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To cite this version:

Christopher Chapple. New once daily formulation for trospium in overactive bladder. International Journal of Clinical Practice, 2010, 64 (11), pp.1535. 10.1111/j.1742-1241.2010.02493.x . hal-00576628

HAL Id: hal-00576628

https://hal.science/hal-00576628v1

Submitted on 15 Mar 2011

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THE INTERNATIONAL JOURNAL OF CLINICAL PRACTICE

New once daily formulation for trospium in overactive bladder

Journal:	*International Journal of Clinical Practice*
Manuscript ID:	IJCP-07-10-0370.FT10.R1
Wiley - Manuscript type:	Systematic Review
Date Submitted by the Author:	26-Jul-2010
Complete List of Authors:	Chapple, Christopher; The Royal Hallamshire Hospital, Department of Urology
Specialty area:	

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22/07/2010

New once daily formulation for trospium in overactive bladder

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Disclosure

Christopher Chapple is a scientific consultant and/or researcher with Allergan, Astellas, Novartis, Ono, Xention, Pfizer and Speciality European Pharma.

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Summary

Aims

To examine the relative efficacy and safety of trospium 20mg bid and 60 mg extended release formulations and position this drug against other antimuscarinic agents

Methods

Data were identified on the pharmacology and pharmacokinetics of trospium chloride. Key publications on trospium 20 mg and 60 mg clinical studies in patients with overactive bladder (OAB) were identified and efficacy and safety compared between these formulations as well as other antimuscarinic agents.

Results

Trospium offers the principal advantage over other antimuscarinic agents that, as it is a quaternary amine, it does not cross the blood-brain barrier and is therefore less likely to cause central nervous system effects observed with several other agents. Moreover, with its minimal liver metabolisation, independent of the main cytochrome pathways, trospium has a low risk of drug-drug interaction in patients taking multiple pharmacological agents. Trospium 60 mg ER is as effective as trospium 20 mg bid in improving the key outcome parameters associated with OAB, but with a lower rate of dry mouth, the most common side-effect of these agents. Trospium has comparable efficacy and safety to the other antimuscarinic agents currently marketed. Good patient persistence with treatment has been reported with trospium.

Conclusion

There are currently a large number of antimuscarinic drugs on the market without clear evidence to distinguish one agent from another in terms of efficacy provided an adequate dose is used in the clinical setting. The new formulation of trospium is

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certainly worth considering as a pharmacological treatment of patients with OAB, particularly the elderly where one wants to avoid the potential for cognitive dysfunction.

Review Criteria

'How did you gather, select and analyze the info you considered in your review?'

A medline search was conducted using the key words trospium and incontinence. Data on all other antimuscarinic agents were based on a comprehensive meta-analysis as well as medline searches on specific adverse events, e.g. cognitive function.

Message for the clinic

'What is the take-home message for the clinician?' Trospium chloride 60 mg ER can be considered a potential addition to the treatment armamentarium for patients with overactive bladder, as it brings with the potential of not crossing the blood brain barrier because of its underlying physico-chemical structure. Further experience is necessary, however, in real life clinical practice as well as results of further controlled studies before more definitive conclusions can be drawn.

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22/07/2010

Introduction

Overactive bladder (OAB) has been defined by International Continence Society (ICS) as a symptom syndrome comprising “urgency with or without urgency incontinence, usually with frequency and nocturia” (1). The condition is common and one in six adults is reported as having symptoms of OAB (2). The primary therapies for this condition are non-surgical comprising bladder training, biofeedback, medication and a combination of these options, while the first-line medical therapy for OAB relies on antimuscarinic agents (3). By blocking the muscarinic M3 receptors, these reduce the symptoms of OAB in part by a direct action on the detrusor muscle (4) as well as potentially affecting the sensory components of the micturition reflex. The widespread occurrence of muscarinic receptors throughout the body, including the central nervous system, eyes, salivary glands, and gastrointestinal tract, however, means that antimuscarinic therapy is associated with a range of adverse effects (AEs). A number of different formulations are available for the various antimuscarinic agents that are currently available. In the past, one such agent, trospium chloride, has been disadvantaged by not being available as a once a day formulation, but this situation has now been resolved by a new 60 mg extended release (ER) formulation. This review examines the background to this compound and draws comparison between the new formulation and the original twice daily preparation, as well as the existing antimuscarinic agents.

