REVIEW ARTICLE

Drug Safety 2002; 25 (12): 867-876
0114-5916/02/0012-0867/$25.00/0

A Benefit-Risk Assessment of Extended-Release Oxybutynin

Martin C. Michel

Department of Medicine, University of Essen, Essen, Germany

Contents

Abstract 867
1. Clinical Background 868
2. Properties of Oxybutynin and *N*-Desethyl-Oxybutynin 869
3. Pharmacokinetics of Oxybutynin Extended-Release (ER) 870
4. Efficacy and Tolerability Comparison of Oxybutynin ER and Oxybutynin Immediate-Release 872
5. Comparison With Other Treatments 873
6. Conclusions 874

Abstract

Oxybutynin is a muscarinic receptor antagonist, which has been available for a number of years in its original immediate-release (IR) formulation. While oxybutynin IR has proven effective for the treatment of overactive bladder, its extended use can be limited by adverse effects, particularly dry mouth.

An extended-release (ER) formulation of oxybutynin based on the OROS®[1] system has recently become available, which allows once daily administration.

In direct comparison to oxybutynin IR, oxybutynin ER has an increased oral bioavailability for the parent compound oxybutynin which is accompanied by a reduced bioavailability for the active metabolite *N*-desethyl-oxybutynin. The latter has been implicated in mediating a major part of the adverse effects of oxybutynin treatment.

Two double-blind, placebo-controlled, randomised studies in patients with overactive bladder have demonstrated that oxybutynin ER has a similar efficacy as oxybutynin IR but with improved tolerability. This is in line with clinical pharmacological studies demonstrating a smaller impairment of saliva production with oxybutynin ER than with oxybutynin IR.

Thus, the ER formulation of oxybutynin maintains the therapeutic benefits and concomitantly improves tolerability.

1 The use of tradenames is for product identification purposes only and does not imply endorsement.

1. Clinical Background

Urinary bladder dysfunction is a highly prevalent disease state.[1] A recent study has found that 57% of patients consulting a physician for any reason show symptoms attributable to bladder dysfunction.[2] Overactive bladder (OAB) is an important form of bladder dysfunction. Urodynamically OAB is characterised by involuntary contractions of the detrusor, i.e. smooth muscle of the bladder, during the filling phase of the micturition cycle; this results in a reduced functional bladder capacity and in unpredictable bothersome symptoms. The clinical diagnosis of OAB is usually based on the symptoms of frequency (>8 micturitions every 24 hours), urgency and urge incontinence which can occur singly or in combination and are not explained by metabolic (e.g. diabetes mellitus) or local pathological factors (e.g. urinary tract infections, kidney stones, interstitial cystitis).[3,4] A population-based study from six European countries has found that 17% of the population aged 40 to 75 years have OAB.[5] This is not only bothersome for the affected patients but also has a considerable socio-economic impact. Thus, it is estimated that incontinence alone is responsible for 40 to 60% of all nursing home admissions and, for example, in the US is causing annual costs of $8.1 billion.[6]

Detrusor contractility is predominantly regulated by parasympathetic nerves originating from the sacral spinal cord, which release the neurotransmitter acetylcholine to activate muscarinic acetylcholine receptors on the smooth muscle cells of the detrusor.[7] Muscarinic receptor antagonists reduce involuntary detrusor contractions both in experimental animals and in humans; this increases the functional bladder capacity and reduces micturition frequency and urge symptoms and episodes of urge incontinence.[8] However, it should be noted that such treatment can only help to control symptoms and does not cure the underlying disease.

Antagonist effects on muscarinic receptors in other tissues can elicit adverse events including dry mouth, blurred vision or constipation. Such adverse events, particularly dry mouth due to blockade of muscarinic receptors in the salivary glands, can be so pronounced that continuation of treatment with muscarinic receptor antagonists becomes intolerable in some patients despite its effectiveness. Since OAB is a chronic disease state, any medical treatment of OAB can only be successful if it is sufficiently well tolerated to allow long-term treatment. Attempts to improve the tolerability of muscarinic receptor antagonists have not only involved the identification of new compounds but also the reformulation of existing compounds. The latter approach is at partly based on the experience that in many drug classes a smoothened pharmacokinetic profile is associated with enhanced tolerability.

Oxybutynin is a muscarinic receptor antagonist, which chemically belongs to the tertiary amines. Numerous clinical studies have documented the efficacy of oxybutynin in the treatment of OAB symptoms.[9,10] Direct comparative studies have demonstrated that the efficacy of oxybutynin is similar to those of all other muscarinic receptor antagonists.[11] Previously, oxybutynin has been available as an immediate release (IR) formulation. Recently, an extended release (ER) formulation of oxybutynin has become available, which is the subject of this article. This ER formulation of oxybutynin is based on an osmotic system (OROS®) to continuously deliver oxybutynin to the gastrointestinal tract over a 24-hour period. This system comprises a semipermeable membrane enclosing a bilayer core, of which one contains oxybutynin and the other one osmotic agents; water entering the capsule from the gastrointestinal tract hydrates oxybutynin to form a suspension and expands the osmotic layer, to push out the oxybutynin at a controlled rate through a tiny laser-drilled hole in the capsule membrane.

