Pharmacokinetics of the R- and S-Enantiomers of Oxybutynin and N-Desethyloxybutynin Following Oral and Transdermal Administration of the Racemate in Healthy Volunteers

R. Howard Zobrist,[1,3] Bernhard Schmid,[2] Alexander Feick,[2] Danyi Quan,[1] and Steven W. Sanders[1]

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Purpose. To characterize the enantiomers of oxybutynin (OXY) and N-desethyloxybutynin (DEO) following transdermal and oral administration.
Methods. OXY was administered either as a single transdermal system over a 96 h wear period or as a single 5 mg immediate-release tablet to 18 healthy male and female subjects in a randomized, open-label, two-way crossover design. Blood samples were collected for 108 h after application of the transdermal system and for 6 h after oral administration. Plasma concentrations of the R- and S-enantiomers of OXY and DEO were assayed by LC-MS/MS. Enantiomer *in vitro* skin flux was evaluated using human cadaver skin.
Results. *In vitro* skin flux studies demonstrated equal absorption of R and S- OXY. Plasma concentrations and pharmacokinetic parameters of the R-enantiomers of OXY and DEO were slightly lower than the S-enantiomers following transdermal OXY. The relative AUC values were S-OXY>S-DEO>R-OXY>R-DEO. The AUC ratios of DEO/OXY were less than 1 for both the R- and S- enantiomers. Following oral dosing, plasma DEO concentrations greatly exceeded OXY resulting in relative AUC values of R-DEO>S-DEO>S-OXY>R-OXY. The mean AUC ratios of S- and R-DEO/OXY were 3.25 and 8.93, respectively.
Conclusions. Stereoselective metabolism of OXY was evident following both transdermal and oral administration of OXY. The reduced pre-systemic metabolism of transdermally administered OXY compared to oral administration resulted in not only significantly lower DEO plasma concentrations, but also a different metabolite pattern. The differences between R-OXY and R-DEO following the two routes of administration support the potential for comparable clinical efficacy and reduced anticholinergic side-effects with transdermal treatment.

KEY WORDS: oxybutynin; N-desethyloxybutynin; transdermal delivery; enantiomers; human; pharmacokinetics.

INTRODUCTION

Oxybutynin (OXY) is a safe and effective drug for the treatment of overactive bladder (1–3). OXY is a tertiary amine with a single chiral carbon and is generally administered as the racemic mixture. The compound possesses both anticholinergic and smooth muscle relaxant activity (4,5). Preclinical studies in isolated tissues and *in vivo* have shown that the anticholinergic activity of R-OXY is approximately 10–100 times greater than S-OXY (6,7). However, there appears to be no stereoselectivity between isomers with regard to OXY's smooth muscle relaxant activities (6,7).

Though OXY is well absorbed from the gastrointestinal tract following oral administration, its systemic bioavailability is less than 10% compared to intravenous dosing due to extensive presystemic metabolism (8). The circulating primary metabolite, N-desethyloxybutynin (DEO), is present in plasma at concentrations approximately 4–10 times those of the parent compound and has similar anticholinergic effects to OXY (9). In therapeutic use, DEO appears to contribute greatly to the anticholinergic side-effects associated with oral administration of OXY (10). The high incidence of anticholinergic adverse effects, dry mouth, constipation, decreased sweating, and mydriasis with poor accommodation, are both dose and treatment-limiting in the majority of patients (10–12).

The present study in healthy male and female subjects examined the pharmacokinetics of the enantiomers of OXY following transdermal (TD) and oral administration.

EXPERIMENTAL METHODS

Subjects

Eighteen healthy, non-smoking subjects, 8 males and 10 females, were enrolled in the study. Subjects ranged in age from 19–45 years and weighed 54–84 kg. Physical examinations, clinical chemistry, hematology, and urinalysis parameters were all normal. On enrollment, subjects were sequentially assigned to receive the two study treatments according to a randomized, crossover design in which subjects received each study treatment once.

