urology 1994; 73: 242–9.

3. Abrams PH. Bladder instability: Concept, clinical associations and treatment. Scand J Urol Nephrol 1984; Suppl 87: 7.

4. Milsom I, Abrams P, Cardozo L, Roberts RG, Thuroff J, Wein AJ. How widespread are the symptoms of an overactive bladder and how are they managed? A population-based prevalence study. Br J Urol Int 2001; 87: 760.

5. Brown JS, Vittinghoff E, Wyman JF *et al.* Urinary incontinence: Does it increase risk for falls and fractures? J Amer Geriatr Soc 2000; 48: 721–5.

6. Zorn BH, Montgomery H, Pieper K, Gray M, Steers WD. Urinary incontinence and depression. J Urol 1999; 162: 82–4.

7. Thom DH, Haan MN, vanden Eeden SK. Medically recognised urinary incontinence and risks of hospitalisation, nursing home admission and mortality. Age Ageing 1997; 26: 367–74.

8. Abrams P, Kleumark, B. Frequency volume charts: an indispensable part of lower urinary tract assessment. Scand J Urol Nephrol Suppl. 1996; 179: 47–53.

9. Jeffcoate TNA, Francis WJA. Urgency incontinence. Am J Obstet Gynaecol 1966; 94: 604.

10. Burgio K, Locher JL, Goode PS *et al*. Behavioural versus drug treatment for urge urinary incontinence in older women. A randomized controlled trial. J Am Med Assoc 1998; 280: 1995– 2000.

11. Burgio K, Locher JL, Goode PS. Combined behavioural and drug therapy for urge incontinence in older women. J Am Geriatr Soc 2000; 48: 370–4.

12. Ouslander JG, Schnelle JF, Uman G *et al*. Does oxybutynin add to the effectiveness of prompted voiding for urinary incontinence among nursing home residents? A placebo controlled trial. J Am Geriatr Soc 1995; 43: 610–7.

13. Bayliss M, Wu C, Newgreen D, Mundy AR, Fry CH. A quantitative study of atropine-resistant contractile responses in human detrusor smooth muscle, from stable, unstable and obstructed bladders. J Urol 1999; 162: 1833–9.

14. Cardozo LD, Stanton SL. An objective comparison of the effects of parenterally administered drug in patients suffering from detrusor instability. J Urol 1979; 122: 58–9.

15. Blaivas JG, Labib KB, Michalik J, Zayed AAH. Cystometric response to propantheline in detrusor hyper-reflexia: therapeutic implications. J Urol 1980; 124: 259–62.

16. Zorzitto ML, Jewett MAS, Fernie GR, Holliday PJ, Bartlett S. Effectiveness of propantheline bromide in the treatment of geriatric patients with detrusor instability. Neurourol Urodyn 1986; 5: 133–40.

17. Jonas U, Hofner K, Madersbacher H, Holmdahl TH. Efficacy and safety of two doses of tolterodine versus placebo in patients with detrusor overactivity and symptoms of frequency, urge incontinence, and urgency: urodynamic evaluation. The International Study Group. [published erratum appears in World J Urol 1997, 15: 210]. World J Urol 1997; 15: 144–51.

18. Hashimoto K, Ohnishi N, Esa A, Sugiyama T, Park Y-C, Kurita T. Clinical efficacy of oxybutynin on sensory urgency as compared with motor urgency. Urologia Int 1999; 62: 12–6.

19. Cardozo LD, Cooper D, Versi E. Oxybutynin chloride in the management of idiopathic detrusor instability. Neurourol Urodyn 1987; 6: 256–7.

20. Moisey CU, Stephenson TP, Brendler CB. The urodynamic and subjective results of treatment of detrusor instability with oxybutynin chloride. Br J Urol 1980; 52: 472–5.

21. Bemelmans BL, Kiemeney LA, Debruyne FM. Low-dose oxybutynin for the treatment of urge incontinence: good efficacy and few side effects. Eur Urol 2000; 37: 709–13.

22. Malone-Lee JG, Lubel D, Szonyi G. Low dose oxybutynin for the unstable bladder. Br Med J 1992; 304: 1053.

23. Kelleher CJ, Cardozo LD, Khullar V, Salvatore S. A medium-term analysis of the subjective efficacy of treatment for women with detrusor instability and low bladder. Br J Obstet Gynaecol 1997; 104: 988–93.

24. Ouslander JG, Schnelle JF, Uman G *et al*. Does oxybutynin add to the effectiveness of prompted voiding for urinary incontinence among nursing home residents? A placebo controlled trial. J Am Geriatr Soc 1995; 43: 610–7.

25. Birns J, Lukkari E, Malone-Lee JG. A randomized controlled trial comparing the efficacy of controlled release oxybutynin tablets (10 mg once daily) with conventional oxybutynin tablets (5 mg twice daily) in patients whose symptoms were stabilized on 5 mg twice daily of oxybutynin. Br J Urol Int 2000; 85: 793–9.

26. Versi E, Appell R, Mobley D, Patton W, Saltzstein D. Dry mouth with conventional and controlled release oxybutynin in urinary incontinence. Obstet Gynecol 2000; 95: 718–21.