Since it has been suggested that an active metabolite of oxybutynin, i.e. *N*-desethyl-oxybutynin, is at least partly responsible for mediating the wanted as well as untoward effects of orally administered oxybutynin and since a change in formulation will affect the relative oral bioavailability of

oxybutynin and *N*-desethyl-oxybutynin,[12,13] this article will also address the possible role of such changes for the benefit-risk ratio of OAB treatment with oxybutynin ER, particularly in light of data which have become available since a previous review on oxybutynin ER.[14]

2. Properties of Oxybutynin and *N*-Desethyl-Oxybutynin

Oxybutynin is extensively metabolised in the liver, and undergoes marked first-pass metabolism upon oral administration.[15] This generates two main metabolites, among which phenylcyclohexylglycolic acid is considered to be pharmacologically inactive, whereas *N*-desethyl-oxybutynin is an active metabolite.[16] Since alterations of intestinal oxybutynin release associated with its ER formulation are accompanied by an altered ratio of parent compound and metabolites in the systemic circulation,[12,13] it appears useful to compare the properties of oxybutynin and its active metabolite *N*-desethyl-oxybutynin.

At present five subtypes of muscarinic receptors are recognised, which are designated as M_1, M_2, M_3, M_4 and M_5.[17] Each of these subtypes has a tissue-specific expression profile in the human body. The efficacy of muscarinic receptor antagonists is primarily attributed to their effects on the smooth muscle of the urinary bladder detrusor, while adverse effects such as dry mouth, blurred vision and constipation are attributed to antagonism of muscarinic receptors in the salivary glands, eye and gut, respectively. Studies in humans and various experimental animal species have demonstrated that the urinary bladder expresses both M_2 and M_3 receptors with the former being more numerous.[18-20] Nevertheless, bladder contraction by exogenous or endogenous agonists is mediated predominantly if not exclusively by M_3 receptors in animals[20-22] and, according to very recent data, also in humans.[23] Studies in experimental animals suggest adverse effects of muscarinic receptor antagonists in the salivary glands, the eye and the gut are also mediated predominantly via M_3 receptors;[22,24-26] definitive data in humans, however, are not available for these tissues.

Studies with oxybutynin at cloned muscarinic receptor subtypes have demonstrated an order of affinity (K_i values) of M_3 (0.7 nmol/L) > M_4 (2.0 nmol/L) ≈ M_1 (2.4 nmol/L) ≥ M_2 (6.7 nmol/L) ≥ M_5 (11.0 nmol/L).[8] Waldeck et al.[27] have compared the affinity and antagonistic effects of oxybutynin and *N*-desethyl-oxybutynin in the human urinary bladder and parotid gland. In radioligand binding studies in the bladder they found an affinity of 6.3 nmol/L for both oxybutynin and *N*-desethyl-oxybutynin, whereas affinities in the human parotid gland were 3.2 nmol/L and 2.0 nmol/L for oxybutynin and *N*-desethyl-oxybutynin, respectively ($p < 0.05$ between tissues for *N*-desethyl-oxybutynin but not for oxybutynin). In the same study the authors also compared the ability of both compounds to inhibit bladder contraction stimulated by the muscarinic receptor agonist carbachol. Both oxybutynin and *N*-desethyl-oxybutynin exhibited competitive antagonism with calculated affinities of 15.8 nmol/L and 25.1 nmol/L, respectively. Finally, the authors have compared the ability of oxybutynin and *N*-desethyl-oxybutynin to inhibit contraction of the human bladder as elicited by endogenous agonists upon field stimulation. Both compounds concentration-dependently inhibited the field stimulation-induced contraction with maximal inhibition by 10 μmol/L oxybutynin being 87 ± 6% and that by 10 μmol/L *N*-desethyl-oxybutynin being 91 ± 3%; the required antagonist concentrations for half-maximal inhibition were 79.4 nmol/L and 50.1 nmol/L, respectively. Taken together these results demonstrate that oxybutynin and its metabolite *N*-desethyl-oxybutynin are similarly efficacious and potent antagonists in the human urinary bladder, but the metabolite *N*-desethyl-oxybutynin appears to have a slightly higher affinity to the receptors in the salivary gland than those in the bladder. The reasons for this minor difference remain unclear, since both tissues are believed to contain the same subtype of muscarinic receptors; hence, other factors such as differential tissue penetration should be considered.