Clinical Materials

The transdermal administration of OXY was accomplished by the application of one OXY transdermal system (TDS) (Watson Laboratories, Inc., Salt Lake, City, UT) to the lower abdomen and worn for 96 h. OXY TDS is a matrix-type transdermal system containing OXY and triacetin (a skin permeation enhancer) dissolved in an acrylic block-copolymer adhesive with a surface area of 39 cm^2 containing 36 mg racemic OXY, designed to continuously deliver OXY over a 3–4 day wear period.

For the oral administration of OXY, subjects were administered one immediate release Ditropan® tablet (5 mg OXY, Alza Pharmaceuticals, Palo Alto, CA) with 100 mL distilled water.

Clinical Protocol

This was a randomized, open-label, two-way crossover study conducted at Gateway Medical Research, Inc, St. Charles, MO, in accordance with the U.S. Code of Federal Regulations (21 CFR 50, 56, and 312), the ethical principles stated in the latest version of the Declaration of Helsinki, and

[1] Watson Laboratories, Inc., Salt Lake City, Utah 84108.
[2] Applied Analytical Industries Deutchland GmbH & Co KG, Nue-Ulm, Germany.
[3] To whom correspondence should be addressed. (e-mail: hzobrist@watsonpharm.com)

ABBREVIATIONS: AUC_{0-t}, area under the time-concentration curve from time 0 to time t; $AUC_{0-\infty}$, area under the time-concentration curve from time 0 to infinity; C_{max}, maximal plasma drug concentration; DEO, N-desethyloxybutynin; OXY, oxybutynin; TD, transdermal; TDS, transdermal system.

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the applicable guidelines for good clinical practice. Institutional Review Board approval was obtained (St. Charles Community Institutional Review Board, St. Charles, MO) and all subjects provided written informed consent prior to study participation.

The treatment phase consisted of two study periods. After an overnight fast, subjects were administered either one 5 mg immediate-release OXY tablet or wore the OXY TDS on the lower abdomen for 96 h. No food was permitted until a standardized meal was served 2 h after dosing. When assigned to wear the transdermal system, subjects were confined for two 12-h intervals to allow for frequent phlebotomy during these intervals. At other phlebotomy time-points, the subjects returned to the study site as outpatients. When taking the oral tablet, subjects were confined for 6 h to allow for frequent phlebotomy. The start of the two study periods was separated by 7 days.

Venous blood samples were collected into heparinized green top Vacutainer™ tubes by direct venipuncture within 30 min prior to application of the OXY transdermal system and then at 2, 4, 6, 8, 10, 12, 24, 48, 72, 96, 96.5, 97, 98, 100, 104, and 108 h following system application. Blood samples were collected within 30 min prior to tablet administration and then at 10, 20, 30, 45, 60, 90, 120, 180, 240, and 360 min after oral OXY administration.

In Vitro Skin Flux Experiments

In vitro human cadaver skin flux studies were conducted using modified Franz non-jacketed permeation cells (13) with typically four replicate determinations being obtained with each donor skin/system combination. Heat separated human epidermal membrane was prepared according to the method of Kligman (14) and cut into rectangular strips. An OXY TDS was cut into circular discs approximately 0.72 cm^2 in diameter. The release liner was peeled away, the circular disc applied to the stratum corneum of the dermatomed human cadaver skin and the skin-matrix loaded into the diffusion cell with the epidermal side facing the receiver compartment. The receiver compartment was filled with 6.3 mL of an aqueous solution containing 0.02% sodium azide as a bacteriostat. The temperature of the skin surface was maintained at 32°C by placing the cells in a circulating water bath positioned over a stirring module. At predetermined sampling intervals over 96 h, the entire contents of the receiver compartment were collected for quantitation of OXY enantiomer concentrations.