Trospium chloride

Pharmacology

Trospium chloride is an antimuscarinic agent indicated for the symptomatic treatment of urgency incontinence and/or increased urinary frequency and urgency

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as may occur in patients with OAB. It is available in two formulations: a 20 mg IR (immediate release) tablet that is taken twice daily or the more recent 60 mg ER (extended release) capsule (Regurin XL®; Urivesc®; Sanctura® XR) for once daily administration. The twice daily formulation is widely available worldwide, while the extended release formulation is currently approved in most EU Countries as well as in the USA and Canada. Trospium is a quaternary amine that has low lipophilicity and is charged at neutral pH (5). Following oral administration, it is absorbed rather slowly, with peak plasma levels reached at 4.5 hours and at 5.0 hours with the IR and ER formulations, respectively (6); no first-pass effect for systemically absorbed trospium has been observed (7,8). Up to 80% of trospium is excreted unchanged in the urine and metabolism by the cytochrome P450 pathway does not occur (8,9), suggesting that no metabolic interactions with other drugs are likely (8).

Antimuscarinic agents interact with muscarinic receptors throughout the body, of which the five known receptor subtypes are all expressed in the central nervous system (CNS) (10). Interactions with the M_1, M_2, and M_4 subtypes have each been implicated in cognitive impairment and the M_1 receptor subtype is particularly relevant in this regard (10,11). In order to be active within the brain, the individual agent has to cross the blood-brain barrier, either through active transport or passive penetration; the latter is more likely with small hydrophilic molecules. Drugs such as oxybutinin (357 kDA) can readily cross the blood-brain barrier and their subsequent negative effects on cognitive function have been documented (12). In contrast, data indicate that trospium was less likely to produce CNS AEs than oxybutinin due to its inability to cross the blood brain barrier (13). Research also suggests that trospium affects general and traffic safety performance to a lesser extent than oxybutinin, tolterodine and propiverine (14). Further support for the lack of CNS AEs comes from

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a study by Staskin and Harnett, which showed that trospium did not increase daytime sleepiness or reduce patient alertness (15). These findings are particularly relevant for the elderly who have cerebrovascular disease or other co-morbidities that alter the permeability of the blood-brain barrier who might be a greater risk of a CNS adverse event.

Efficacy

No head to head studies have been conducted on trospium 20 mg immediate release and the 60 mg ER formulations. Considering the outcomes from individual studies (Table 1) (16–19), three key outcome parameters are reported, i.e. reduction in daily incontinence episode rate, daily micturition rate and daily urgency episodes, which show significant improvements with both dosages of trospium over placebo. No distinction can be observed between the two dosage forms for any of these parameters, albeit, the duration of treatment is longer in one of the lower dosage studies. This latter study actually reports the longest term outcome for trospium 20 mg bid and at 1 year confirms the durability of the therapy.

Additional data on the efficacy of trospium 20 mg bid dosage come from a 3-week randomized placebo controlled study of 208 patients with detrusor overactivity (20). Efficacy was based on urodynamic assessments including maximum cystometric bladder capacity, volume at first overactive and maximum contraction, detrusor pressures at different bladder states. Results showed that trospium produced significant improvements in a number of urodynamic parameters (Table 2). In addition, most patients treated with trospium rated the acceptability of study medication as good or very good; 50% and 37%, respectively compared with 40% and 29%, respectively, with placebo.