3. Pharmacokinetics of Oxybutynin Extended-Release (ER)

The pharmacokinetic properties of oxybutynin IR upon oral administration have been comprehensively reviewed.[8,9] The pharmacokinetic properties of oxybutynin IR upon direct intravesical administration have also been reported,[28,29] but do not appear relevant in the present context. Since most pharmacokinetic studies with oxybutynin ER have been performed in direct comparison with oxybutynin IR, they will be discussed together.

The pharmacokinetic properties of oxybutynin IR show marked inter-individual variation. Due to an extensive first-pass metabolism, the oral bioavailability of oxybutynin IR is low, i.e. ≤6%.[15] First-pass metabolism of oxybutynin generates the metabolite *N*-desethyl-oxybutynin which has similar effects on muscarinic receptors as oxybutynin itself.[27] Upon oral administration maximal plasma concentrations of oxybutynin are reached after 0.5 to 0.8h in young healthy, elderly healthy and elderly frail subjects, both in single dose studies and during steady state.[16] Peak concentrations upon single oral administration of oxybutynin IR 5mg in young and elderly healthy subjects are 13.4 and 16.7 μg/L, respectively, but reach values of 32.0 μg/L in elderly frail subjects; in the latter group, similar values were also observed during steady state.[16] The terminal half life after single oral administration was reported to be 2.0 and 2.3 hours in young and elderly healthy subjects but 4.6 hours in elderly frail subjects ($p < 0.05$ *vs* elderly healthy subjects).[16] During steady state, the respective values for elderly healthy and frail subjects were 3.1 and 5.4 hours.[16] Taken together this resulted in a gradual increase in estimated areas under the concentration-time curve (AUC) values following single oral administration with oxybutynin IR 5mg of 21.4 μg/L • h in young healthy subjects, of 31.8 μg/L • h in elderly healthy subjects and of 48.4 μg/L • h in elderly frail subjects ($p < 0.05$ *vs* elderly healthy subjects). During steady state treatment with oxybutynin IR 5mg three times daily in elderly healthy subjects, an AUC of 36.9 μg/L • h was reported, while in elderly frail subjects with the lower dose of oxybutynin IR 5mg twice daily, an AUC of 106.3 μg/L • h was reached ($p < 0.02$ *vs* elderly healthy subjects).[16] Following intravenous administration oxybutynin has a half-life of 2 to 5 hours, and its clearance is 26 to 34 L/h.[15] No major gender differences in pharmacokinetic parameters of oxybutynin IR were observed in young healthy volunteers.[15,16] Administration of oxybutynin IR with a meal delayed its absorption and enhanced systemic bioavailability of the parent compound in young healthy subjects by 25%.[30] In a comparison of elderly frail with young healthy subjects, the bioavailability of oxybutynin more than doubled, while at the same time that of *N*-desethyl-oxybutynin increased by less than 25%.[16] In another study, a similar trend for an increased bioavailability in the elderly was also seen but failed to reach statistical significance.[31]

The pharmacokinetics of oxybutynin ER have been characterised in direct comparative studies with oxybutynin IR. In a randomised, open-label, two-way, cross-over study 13 healthy women (aged 41 to 68 years) received either three tablets of oxybutynin ER 5mg once daily or oxybutynin IR 5mg three times daily for 4 days with a wash-out phase of 5 to 7 days between treatments.[12] Blood samples for the pharmacokinetic studies were obtained on day 1 (first dose) and day 4 (steady state), and the resulting data are summarised in table I. In this study, the ER formulation delayed oxybutynin release and therefore produced smoother blood concentration profiles for both oxybutynin and *N*-desethyl-oxybutynin during the day. Administration of the ER formulation also resulted in an increased oxybutynin AUC relative to that of oxybutynin IR and, in addition, the AUC of *N*-desethyl-oxybutynin was reduced following administration of oxybutynin ER. Thus, with administration of oxybutynin IR the AUC of *N*-desethyl-oxybutynin was approximately six times as large as that of oxybutynin, whereas it was less than three times that of oxybutynin with administration of oxybutynin ER. Accordingly, the administration of oxybutynin ER increased the bioavailability of oxybutynin by

Table I. Pharmacokinetics of oxybutynin and its metabolite *N*-desethyl-oxybutynin with administration of the immediate release (IR) and extended release (ER) formulation. Data are means ± standard deviation of 13 women and taken from Gupta and Sathyan[12]