Analytical Methods

Clinical Study Sample Analysis

Plasma OXY and DEO enantiomeric concentrations were determined by a validated high performance liquid chromatography-mass spectrometry/mass spectrometry (HPLC-MS/MS) method. OXY and DEO were extracted from 1.0 mL of plasma spiked with 10 ng of drofenin HCl internal standard (Sigma-Aldrich Co., St. Louis, MO, USA) dissolved in 25 μl of methanol. All samples were mixed with 200 μl of Na_2CO_3 buffer (1M, pH 9.5) and 7 mL of n-hexane. The plasma samples were extracted in an overhead shaker for 20 min, the organic phase transferred to a fresh vial and evaporated to dryness under a nitrogen stream at 50°C. The dried residue was reconstituted in 50 μl of HPLC mobile phase (acetonitrile/10 mM ammonium formate buffer, 90/10 v/v) and a 25 μL aliquot injected onto a ChromTech Chiral-AGP 150.2 LC-column (150 mm × 2 mm, particle size 5 μm) (mobile phase flow rate - 0.15 mL/min) interfaced with a Perkin-Elmer Sciex API 300 LC-MS/MS system. R- and S- isomers were detected separately with detection performed in the ESI mode with the MS detector operated in the MS/MS mode. Selected ions were 141.5 m/z (daughter ion of 358.2 m/z) for OXY, 312.7 m/z (daughter ion of 329.8 m/z) for DEO, and 162.7 m/z (daughter ion of 317.9 m/z) for drofenin. Calibration curves were constructed using R- and S-OXY and DEO and were linear over the assay range (0.5–75.0 ng/mL) with the lower limit of quantitation at 0.50 ng/mL using 1.0 mL plasma samples. The overall precision (%CV) for the calibration standards and quality controls were all within 10% at all concentrations.

Transdermal System Residual Analysis

Residual racemic OXY content of the used transdermal systems was determined by a validated HPLC method. Following removal from the volunteers, the used transdermal systems were stored frozen prior to analysis. Individual systems were extracted by mechanical shaking in acetonitrile at room temperature for 24 h and the extracted OXY quantified by HPLC. A 35:65 (v:v) mixture of acetonitrile and phosphate buffer (0.02 M KH_2PO4, 0.005 M sodium hexane sufonate, 0.3% [v/v] triethylamine, adjusted to pH 4.5 with phosphoric acid) was used as mobile phase at a flow rate of 1.2 mL/min. A sample volume of 20 μL was injected onto a Cosmosil 5CN-MS column (4.6 mm × 250 mm, particle size 5 μm), maintained at 40°C in a column oven, with a CN guard column. Eluents were analyzed at 220 nm. Standard curves were constructed from five independently prepared racemic OXY standards and were linear over the assay range (60–370 μg/mL). The resulting standard curve equation was used to calculate the value of the unknown samples. Standard concentration samples were analyzed with each analytical run and the method demonstrated a precision of ≤ 2%.

Skin Flux Sample Analysis

The sample solution from skin flux experiments was loaded onto Sep-Pak® C18 solid phase extraction cartridges, pre-activated with 5 mL of 75:25 hexane:isopropanol (%, v/v) and 10 mL of distilled water. The cartridge was rinsed with 10 mL of water and dried by centrifugation. The free base oxybutynin retained on the cartridge was extracted with 2 mL of 75:25 hexane:isopropanol (%, v/v), and the eluent used for R- and S-OXY determination.

R- and S-OXY concentrations were quantified by a validated HPLC method. A 98:2 (%, v/v) mixture of hexane and isopropanol was used as mobile phase at a flow rate of 1.0 mL/min. A sample volume of 100 μL was injected onto a Chiralpak AD column (250 mm × 4.6 mm, particle size 5 μm) maintained at ambient temperature. Eluents were analyzed at 254 nm. Standard curves were constructed from seven independently prepared racemic OXY standards and were linear over the assay range (10.5–330 μg/mL). The resulting standard curve equation was used to calculate the value of the unknown samples. Standard concentration samples were

analyzed with each analytical run and the method demonstrated a precision of ≤ 2%.

Pharmacokinetics

The area under the plasma concentration-time curves to the last quantified sample time point ($AUC_{0\text{-}t}$) for R- and S-OXY and DEO were calculated by the trapezoidal method (15). $AUC_{0\text{-}\infty}$ following oral dosing was determined by the sum of the $AUC_{0\text{-}t}$ plus the concentration at the last quantified time point divided by the estimated elimination rate constant, k (estimated based on linear regression of the log-transformed plasma concentration data in the terminal log-linear phase of the plasma concentration profile). The apparent oral half-life ($t_{1/2}$) value was calculated as ln(2)/k. The time of maximum plasma concentration (T_{max}) and the maximum plasma concentration (C_{max}) were determined by inspection of individual plasma concentration-time profiles.

