

TRANSDERMAL OXYBUTYNYN IN OVERACTIVE BLADDER

By ANTHONY GROSSO, MRPHARMS and CAROLYN GATES, MRPHARMS

Although yet to gain a UK licence, transdermal oxybutynin, which is claimed to reduce the incidence of anticholinergic side effects, is being requested by many prescribers. This article, part of an occasional feature of new drug reviews, examines the clinical evidence

Overactive bladder (OB) is a symptom complex that includes urinary urgency (sudden and compelling desire to pass urine which is difficult to defer), with or without urge incontinence (involuntary leakage of urine with the feeling of urgency), urinary frequency (voiding more than seven times a day) and nocturia (waking to void more than once at night).¹ OB usually results from sudden involuntary contractions of the detrusor muscle in the wall of the bladder, although other conditions can contribute to or cause symptoms.²

OB affects approximately 10 per cent of the adult population³ and is particularly prevalent in older people, with one study suggesting a prevalence of 30–42 per cent in those over 75 years of age.⁴

Overall, the symptoms of OB can have a profound effect on the quality of life of an individual by affecting social activities, disturbing sleep and causing feelings of isolation and depression. Non-pharmacological treatment options are varied (eg, pelvic muscle rehabilitation, behavioural therapies, management of oral fluid intake, etc) and are often used in conjunction with traditional pharmacological therapy such as antimuscarinic agents, alpha adrenergic antagonists (for men with concurrent benign prostatic hypertrophy) and vaginal oestrogen preparations for women.

The antimuscarinic agents (oxybutynin, tolterodine, propiverine and trospium) block the parasympathetic pathway to the bladder, thereby reducing detrusor contractions and increasing bladder capacity (oxybutynin and propiverine also have a direct relaxant effect on urinary smooth

muscle). While there are differences between these agents, none specifically target the M2 or M3 muscarinic receptors of the bladder and can therefore cause troublesome side effects by affecting other muscarinic receptors in the body, ie, causing dry mouth, constipation, gastro-oesophageal reflux, blurred vision, urinary retention and of particular concern in the elderly, cognitive side effects. Different preparations of oxybutynin have therefore been formulated in an attempt to maintain efficacy but with a view to reducing these common side effects. The next generation of antimuscarinics (such as solifenacin and darifenacin) are purported to demonstrate M3 selectivity but will not be considered further within this article.

Transdermal oxybutynin (Oxytrol, Watson Pharmaceuticals), releasing 3.9mg oxybutynin per day, is currently unlicensed in the UK. The patches need only to be applied twice weekly to maintain efficacy. The transdermal route avoids the first-pass metabolism that is seen with the oral route, resulting in significantly less of the active metabolite, N-desethyloxybutynin (the compound thought to be responsible for anticholinergic side effects, such as dry mouth) being produced.

EFFICACY

One study (n=520) compared transdermal oxybutynin to placebo in a 12-week double-blinded randomised controlled trial.⁵ Both primary and secondary efficacy measures were all statistically superior in the transdermal group receiving 3.9mg/day. Lower doses were shown not to be statistically different from placebo.

Another trial (n=76) compared transdermal oxybutynin to immediate-release (IR) oral oxybutynin in a 6-week dose-titration study.⁶ Sixty-eight per cent of patients in the transdermal group reached the maximum dose of 5.2mg per day, while only 32 per cent of patients in the oral group reached the maximum dose of 7.5mg three

times a day. Both routes were shown to be effective in terms of increasing maximum bladder capacity although no statistical analysis was presented to compare the two. The number of incontinent episodes from washout to the end of treatment was reduced for both groups ($P<0.0001$) and there was no statistical difference between the two groups upon comparison ($P=0.39$). This study however, only included patients responsive to oxybutynin and excluded patients known to be intolerant to transdermal drug delivery systems.

No data are currently available directly comparing transdermal oxybutynin to oxybutynin extended release (ER), trospium or propiverine. A randomised controlled trial (n=361) compared tolterodine ER 4mg daily, transdermal oxybutynin 3.9mg and placebo.⁷ Both drugs were shown to be statistically superior to placebo in terms of efficacy and no statistical difference was seen between the two active drugs on comparison.