27. Anderson R, Mobley D, Blank B, Saltzstein D, Susset J, Brown J. Once daily controlled versus immediate release oxybutynin for urge urinary incontinence. J Urol 1999; 161: 1809–12.

28. Nilvebrandt L, Hallen B, Larsson G. Tolterodine – A new bladder selective antimuscarinic agent. Eur J Pharmacol 1997; 327: 195–207.

29. Nilvebrandt L, Gillberg PG, Sparf B. Antimuscarinic potency and bladder selectivity of PNU-200577, a major metabolite of tolterodine. Pharmacol Toxicol 1997; 81: 169–72.

30. Abrams P, Freeman R, Anderstrom C, Mattiasson A. Tolterodine, a new antimuscarinic agent: as effective but better tolerated than oxybutynin in patients with an overactive bladder. Br J Urol 1998; 81: 801–10.

31. Millard R, Tuttle J, Moore K *et al*. Clinical efficacy and safety of tolterodine compared to placebo in detrusor overactivity. J Urol 1999; 161: 1551–5.

32. Malone-Lee JG. Abstract A188. Proceedings of the International Continence Society, 1997.

33. Malone-Lee JG, Walsh JB, Maugourd MF. Tolterodine: a safe and effective treatment for older patients with overactive bladder. J Am Geriatr Soc 2001; 49: 700–5.

34. Lawrence M, Guay DR, Benson SR, Anderson MJ. Immediate-release oxybutynin versus tolterodine in detrusor overactivity: a population analysis. Pharmacotherapy 2000; 20: 470–5.

35. Appell RA, Abrams P, Drutz HP, Van Kerrebroeck PE, Millard R, Wein A. Treatment of overactive bladder: long-term tolerability and efficacy of tolterodine. World J Urol 2001; 19: 141–7.

36. Mattiason A. Simplified bladder training augments tolterodine treatment in overactive bladder patients. Neurourol Urodyn 2001; 20: 403–4.

37. Olsson B, Szamosi J. Food does not influence the pharmacokinetics of a new extended release formulation of tolterodine for once daily treatment of patients with overactive bladder. Clin Pharmacokinet 2001; 40: 135–43.

38. Diokno AC, Hyndman CW, Hardy DA, Lapides J. Comparison of action of imipramine (Tofranil) and propantheline (Propanthine) on detrusor contraction. J Urol 1972; 107: 42–3.

39. Managing incontinence due to detrusor instability. Drug Ther Bull 2001; 39: 59–63.

40. Castleden CM, Duffin HM, Gulati RS. Double blind study of imipramine and placebo for incontinence due to bladder instability. Age Ageing 1986; 15: 299–303.

41. Castleden CM, George CF, Renwick AG, Asher MJ. Imipramine—a possible alternative to current therapy for urinary incontinence in the elderly. J Urol 1980; 125: 318–9.

42. Stohrer M, Madersbacher H, Richter R, Wehnert J, Dreikorn K. Efficacy and safety of propiverine in SCI-patients suffering from detrusor hyperreflexia—a double-blind, placebo-controlled clinical trial. Spinal Cord 1999; 37: 196–200.

43. Madersbacher H, Halaska M, Voigt R, Alloussi S, Hofner KA. A placebo-controlled, multicentre study comparing the tolerability and efficacy of propiverine and oxybutynin in patients with urgency and urge incontinence. Br J Urol Int 1999; 84: 646–51.

44. Halaska M, Dorschner W, Frank M. Treatment of urgency and incontinence in elderly patients with propiverine hydrochloride. Neurourol Urodyn 1994; 13: 428–30.

45. Fuertes ME, Garcia Matres MJ, Gonzalez Romojaro V *et al*. Ensayo clinico para evaluar la eficacia y tolerancia del cloruro de trospio (Uraplex) en pacientes con incontinencia por inestabilidad del detrusor y su repercusion en la calidad de vida. Arch Esp Urol 2000; 53: 125–36.

46. Cardozo L, Chapple CR, Toozs-Hobson P *et al*. Efficacy of trospium chloride in patients with detrusor instability: a placebo-controlled, randomized, double-blind, multicentre clinical trial. Br J Urol Int 2000; 85: 659–64.

47. Madersbacher H, Stohrer M, Richter R, Burgdorfer H, Hachen HJ, Murtz G. Trospium chloride versus oxybutynin: a randomized, double-blind, multicentre trial in the treatment of detrusor hyper-reflexia. Br J Urol 1995; 75: 452–6.

48. Donnellan CA, Fook L, McDonald P, Playfer JR. Oxybutynin and cognitive dysfunction Br Med J 1997; 315: 1363–4.

49. Katz IR, Sands LP, Bilker W, DiFilippo S, Boyce A, D'Angelo K. Identification of medications that cause cognitive impairment in older people: the case of oxybutynin chloride. J Am Geriatr Soc 1998; 46: 8–13.

50. Todorova A, Vonderheid-Guth B, Dimpfel W. Effects of tolterodine, trospium chloride, and oxybutynin on the central nervous system. J Clin Pharmacol 2001; 41: 636–44.