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The pivotal randomized controlled trials on trospium 60 mg ER formulation were conducted in the US and involved over 1000 patients at over 100 sites (18,19). The study by Staskin et al indicated that in addition to the primary efficacy variables shown in Table 2, twice as many patients treated with trospium achieved normalization (no urinary urgency episodes and a daily void frequency of ≤ 8) compared with placebo (20.5% vs. 11.3%; $p < 0.01$) (18).There were also significant improvements in other secondary outcome measures (urgency urinary incontinence [UUI] episodes per week, urgency severity associated with toilet voids, volume voided per void, daily frequency of urgency-associated voids and OAB-SCS). The time to onset of clinical benefit was superior for trospium compared with placebo, with benefits being observed in week 1 of the 12-week study for several of the primary and secondary outcomes. In the Dmochowski et al study, from week 1 significantly more patients were dry in the trospium group than in the placebo group and at week 12 this rose to 36% and 21%, respectively ($P < 0.001$) (19). Similarly, significantly more patients treated with trospium were normalized from week 4 and at week 12, 21% vs. 11% were normalized in the trospium and placebo groups, respectively ($P < 0.01$).

A *post hoc* analysis was conducted on pooled data from the two US 12-week, studies (21). Patients were stratified by the mean number of UUI episodes/day at baseline (1.0, > 1.0–2.0, > 2.0–5.0 or > 5.0). Results showed that baseline UUI levels were inversely correlated with the week 12 percentage of patients continent and that more patients were continent with trospium compared with placebo at all degrees of severity. Complete continence was achieved in 75% of trospium recipients with 1.0 UUI/day at baseline and 48% of those with > 1.0–2.0 UUIs/day at baseline indicating that patients with less severe OAB could anticipate higher 'dry

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rates' following treatment. A further *post-hoc* analysis on the two studies examined the effects of obesity on outcome. Increased body mass index has been shown to be associated with severity of OAB in a number of studies in both men and women (22,23). The analysis showed that trospium was more effective than placebo at reducing the primary endpoints (number of daily voids and UUI; $P < 0.0001$) and at improving the secondary end-points (percent patients continent and urgency severity; $P < 0.0001$) for WHO obesity levels I and II.

Safety

Comparison is made in Table 3 of the most frequent AEs reported with the two formulations of trospium (16–19). This shows a lower rate of AEs with the 60 mg ER dose than the 20 mg bid. There was a marked decrease in the incidence of dry mouth with trospium ER; the rates reported for the 20 mg and 60 mg formulations were 21–33% and 8.7–12.9%, respectively. Improved formulations and extended release delivery systems developed for other antimuscarinic drugs have demonstrated an improved therapeutic index, namely by maintaining efficacy but improving the safety profile (24). This is combined with a significantly better improvement in mean number of urgency incontinence episodes per week with the ER formulation. The lower rate of AE has indeed been suggested to be related to the pharmacokinetic profile of this novel formulation; in particular, the systemic exposure to trospium at steady state is lower following administration of the ER formulation, as compared with the IR one, possibly by reducing the chance of reaching the threshold serum level at which AEs occur (6).

A recent open label, non comparative, evaluation study of 12 healthy volunteers, insinuated the ability of trospium extended release to penetrate the blood brain

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barrier. This looked at serum plasma levels as well as levels in the cerebral spinal fluid at up to 24 hours post dose, when a steady state had been reached at 10 days after starting dosing. All of the volunteers were aged 65-75. No clinically meaningful drug effect was seen after neuro-cognitive measurement and trospium chloride was undetectable to multiple time points in these patients. The study concluded that pharmacological and behavioural results supported a lack of CNS penetration in potentially neuro-cognitively vulnerable elderly people (25).

Comparison to other antimuscarinic agents

A meta-analysis was conducted in 2008 on the safety and efficacy of antimuscarinic agents for OAB, which involved an analysis of published randomized controlled trials on drug dosages that were licensed for use in Europe (26). The cutpoint for publication was 18 October 2007. Comparison can now be made to the two RCTs on trospium 60 mg ER that have subsequently been published, namely the studies by Staskin et al (18) and Dmochowski et al. (19). The meta-analysis reported pooled differences in mean change in incontinence episodes of 0.4 to 1.1 episodes per day. The data on trospium compares favourably with this at 0.5—2.4. Pooled differences for mean change in number of micturitions per day ranged from 0.5 to 1.3 episodes in the meta-analysis compared with 0.3 to 7.9 in the trospium studies. With regard to urgency episodes per day, the trospium studies show a change in rate of 0.3 to 6.7 compared with 0.64 to 1.56 episodes per day in the meta-analysis. These findings suggest that trospium at both dosage forms is as effective as the other antimuscarinic agents available. The safety of trospium is comparable to the other antimuscarinic agents reported in the meta-analysis with the exception of dry mouth

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where the 8.7% incidence (placebo 3.0%) with the 60 mg ER dosage (18) was the lowest reported for any oral antimuscarinics.