	Oxybutynin		*N*-Desethyl-oxybutynin	
	IR	ER	IR	ER
Day 1				
C_{max} (ng/L)	12.0 ± 5.0	4.2 ± 1.6[a]	43.1 ± 11.7	13.9 ± 6.6[a]
t_{max} (h)	3.2 ± 4.0	13.2 ± 6.9[a]	3.5 ± 4.0	15.0 ± 5.8[a]
AUC (ng/L • h)	72 ± 39	117 ± 50[a]	443 ± 224	310 ± 184[a]
Ratio of oxybutynin/*N*-desethyl-oxybutynin			0.17 ± 0.07	0.48 ± 0.29[a]
Day 4				
C_{max} (ng/L)	12.4 ± 4.1	6.7 ± 2.1[a]	44.7 ± 20.3	22.5 ± 13.6[a]
t_{max} (h)	5.0 ± 4.2	5.2 ± 3.7	1.8 ± 2.2	7.1 ± 4.2
C_{min} (ng/L)	1.4 ± 1.2	2.8 ± 1.6[a]	5.8 ± 6.5	7.1 ± 6.0
$t_{1/2}$ (h)	9.0 ± 2.4	13.8 ± 2.9[a]	4.0 ±1.4	8.3 ± 2.5[a]
AUC (ng/L • h)	81 ± 43	109 ± 43[a]	483 ± 281	304 ± 145[a]
Ratio of oxybutynin/*N*-desethyl-oxybutynin			0.18 ± 0.08	0.40 ± 0.18[a]
Bioavailability (% of oxybutynin IR)		153 ± 67		69 ± 23

a All paired comparisons between oxybutynin IR and oxybutynin ER marked are statistically significant ($p < 0.05$).

AUC = area under the concentration-time curve; $\mathbf{C_{max}}$ = maximum plasma drug concentration after single-dose administration; $\mathbf{C_{min}}$ = minimum plasma drug concentration after single-dose administration; $\mathbf{t_{1/2}}$ = elimination half-life; $\mathbf{t_{max}}$ = time to reach maximum concentration following drug administration.

approximately 50%, but reduced that of *N*-desethyl-oxybutynin by approximately 30%.

Since *N*-desethyl-oxybutynin had exhibited a slightly less beneficial ratio of effects on the bladder relative to those on salivary glands than oxybutynin in *in vitro* studies,[27] these pharmacokinetic data suggest that the ER formulation of oxybutynin shifts the ratio of parent compound and metabolite towards the parent compound. This could contribute to an enhanced tolerability *in vivo*. Since parent compound and metabolite have a very similar affinity to the muscarinic receptors in the human bladder,[27] the ER formulation is unlikely to affect the efficacy of oxybutynin treatment.

This hypothesis has been tested in a pharmacokinetic/pharmacodynamic study in 29 young, healthy subjects.[13] In a randomised, double-blind, two-period, cross-over design volunteers received either oxybutynin ER 10mg in the morning and placebo 8 hours later or oxybutynin IR 5mg in the morning and 8 hours later for 4 days. Prior to treatment and on the first and fourth day of each treatment period, salivary secretion and the pharmacokinetics of oxybutynin and *N*-desethyl-oxybutynin were monitored for 16 hours. The pharmacokinetic part of that study confirmed the findings of Gupta and Sathyan,[12] specifically with regard to a shift in the ratio of oxybutynin and *N*-desethyl-oxybutynin towards the latter upon administration of oxybutynin ER. In addition, subjects receiving oxybutynin ER reported less dry mouth than those receiving oxybutynin IR on day 4 of the study ($p < 0.05$). This observation was confirmed objectively by measuring salivation, which was reduced by 38.4 and 15.5%, upon administration of oxybutynin IR and oxybutynin ER, respectively ($p < 0.001$). In a combined analysis of both treatment groups, both subjective assessment of dry mouth and objective measurement of salivation correlated significantly with plasma concentrations of *N*-desethyl-oxybutynin but not with those of oxybutynin. These data support the hypothesis that the adverse event dry mouth is mediated largely by the oxybutynin metabolite *N*-desethyl-oxybutynin.

Taken together these data demonstrate that the ER formulation of oxybutynin not only yields a smoother pharmacokinetic profile but also increases the bioavailability of the parent compound oxybutynin and concomitantly reduces the bioavailability of

the metabolite *N*-desethyl-oxybutynin. This finding gains importance in light of the reports that: (i) oxybutynin exhibits a slightly more favourable affinity relationship between bladder and salivary glands than *N*-desethyl-oxybutynin;[27] and (ii) that the occurrence of dry mouth is correlated with the plasma concentrations of *N*-desethyl-oxybutynin but not those of oxybutynin.[13] However, it should be noted that similar pharmacokinetic alterations upon administration of oxybutynin IR have been observed in elderly frail patients[16] and in young healthy subjects in conjunction with a meal[30] as compared with young healthy subjects receiving oxybutynin IR without a meal. Therefore, it would be interesting to know whether the effects of being a frail elderly person and/or of taking oxybutynin with a meal are additive with those of the ER formulation of oxybutynin, but no such studies have yet been reported.