The estimated daily transdermal delivery rate was calculated as the total OXY delivered over the 96 h wear period divided by 4 days. The systemic availability of OXY following oral treatment was calculated from the $AUC_{0\text{-}\infty}$ value assuming a clearance value of 34.02 L/hr (8).

Statistical Methods

Individual parameters were compared using two-sided t-tests (SAS version 6.12, Cary, NC). Significance was assumed at $P < 0.05$.

RESULTS

Skin samples from six human donors were used in the *in vitro* skin flux experiments. The results of this skin flux study showed equal permeation through human epidermis for R- and S-OXY with a mean ratio (± SD) of R-OXY to S-OXY of 1.00 ± 0.02 (Table I).

Sixteen subjects completed the clinical study. Two female subjects withdrew from the study, one for non study-related reasons, and the second due to side-effects (headache, nausea, and vomiting) experienced during both the oral delivery and transdermal delivery treatment periods.

The transdermal system delivered OXY continuously over the 4-day wear period. After an initial lag time, consistent with a skin depot effect, plasma R- and S-OXY increased gradually for 24–48 h, thereafter remaining relatively constant for the duration of the 96 h wear period (Fig. 1). A small, transient increase in plasma OXY concentrations were seen 30 min after system removal and was followed by a rapid decline in plasma OXY concentrations. Plasma R- and S-DEO concentrations followed a similar pattern.

Table I. Cumulative *In Vitro* R- and S-OXY Skin Permeation over a 96 h Application Period (mean ± SD)

Skin I.D.	Number of cells	R-OXY (μg/cm²)	S-OXY (μg/cm²)	R/S ratio
4758-001-07	4	143 ± 25	141 ± 27	1.02 ± 0.03
CP 00147-1	4	142 ± 26	142 ± 26	1.00 ± 0.01
LL 99148	4	137 ± 16	134 ± 14	1.02 ± 0.02
NE 0002109	4	168 ± 19	169 ± 16	0.99 ± 0.02
NE 0008002	4	132 ± 17	133 ± 17	0.99 ± 0.02
WR 00182-6	4	114 ± 16	114 ± 16	1.00 ± 0.02
Overall	24	139 ± 24	139 ± 24	1.00 ± 0.02

Following oral administration, plasma R- and S-OXY concentrations increased rapidly, reaching peak plasma concentrations within 1 h of administration and declining rapidly thereafter (Fig. 2). Plasma R- and S-DEO concentration-time curves were similar in shape, but several fold greater, compared to R- and S-OXY.

Mean pharmacokinetic parameters are summarized in Table II. Following TDS application, the mean plasma R-OXY C_{max} (1.2 ± 0.3 ng/mL) and $AUC_{0\text{-}t}$ (85.8 ± 26.4 ng · h/mL) were both significantly lower ($P < 0.0001$) than the mean plasma S-OXY C_{max} (1.6 ± 0.4 ng/mL) and $AUC_{0\text{-}t}$ (121.4 ± 34.0 ng · h/mL). Mean plasma R-DEO C_{max} (1.2 ± 0.5 ng/mL) and $AUC_{0\text{-}t}$ (83.9 ± 43.0 ng · h/mL) were non-significantly lower (P = 0.0899 and 0.0607, respectively) than the mean S-DEO C_{max} (1.4 ± 0.7 ng/mL) and $AUC_{0\text{-}t}$ (101.1 ± 52.6 ng · h/mL).