The efficacy of the antimuscarinics has to be balanced against the side-effects observed and patient tolerability of these effects. Persistence rates with the different antimuscarinic vary between rates reported in long-term clinical trials and real life situations. Very good long-term persistence has been reported for several antimuscarinic agents including, 75% for trospium at 12 months (16), 81% for solifenacin at 40 weeks (27), 71% for tolterodine at 1 year (28) and 66% for darifenacin at 2 years (29). In contrast, a much lower rate of 44% has been reported for real-life prescription renewal for tolterodine ER after 30 days and this reduced to 9% at 1 year (30). A more recent report has examined the persistence of antimuscarinics based on a Danish database of reimbursed prescriptions in 2006 in a sample of the population representative of the country as a whole (31). Results showed that apart from trospium, all drugs had continuation rates of less than 50% at 6 months, less than 25% at 1 year and less than 10% at 2 years and longer (Fig. 1).

The continuation rates for trospium were 46%, 36%, 22% and 16% at 6 months, 1, 2 and 3 years, respectively. The authors speculated that the higher persistence rates seen with trospium might be due to its lack of interaction with concomitant medications, making it a safer option particularly in the elderly. Factors affecting discontinuation likelihood were gender (men > women), age (young > old), dose (high > low) and previous experience with OAB drugs.

Conclusion

There are currently a large number of antimuscarinic drugs on the market with little clear evidence to distinguish one agent from another in terms of efficacy provided an

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adequate dose is used in the clinical setting. In particular, this is due to the paucity of head to head clinical studies. The principal difference between compounds relates to pharmacological and pharmacokinetic factors. Another important aspect is ease of administration and the once daily formulations clearly provide additional patient benefit. Trospium, now available as a new once daily formulation, has the added advantage that it does not cross the blood brain barrier, so it may well be beneficial in elderly patients who are at higher risk of potential effects on the CNS. It is unclear as to whether direct excretion of trospium in the urine is relevant to its clinical use, but this certainly may be important in its profile of action. Indeed, it has been suggested (18,19) that the relative accumulation of active drug in urine, and its consequent anticholinergic effect exerted on the urothelium (32) , may improve the control of urgency. Future work should include further controlled studies, possibly head-to-head comparisons with other once daily antimuscarinics, in order to provide additional insights into the relative benefits of alternative treatment options.

Figure legend

Figure 1. Kaplan-Meier plots of persistence with antimuscarinic drugs for the treatment of overactive bladder. Data expressed as proportion of treatment episodes over time. With kind permission from Spingerlink, Eur J Clin Pharmacol, Persistence with antimuscarinic drug use, 65(3), 2008, 312, Brostrom S, Hallas J, Fig. 1.

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22/07/2010

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Table 1 Efficacy of trospium chloride compared with placebo; results shown represent change from mean baseline values at 12 weeks except where indicated

Study	Dosage	No. patients	Incontinence episodes/day	Micturition/day	Urgency episodes/day
Halaska et al. 2003 (16)	20 mg bid TC[1]	267	-0.5	-7.9	-6.7
Zinner et al. 2004 (17)	20 mg bid TC	256	-2.3[a]	-0.3[a]	-0.3[a]
	Placebo	256	-1.9	-0.2	-0.1
Staskin et al. 2007 (18)	60 mg ER TC	292	-2.48[c]	-2.81[b]	-3.11[b]
	Placebo	300	-1.93	-1.99	-2.12
Dmochowski et al. 2008 (19)	60 mg ER TC	267	-2.4[d]	-2.5[e]	-
	Placebo	276	-1.6	-1.8	-

[1]At week 52

Comparison to placebo: [a]$P \leq 0.0001$; [b]$P < 0.0001$; [c]$P = 0.0022$; [d]$P < 0.001$; [e]$P \leq 0.001$

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Table 2 Improvement in urodynamic parameters with trospium 20 mg bid