4. Efficacy and Tolerability Comparison of Oxybutynin ER and Oxybutynin Immediate-Release

The efficacy and tolerability of oxybutynin ER in the treatment of OAB symptoms has been tested in two randomised, double-blind, direct comparative studies with oxybutynin IR. Since efficacy partly depends on the achievable dose with adequate tolerability, the efficacy and tolerability of the two formulations will be discussed together. Anderson et al.[32] reported on a multicentre, randomised, double-blind, double-dummy dose-finding study in which the efficacy of oxybutynin IR and oxybutynin ER was compared in 97 women and eight men (aged 34 to 76 years) with urge incontinence or mixed incontinence. By design this study has included only patients who were known responders to oxybutynin IR. Following a one-week run-in phase, the patients were randomised to receive either oxybutynin ER 5 to 30mg once daily or oxybutynin IR 5mg one to four times per day. In all patients the starting dose was oxybutynin 5mg once daily. This dose was increased in 4 to 7 day intervals until one of three end-points had ben reached [no more urge incontinence episodes during the last two days, maximum tolerated dose (defined as 5mg less than the dose at which intolerable anti-muscarinic effects occurred) or reaching the maximum dose permissible according to study protocol]; the mean final oxybutynin dose in the two groups was not reported. The primary efficacy parameter in this study was the reduction in the number of urge incontinence episodes per week. Oxybutynin IR and oxybutynin ER reduced the mean number of urge incontinence episodes from 23.4 to 3.8 and from 27.4 to 4.8 episodes per week, respectively (not significantly different). Both oxybutynin formulations also similarly improved various secondary efficacy parameters. Most importantly, 52 and 51% of patients treated with oxybutynin ER and oxybutynin IR, respectively, were free of urge incontinence episodes at the end of the study; however, this should be interpreted in light of the fact that only known oxybutynin responders had been included into the study. Dose-dependency was not apparent within the investigated dosage range, but interpretation of this is difficult due to small patient numbers. At least one adverse event was observed in 87% of patients treated with oxybutynin ER and 94% of those treated with oxybutynin IR. As expected dry mouth was the most frequent adverse event and occurred in 68% of patients receiving oxybutynin ER and 87% of those receiving oxybutynin IR ($p = 0.04$). Moderate to severe dry mouth was also significantly less frequent with oxybutynin ER than with oxybutynin IR (25 *vs* 46%, $p = 0.03$). Taken together this study demonstrated a similar efficacy of both oxybutynin formulations but a statistically significant improvement of tolerability for oxybutynin ER relative to oxybutynin IR.

In a second study, the efficacy and safety of oxybutynin ER and oxybutynin IR were compared in 226 patients (mean age 58.8 *vs* 59.6 years and percentage of females 88.3 *vs* 90.4%, respectively) with seven to 45 incontinence episodes per week.[33] All study participants were known responders to muscarinic receptor antagonists. Following a 2-week run-in phase, the patients were randomised to receive oxybutynin ER 5mg once

daily or oxybutynin IR 5mg once daily. The dosage of both formulations was increased every 7 days in 5mg steps up to maximal daily doses of 20mg until an optimal relationship between efficacy and tolerability was achieved. When unacceptable antimuscarinic effects were observed, the dose was reduced by 5mg. After the optimal dose had been reached, treatment was continued for 1 week, but the final oxybutynin dose in both groups was not reported. The dose-dependent risk to develop dry mouth was analysed by post-hoc Kaplan-Meier curves, in which the percentage of patients starting to experience dry mouth was plotted against dose. Both formulations of oxybutynin were similarly efficacious since oxybutynin ER and oxybutynin IR reduced incontinence episodes from 18.6 to 2.9 and from 19.8 to 4.4 per week, respectively (not significantly different). The occurrence of dry mouth was dose-dependent with both formulations. At each dose level, there was a trend for a lower incidence of dry mouth with oxybutynin ER as compared with oxybutynin IR, and this reached statistical significance for both moderate to severe dry mouth ($p = 0.007$) and for all severities of dry mouth ($p = 0.003$) if the entire dose-response-curve was analysed as a Kaplan-Meier curve.

Indirect conclusions regarding the tolerability of oxybutynin ER can be drawn from an open-label study involving 256 patients with urge or mixed incontinence as reported by Gleason et al.[34] In this study, oxybutynin ER was initially administered in a dosage of 5mg once daily, and this could be increased in 5mg increments in weekly intervals until continence was achieved for at least 2 days or until the best balance between continence and adverse effects had been reached. After reaching this dose level, oxybutynin ER treatment continued for 12 weeks. The incidence of dry mouth was dose-dependent since it was reported to be 28, 32, 52 and 54% at a dose of 5, 10, 15 and ≥20 mg/day; at these dosage levels the incidence of moderate to severe dry mouth was 4, 15, 17 and 19%, respectively. While this study did not have a control group, the reported incidence of dry mouth is in good agreement with values reported from the active treatment arm of controlled studies with oxybutynin ER but considerably lower than values reported for oxybutynin IR.[32,33] Hence, this open-label study confirms the improved tolerability of oxybutynin ER.