A different pattern was observed following oral OXY administration. In this case, the mean plasma R-OXY C_{max} (2.2 ± 1.7 ng/mL) and $AUC_{0\text{-}t}$ (3.8 ± 3.1 ng · h/mL) were both significantly lower ($P < 0.0001$) than the S-OXY C_{max} (4.1 ± 2.8 ng/mL) and $AUC_{0\text{-}t}$ (5.5 ± 3.3 ng · h/mL) whereas the mean R-DEO C_{max} (15.5 ± 3.7 ng/mL) and $AUC_{0\text{-}t}$ (45.7 ± 17.1 ng · h/mL) were both significantly ($P < 0.0001$) higher than the S-DEO C_{max} (10.9 ± 3.1 ng/mL) and $AUC_{0\text{-}t}$ (31.8 ± 11.7 ng · h/mL).

The average $AUC_{0\text{-}t}$ ratios, R-DEO:R-OXY (1.0 ± 0.4) and S-DEO:S-OXY (0.8 ± 0.4), following TDS application were significantly lower than the corresponding ratios (15.1 ± 6.3 and 6.7 ± 2.4, respectively) following oral administration ($P < 0.0001$). Likewise, average C_{max} ratios following TDS application, R-DEO:R-OXY (1.0 ± 0.4) and S-DEO:S-OXY (0.8 ± 0.4), were significantly lower than the corresponding ratios (8.9 ± 4.5 and 3.3 ± 1.2, respectively) following oral administration ($P < 0.0001$).

Following oral administration, apparent mean (SD) elimination half-lives for R-OXY (1.4 ± 0.6 hs), S-OXY (0.9 ± 0.4 hs), R-DEO (2.3 ± 1.1 hs), and S-DEO (2.1 ± 0.8 hs), respectively, were similar to estimated elimination half-lives for racemic OXY following intravenous (1.9 ± 0.4 hs) and oral (2.4 ± 0.4 hs) administration (8). Following removal of the TDS, the plasma enantiomer concentrations in a majority of the subjects fell to values near or below the lower limit of quantitation for the assay method, resulting in widely varying and potentially inaccurate estimates of the apparent elimination rate constant. $AUC_{0\text{-}\infty}$ was therefore not calculated for the enantiomers of oxybutynin and DEO following the oxybutynin TDS treatment.

The average estimated total OXY dose (mean ± SD) delivered by the transdermal system was 12.0 ± 2.0 mg or an estimated average daily OXY delivery of 3.0 mg/day. The estimated absorbed oral dose, based on combined R- and S-OXY $AUC_{0\text{-}\infty}$ values (9.3 ± 6.3 ng · h/mL), a 34 L/hr clearance value for OXY (8), and an administered OXY dose of 5 mg, was 0.32 ± 0.22 mg, yielding an estimated oral bioavailability of 6.4 ± 4.4%, consistent with a literature value of 6.2 ± 1.2 % following both i.v. and oral administration (8).

DISCUSSION

Transdermal delivery of OXY offers several possible therapeutic advantages over oral administration. These in-

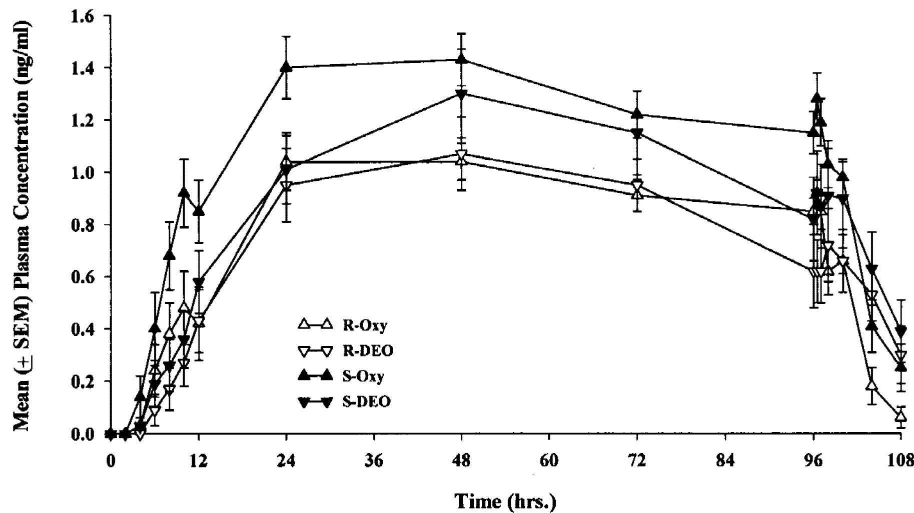

Fig. 1. Mean (± SEM) plasma R- and S-OXY and -DEO concentrations verses time following the 96 h application of a single OXY transdermal system.