ADVERSE EFFECTS

When transdermal oxybutynin was compared with placebo, 5.6 per cent of patients developed local erythema with 3.9mg/day oxybutynin patches (placebo 2.3 per cent), 16.8 per cent developed pruritus (6.1 per cent placebo) and 4.4 per cent of patients required treatment with topical corticosteroids or antihistamines. Dry mouth incidence was similar in both groups (7 per cent transdermal oxybutynin, 8.3 per cent placebo). Other side effects were infrequent and non-remarkable.⁵

Results in favour of transdermal oxybutynin were reported in the dose titration trial comparing transdermal oxybutynin to IR oxybutynin.⁶ However the incidence of adverse effects is difficult to compare due to the variety of doses being taken by each group.

No data are currently available directly comparing the safety of transdermal oxybutynin to ER oxybutynin.

Mr Grosso is principal pharmacist, formulary and medicines management and Ms Gates is lead directorate pharmacist, medicine and emergency services, University College London Hospitals NHS Foundation Trust. This article has been reviewed by other pharmacists at the trust, but the opinions expressed remain those of the authors

Panel 1: Monthly cost comparison

Drug	Dose*	Cost excluding VAT
Trospium	20mg bd	£26.00
Tolterodine ER	4mg od	£29.03
Oxybutynin IR	5mg tds	£13.34
Oxybutynin ER	5mg od	£12.34
Transdermal oxybutynin	3.9mg/24h bi-weekly	Not known until UK launch

*Illustrated doses do not indicate equivalent efficacy

Systemic anticholinergic side effects were slightly greater in the tolterodine arm on comparison with the transdermal oxybutynin arm in the randomised controlled trial comparing the two agents to placebo: dry mouth (7.3 per cent vs 4.1 per cent respectively; placebo 1.7 per cent) constipation (5.7 per cent vs 3.3 per cent respectively). No comparative statistics were presented. Total systemic side effects reported for tolterodine and oxybutynin were 23.6 per cent and 19 per cent respectively. Total localised site reactions for oxybutynin and tolterodine were 26.4 per cent and 5.7 per cent respectively. Treatment was discontinued due to adverse effects in 10.7 per cent of patients in the transdermal oxybutynin group (mainly due to application site reactions) compared to only 1.6 per cent in the tolterodine group.⁷

SUMMARY

Transdermal oxybutynin appears to have comparable efficacy to tolterodine ER 4mg. The advantage of using transdermal oxybutynin over tolterodine ER is that it appears to have a lower incidence of systemic anticholinergic side-effects. However this benefit when looked at in terms of dry mouth and constipation incidence, yields an overall absolute risk reduction of only 3.2 per cent and 2.4 per cent respectively.

The calculated number needed to treat (NNT) derived from the absolute difference in dry mouth incidence is 31 (12 week trial). Therefore one would have to treat 31 patients with transdermal oxybutynin rather than ER tolterodine over 12 weeks to prevent one additional observed case of dry mouth. The cost differential between the two treatments, once known, will have to be incorporated into this comparison so as to fully assess the apparent treatment benefit versus cost implication.

Twice weekly patch administration is likely to affect concordance in some patients. However, this may be advantageous for some older patients, eg, patients who are assisted by statutory carers. The transdermal route is an obvious advantage if the patient is unable to swallow tablets properly.

In summary, due to the low absolute difference in dry mouth incidence, UK

unlicensed status, high incidence of local site reactions and the high withdrawal rate the authors recommend that transdermal oxybutynin is not approved for general formulary inclusion in UK NHS trusts just yet. In addition, no studies to date have investigated transdermal oxybutynin in the cohort of patients that are likely to warrant a trial of this novel formulation, ie, in patients who are unable to tolerate oral therapy due to anticholinergic side effects. It should be borne in mind that the transdermal patch may be the only realistic pharmacological treatment option for patients who are unable to swallow oral medication in any form.

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