Although bladder dysfunction can also occur in children, only very limited data are available for its treatment in this patient group. A recent retrospective analysis of 25 children (14 with neurogenic bladder dysfunction, 11 with OAB without signs of neurological abnormalities) reported that the efficacy of oxybutynin ER was at least as good as that of oxybutynin IR, whereas tolerability tended to be better.[35] Accordingly, families reported a much better compliance with oxybutynin ER than with oxybutynin IR.

5. Comparison With Other Treatments

Oxybutynin IR and oxybutynin ER have not only been compared with placebo and with each other but also with other medical treatment modalities. Several studies have compared the efficacy and tolerability of oxybutynin IR relative with that of propiverine, tolterodine or trospium chloride (for reviews see Malone-Lee[11] and Harvey et al.[36]). While all of these studies have reported similar efficacy of oxybutynin and the comparison drug, the tolerability of oxybutynin did not match that of the others. Since oxybutynin ER appears to have similar efficacy but improved tolerability relative to oxybutynin IR, direct comparative studies have been performed with oxybutynin ER and other muscarinic receptor antagonists, most notably tolterodine. In the analysis of such comparisons, it should be borne in mind that tolterodine was originally marketed in a IR formulation but is now also available in a ER formulation which allows once daily administration.[37]

A single-dose, randomised, double-blind, four-treatment, four-period, cross-over study has compared the effects of placebo, oxybutynin IR 5mg, oxybutynin ER 10mg and tolterodine IR 2mg in 36 healthy volunteers over a period of 12 hours.[38] While all three active treatments decreased saliva output relative to placebo, saliva production dur-

ing the entire observation period assessed as AUC was similar for oxybutynin ER and tolterodine IR with both producing significantly less inhibition than oxybutynin IR ($p < 0.01$).

Appell et al.[39] have reported the results from a randomised, double-blind comparative study between oxybutynin ER and tolterodine IR in 378 patients (83% females) with OAB and 7 to 50 episodes of urge incontinence per week. The patients were randomised to receive either oxybutynin ER 10mg once daily or tolterodine IR 2mg twice daily for 12 weeks. The randomisation was performed within predefined strata of OAB severity, and both groups had similar basal numbers of urge incontinence episodes (25.5 *vs* 24.6 per week), total incontinence episodes (28.4 *vs* 28.0 per week) and micturition frequency (92.9 *vs* 91.8 voids per week). After 12 weeks of treatment, the mean remaining urge incontinence (6.1 *vs* 7.8 episodes/week, $p = 0.03$), total incontinence (7.1 *vs* 9.3 episodes/week, $p = 0.02$) and micturition frequency (67.1 *vs* 71.5 voids/week, $p = 0.02$) were less in patients treated with oxybutynin ER than in those treated with tolterodine IR. Concomitantly, the incidence of dry mouth (28.1 *vs* 33.2%), moderate to severe dry mouth (10.2 *vs* 10.9%) and various other adverse events did not significantly differ between oxybutynin ER and tolterodine IR treatment. The tolerability results of this study are in line with previous studies since both oxybutynin ER[32,33] and tolterodine IR[36] were reported to be better tolerated than oxybutynin IR. The efficacy results of the above study, however, are not easily reconciled with previous findings since four studies have demonstrated that oxybutynin IR is similarly effective as tolterodine IR and two studies have reported that oxybutynin IR is similarly effective as oxybutynin ER.[32,33] Against this background further data are required for a definitive assessment of the efficacy of oxybutynin ER relative to tolterodine IR.

The efficacy and tolerability of oxybutynin ER 10mg once daily has also been compared with that of tolterodine ER 4mg once daily in a randomised, double-blind study lasting 8 weeks and involving 1290 patients (73% females) with OAB. A preliminary analysis of the first 103 patients from that study has recently been presented.[40] According to this preliminary analysis, oxybutynin ER and tolterodine ER similarly reduced the number of daily incontinence episodes by 2.64 and 2.65, respectively. The occurrence of dry mouth during treatment was assessed both as a categorical variable and on a visual analogue scale. Either assessment revealed a greater incidence of dry mouth during oxybutynin ER than tolterodine ER treatment, but the difference was more pronounced using the visual analogue scale (increase over baseline 1457% for oxybutynin ER *vs* 479% for tolterodine ER, $p < 0.01$). In addition, the percentage of patients dropping-out of the study was also significantly greater for oxybutynin ER than for tolterodine ER (33 *vs* 17.5%, $p < 0.01$). A definitive interpretation of these findings has to await publication of the full study.