clude the avoidance of pre-systemic metabolism, reducing exposure to the N-desethyl metabolite, and continuous delivery, reducing peak to trough fluctuations in plasma concentrations that occur with intermittent oral administration. The stereoselective metabolism of oxybutynin reported in the current study leads to relatively greater plasma concentrations of active R-OXY during TD compared to oral administration. This further supports the rationale and conceptual framework for transdermal delivery as a therapeutic alternative to oral drug administration.

The disposition of the individual enantiomers of OXY and DEO contribute further to the understanding of potential

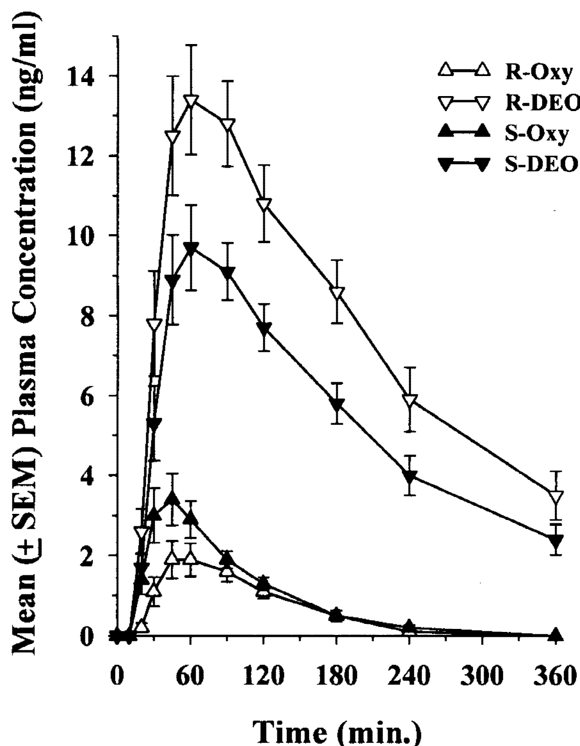

Fig. 2. Mean (± SEM) plasma R- and S-OXY and -DEO concentrations verses time following the oral administration of a 5 mg immediate-release OXY tablet.

route of administration differences in the efficacy and tolerability of OXY. The stereo-selective metabolism of the R-isomer of OXY reduces its systemic bioavailability by producing relatively higher circulating concentrations of the metabolite, R-DEO. Since the R-enantiomers of both OXY and DEO have greater potency than the S-enantiomers, the high circulating concentrations of R-DEO may contribute to anticholinergic side effects with oral dosing (6,7,16). Approximately equal plasma concentrations of R-OXY and R-DEO were present during transdermal administration, potentially preserving efficacy but minimizing the potential for undue side effects. Stereo-selective metabolism has been demonstrated for some compounds that undergo oxidative hepatic metabolism (17–19). In many cases, the preferential metabolism of the more active R-isomers was also observed. The small differences between R- and S-OXY plasma concentrations during transdermal administration could be a result of differences in transdermal absorption and/or elimination as well as metabolism. The *in vitro* skin flux experiments demonstrated that transdermal delivery of R- and S-OXY is not stereoselective with both enantiomers crossing the human cadaver skin in approximately equal concentrations thus supporting equal absorption of R- and S-OXY. Although accurate estimation of elimination following removal of the TDS were not possible, no significant differences were observed between the elimination rates for R- and S-OXY or DEO following oral administration. The oral plasma concentrations profiles are consistent with selective R-OXY metabolism.

Transdermal delivery clearly avoids the extensive presystemic metabolism that occurs following oral administration, (8) significantly reducing the formation of DEO. The stratrum corneum is the structural barrier between the body and the environment and controls the absorption of oxybutynin from the TDS. Once the drug is absorbed, the skin is a potential site of metabolic activity containing multiple cytochrome P450 isozymes (20). Although skin flux studies reported here showed equal absorption of R- and S-OXY, it is plausible that dermal metabolism may occur. The extent of dermal metabolism, however, is most likely minimal in view of the low P450 content (approximately 5% of the liver) in the epidermis (21).