Parameter	**Mean treatment effect compared with placebo**	**P value**
Max cystometric bladder capacity (ml)	+37.3	0.0054
Vol at first unstable contraction (ml)	+63.6	0.0015
Vol at max contraction (ml)	+29.2	0.0113
Bladder compliance (ml/cmH_2O)	-1.2	0.1072
Residual urine (ml)	+5.5	0.0285
Max detrusor pressure at first unstable contraction (cmH_2O)	-5.2	0.1278

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Table 3 Treatment emergent adverse events (AEs) at least possibly related to study medication. Data shown are number of events (%)

AE	Halaska et al. 2003 (16)	Zinner et al 2004[1] (17)		Staskin et al 2007[2] (18)		Dmochowski et al. 2008 (19)	
	Trospium 20 mg bid	Placebo	Trospium 20 mg bid	Placebo	Trospium 60 mg ER	Placebo	Trospium 60 mg ER
Gastrointestinal							
Dry mouth	87 (33%)	17 (6.5%)	57 (21.8%)	9 (3.0%)	26 (8.7%)	13 (4.6%)	36 (12.9%)
Constipation	18 (7%)	10 (3.8%)	25 (9.5%)	4 (1.3%)	28 (9.4%)	5 (1.8%)	13 (4.6%)
Abdominal pain	5 (2%)	3 (1.1%)	8 (3.1%)	2 (0.7%)	3 (1.0%)	–	–
Lower abdominal pain	–	–	–	3 (1.0%)	3 (1.0%)	–	–
Abdominal distension	–	–	–	1 (0.3%)	3 (1.0%)	–	–
Constipation aggravated	–	–	–	3 (1.0%)	3 (1.0%)	–	–
Nausea	6 (2%)	–	–	2 (0.7%)	3 (1.0%)	–	–
Dyspepsia	13 (5%)	–	–	3 (1.0%)	6 (2.0%)	–	–
Diarrhoea	2 (1%)	14 (5.4%)	8 (3.1%)	–	–	–	–
Dysphagia	9 (3%)	–	–	–	–	–	–
Nervous system							

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Headache	11 (4%)	12 (4.6%)	17 (6.5%)	8 (2.6%)	3 (1.0%)	–	–
Blurred vision	9 (3%)	–	–	2 (0.7%)	3 (1.0%)	–	–
Renal							
UTI	33 (12%)	–	–	3 (1.0%)	6 (2.0%)	–	–
Urinary retention	–	–	–	1 (0.3%)	4 (1.3%)	–	–
Other							
Dry eye	–	–	–	1 (0.3%)	4 (1.3%)	–	–
Sleeplessness	10 (4%)	–	–	–	–	–	–

[1]Events with ≥ 3% incidence ; [2] Events with ≥ 1% incidence

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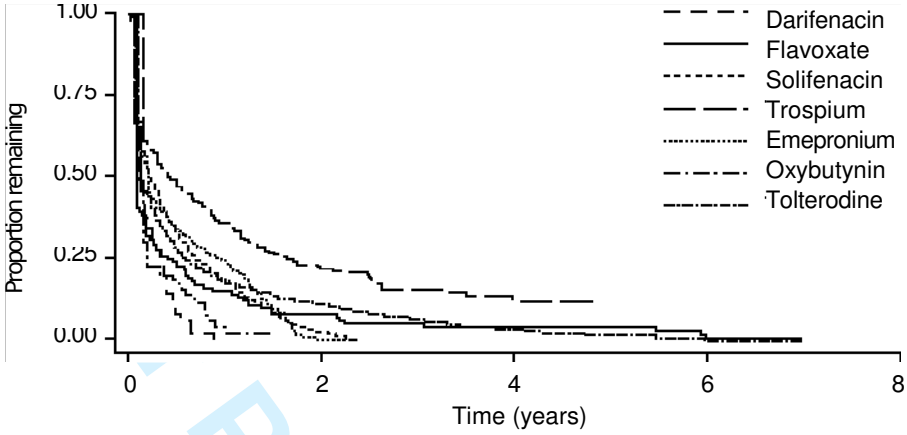

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