Taken together, comparative studies indicate that oxybutynin ER is at least as effective as other drugs such as tolterodine. While an inferior tolerability for oxybutynin IR relative to tolterodine IR[36] seems to have been overcome by oxybutynin ER,[39] preliminary data indicate that the improved tolerability of oxybutynin ER may not be sufficient to match that of tolterodine ER.[40]

6. Conclusions

The overall data demonstrate that oxybutynin ER is effective in the treatment of OAB, particularly with regard to the reduction of incontinence episodes. Its efficacy is similar to that of oxybutynin IR and at least as good as that of tolterodine. The improvement of OAB symptoms with oxybutynin ER treatment is achieved with fewer adverse effects, particularly less dry mouth, than with oxybutynin IR.[32,33] Open-label studies in adult[34] and paediatric patients[35] as well as clinical pharmacological studies of saliva production[13,38] confirm the improved tolerability of oxybutynin ER. The underlying mechanisms appear to involve a smoothened pharmacokinetic profile, enhanced bioavailability of the parent compound

oxybutynin and concomitantly reduced bioavailability of the metabolite *N*-desethyl-oxybutynin which may be responsible for a major part of the adverse effects.[12,13]

Since OAB is a chronic symptom complex which cannot be cured by currently available medications, long-term effectiveness of medical treatment is necessary to improve the quality of life of patients with this condition and to ease the socioeconomic burden. This can only be achieved if the medications used to treat this condition are not only effective but also have acceptable tolerability. In this regard oxybutynin ER represents incremental progress relative to oxybutynin IR. The size of this benefit remains to be determined under real-life conditions and for long-term use, allowing a cost-effectiveness analysis. Moreover, the potential benefit of oxybutynin ER must be compared in greater detail to other currently available treatment options.

Acknowledgements

The authors have provided no information on sources of funding or on conflicts of interest directly relevant to the content of this review.

References

1. Hunskaar S, Arnold EP, Burgio K, et al. Epidemiology and natural history of urinary incontinence (UI). In: Abrams P, Khoury S, Wein A, editors. Incontinence. Plymouth: Plymbridge Distributors Ltd, 1999: 197-226
2. Goepel M, Hoffmann J, Piro M, et al. Prevalence and physician awareness of symptoms of urinary bladder dysfunction. Eur Urol 2002; 41: 234-9
3. Bulmer P, Abrams P. The overactive bladder. Rev Contemp Pharmacother 2000; 11: 1-11
4. Wyndaele JJ. The overactive bladder. BJU Int 2001; 88: 135-40
5. Milsom I, Abrams P, Cardozo L, et al. How widespread are the symptoms of an overactive bladder and how are they managed? a population-based prevalence study. BJU Int 2001; 87: 760-6
6. Luscombe FA. Socioeconomic burden of urinary incontinence with focus on overactive bladder and tolterodine treatment. Rev Contemp Pharmacother 2000; 11: 43-62
7. Andersson K-E. Pharmacology of lower urinary tract smooth muscles and penile erectile tissues. Pharmacol Rev 1993; 45: 253-308
8. Chapple CR. Muscarinic receptor antagonists in the treatment of overactive bladder. Urology 2000; 55 Suppl. 5A: 33-46
9. Yarker YE, Goa KL, Fitton A. Oxybutynin: a review of its pharmacodynamic and pharmacokinetic properties, and its therapeutic use in detrusor instability. Drugs Aging 1995; 6: 243-62
10. Andersson K-E, Chapple CR. Oxybutynin and the overactive bladder. World J Urol 2001; 19: 319-23
11. Malone-Lee JG. The efficacy, tolerability and safety profile of tolterodine in the treatment of overactive/unstable bladder. Rev Contemp Pharmacother 2000; 11: 29-42
12. Gupta SK, Sathyan G. Pharmacokinetics of an oral once-a-day controlled-release oxybutynin formulation compared with immediate-release oxybutynin. J Clin Pharmacol 1999; 39: 289-96
13. Sathyan G, Chancellor MB, Gupta SK. Effects of OROS controlled-release delivery on the pharmacokinetics and pharmacodynamics of oxybutynin chloride. Br J Clin Pharmacol 2001; 52: 409-17
14. Comer AM, Goa KL. Extended-release oxybutynin. Drugs Aging 2000; 16: 149-55
15. Douchamps J, Derenne F, Stockis A, et al. The pharmacokinetics of oxybutynin in man. Eur J Clin Pharmacol 1988; 35: 515-20
16. Hughes KM, Lang JC, Lazare R, et al. Measurement of oxybutynin and its N-desethyl metabolite in plasma, and its application to pharmacokinetic studies in young, elderly and frail elderly volunteers. Xenobiotica 1992; 22: 859-69
17. Caulfield MP, Birdsall NJ. International Union of Pharmacology: XVII. classification of muscarinic acetylcholine receptors. Pharmacol Rev 1998; 50: 279-90
18. Wang P, Luthin GR, Ruggieri MR. Muscarinic acetylcholine receptor subtypes mediating urinary bladder contractility and coupling to GTP binding proteins. J Pharmacol Exp Ther 1995; 273: 959-66
19. Goepel M, Gronewald A, Krege S, et al. Muscarinic receptor subtypes in porcine detrusor: comparison with humans and regulation by bladder augmentation. Urol Res 1998; 26: 149-54
20. Yamanishi T, Chapple CR, Yasuda K, et al. The role of M2-muscarinic receptors in mediating contraction of the pig urinary bladder in vitro. Br J Pharmacol 2000; 131: 1482-8
21. Hegde SS, Choppin A, Bonhaus D, et al. Functional role of M2 and M3 muscarinic receptors in the urinary bladder of rats in vitro and in vivo. Br J Pharmacol 1997; 120: 1409-18
22. Choppin A, Eglen RM, Hegde SS. Pharmacological characterization of muscarinic receptors in rabbit isolated iris sphincter muscle and urinary bladder smooth muscle. Br J Pharmacol 1998; 124: 883-8
23. Fetscher C, Fleichman M, Schmidt M, et al. M3 muscarinic receptors mediate contraction of human urinary bladder. Br J Pharmacol 2002; 136: 641-4
24. Tobin G. Muscarinic receptor subtypes in the submandibular gland and the urinary bladder of the rabbit: *in vivo* and *in vitro* functional comparisons of receptor antagonists. J Auton Pharmacol 1995; 15: 451-63
25. Eglen RM, Hegde SS, Watson N. Muscarinic receptor subtypes and smooth muscle function. Pharmacol Rev 1996; 48: 531-65
26. Choppin A, Eglen RM. Pharmacological characterization of muscarinic receptors in dog isolated ciliary and urinary bladder smooth muscle. Br J Pharmacol 2001; 132: 835-42
27. Waldeck K, Larsson B, Andersson KE. Comparison of oxybutynin and its active metabolite, N-desethyl-oxybutynin, in the human detrusor and parotid gland. J Urol 1997; 157: 1093-7
28. Madersbacher H, Knoll M. Intravesical application of oxybutynin: mode of action controlling detrusor hypereflexia: preliminary results. Eur Urol 1995; 28: 340-4
29. Di Stasi SM, Giannantoni A, Navarra P, et al. Intravesical oxybutynin: mode of action assessed by passive diffusion and electromotive administration with pharmacokinetics of oxy-