Table II. R- and S-Oxybutynin And DEO Pharmacokinetics (Mean ± SD)

	C_{max} (ng/ml)	$AUC_{0\text{-}t}$ (ng · hr/ml)	$AUC_{0\text{-}\infty}$[a] (ng · hr/ml)	T_{max} (median hours)
		Oxybutynin TDS		
R-Oxy	1.2 ± 0.3	85.8 ± 26.4	—	48.0
R-DEO	1.2 ± 0.5	83.9 ± 43.0	—	48.0
R-DEO:R-Oxy ratio	1.0 ± 0.4	0.95 ± 0.44	—	—
S-Oxy	1.6 ± 0.4	121.4 ± 34.0	—	48.0
S-DEO	1.4 ± 0.7	101.1 ± 52.6	—	48.0
S-DEO:S-Oxy ratio	0.84 ± 0.37	0.79 ± 0.34	—	—
		Immediate-Release Oral Oxybutynin		
R-Oxy	2.2 ± 1.7	3.8 ± 3.1	3.8 ± 3.1	1.0
R-DEO	15.5 ± 3.7	45.7 ± 17.1	62.3 ± 30.8	1.0
R-DEO:R-Oxy ratio	8.93 ± 4.49	15.14 ± 6.31	21.5 ± 10.5	—
S-Oxy	4.1 ± 2.8	5.5 ± 3.3	5.5 ± 3.3	0.8
S-DEO	10.9 ± 3.1	31.8 ± 11.7	42.2 ± 19.4	1.0
S-DEO:S-Oxy ratio	3.25 ± 1.15	6.69 ± 2.42	8.3 ± 2.3	—

[a] Following removal of the TDS, most plasma enantiomer concentrations fell to values near or below the lower limit of quantitation for the assay method, producing inaccurate estimates of the apparent elimination rate constant. $AUC_{0\text{-}\infty}$ was therefore not calculated for the enantiomers of oxybutynin and DEO following the oxybutynin TDS treatment.

Clinical observations of reduced side-effects during intravesicular administration of OXY support the hypothesis that the side-effects are primarily mediated by DEO (10,12,22). Patients treated by intravesicular administration achieve efficacy and report few, if any, anticholinergic side effects. Plasma OXY concentrations with this form of treatment are comparable to those measured following oral dosing, however, DEO concentrations are significantly lower (12,22). These clinical observations are also supported by *in vitro* evaluations of the antimuscarinic actions of OXY and DEO on bladder muscle and parotid gland tissues (23). Although measured differences in potency and receptor binding affinity are small, OXY appears somewhat more active on detrusor muscle than DEO, while the reverse is true on the parotid gland. DEO yielded higher affinity binding to parotid tissue relative to bladder muscle, with no significant difference observed for OXY (23). The relative plasma concentrations of R- and S-DEO may further explain the side-effects observed following oral administration. Selective metabolism of R-OXY leads to high concentrations of the active R-DEO isomer which would be expected to result in side-effects. Therefore, maintaining R-OXY plasma concentrations with reduced R-DEO concentrations, as observed during transdermal delivery, may improve the therapeutic index during transdermal treatment.

The sustained delivery of OXY during transdermal administration was clearly demonstrated in the study and resulted in substantially less fluctuation in plasma concentrations over the dosing interval compared to what was reported by Douchamps et. al., (8) following administration of 5 mg OXY tablets three times daily at 5 h intervals for 1 week. The peak and trough drug concentrations observed during this repeated oral dosing may also lead to adverse effects during peak drug concentration times and sub-therapeutic levels at trough times.

In summary, the present study confirmed a reduction of pre-systemic metabolism of OXY during transdermal compared to oral administration, demonstrated stereo-selective OXY metabolism, and supports the potential of an improved therapeutic index for transdermal compared to oral OXY treatment. Additional clinical results will be required to confirm these relationships.

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