butynin and N-desethyl-oxybutynin. J Urol 2001; 166: 2232-6
30. Yong C-L, Yu D, Eden L, et al. Effect of food on the pharmacokinetics of oxybutynin in normal subjects [abstract]. Pharm Res 1991; 8 Suppl.: S-320
31. Ouslander JG, Blaustein J, Connor A, et al. Pharmacokinetics and clinical effects of oxybutynin in geriatric patients. J Urol 1988; 140: 47-50
32. Anderson RU, Mobley D, Blank B, et al. Once daily controlled versus immediate release oxybutynin chloride for urge urinary incontinence. J Urol 1999; 161: 1809-12
33. Versi E, Appell R, Mobley D, et al. Dry mouth with conventional and controlled-release oxybutynin in urinary incontinence. Obstet Gynecol 2000; 95: 718-21
34. Gleason DM, Susset J, White C, et al. Evaluation of a new once-daily formulation of oxybutynin for the treatment of urinary urge incontinence. Urology 1999; 54: 420-3
35. Youdim K, Kogan BA. Preliminary study of the safety and efficacy of extended-release oxybutynin in children. Urology 2002; 59: 428-32
36. Harvey MA, Baker K, Wells GA. Tolterodine versus oxybutynin in the treatment of urge urinary incontinence: a meta-analysis. Am J Obstet Gynecol 2001; 185: 56-61
37. van Kerrebroeck P, Kreder K, Jonas U, et al. Tolterodine once-daily: superior efficacy and tolerability in the treatment of overactive bladder. Urology 2001; 57: 414-21
38. Chancellor MB, Appell RA, Sathyan G, et al. A comparison of the effects on saliva output of oxybutynin chloride and tolterodine tartrate. Clin Ther 2001; 23: 753-60
39. Appell RA, Sand P, Dmochowski R, et al. Prospective randomized controlled trial of extended-release oxybutynin chloride and tolterodine tartrate in the treatment of overactive bladder: results of the OBJECT Study. Mayo Clin Proc 2001; 76: 358-63
40. Sussman D. Dry mouth is more pronounced in patients with overactive bladder treated with extended release oxybutynin compared to tolterodine [abstract]. Eur Urol Suppl 2002; 1: 133

Correspondence and offprints: Dr *Martin C. Michel*, Mediziuische Klinik, Universitätsklinikum Essen, Essen, 45122, Germany.
E-mail: martin.michel@uni-essen.de