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PHARMACOKINETIC PROFILE OF OXYBUTYNIN AND ITS ACTIVE METABOLITE N-DESETHYLOXYBUTYNIN IN RELATION TO SALIVARY PRODUCTION IN HEALTH VOLUNTEERS

Aims of Study

N-desethyloxybutynin (DEO), the active metabolite of oxybutynin (OXY), is associated with occurrence and severity of anticholinergic side effects, particularly dry mouth, during oral administration. Transdermal (TDS) administration of OXY avoids presystemic gastrointestinal and hepatic first pass metabolism, leading to significantly lower plasma levels and an improved anticholinergic side effect profile (*J Urol*. 2001;166:140-5). This study evaluated salivary secretion in relation to steady-state pharmacokinetics and metabolism of TDS and oral OXY extended release (ER) (Ditropan XL).

Methods

The study was a randomized 2-way crossover trial in 12 healthy male or female volunteers. Plasma concentrations and salivary output (chewed Parafilm® for 2 min) were measured at matched steady-state sample times during the second of two OXY TDS (3.9 mg/d) applications and during the final 4 days of 6 daily OXY ER (10 mg/d) doses. Plasma concentrations of OXY and DEO were measured by LC/MS. Paired t-test used for comparisons.

Results

Total salivary weight following OXY TDS (15.7 ± 9.3 g) was significantly (p = 0.0162) greater than OXY ER (12.2 ± 6.8). OXY TDS resulted in lower plasma DEO concentrations, with a significant linear relationship (r^2=0.52, p=0.008) observed for the reduction in plasma DEO and related increase in saliva output. Average plasma OXY concentrations was 3.1 ng/ml during OXY TDS compared to 2.3 ng/mL during OXY ER administration. Peak to trough fluctuation was also lower for OXY TDS (0.7 ± 0.2) compared to OXY ER (1.3 ± 0.5). The ratio of DEO to OXY plasma concentration for TDS was 1.2 ± 0.3 compared to 4.1 ± 0.9 for OXY ER. The table below summarizes additional pharmacokinetic values.

PK Parameter	Descriptive Statistic	OXY TDS		OXY ER	
		Oxy	DEO	Oxy	DEO
C_{max} (ng/mL)	Mean ± SD Range	4.2 ± 1.0 2.5 – 5.7	4.9 ± 2.0 2.7 – 9.8	4.0 ± 1.5 1.4 – 6.2	15.2 ± 6.7 7.4 – 31.4
C_{min} (ng/mL)	Mean ± SD Range	2.1 ± 0.3 1.5 – 2.4	2.8 ± 1.1 1.4 – 5.6	1.3 ± 0.7 0.2 – 2.6	5.5 ± 4.1 0.4 – 13.3
AUC_{0-84} (ng hr/mL)	Mean ± SD Range	259 ± 57 177 – 351	321 ± 114 172 – 594	194 ± 68 59 – 325	802 ± 369 304 – 1596
T_{max} (hours)	Median Mean ± SD Range	28.1 33.3 ± 13.1 12.1 – 56.1	28.1 31.9 ± 16.6 0.0 – 60.1	52.1 53.6 ± 27.1 4.1 – 84.1	48.1 46.8 ± 27.9 0.0 – 84.1
Fluctuation Index	Mean ± SD Range	0.7 ± 0.2 0.4 – 1.0	0.5 ± 0.1 0.3 – 0.8	1.3 ± 0.5 0.6 – 2.5	1.1 ± 0.4 0.6 – 2.0

Conclusions

Greater salivary output during OXY TDS compared to OXY ER administration, along with decreased metabolism of OXY to DEO with OXY TDS delivery, may explain the low incidence of dry mouth side effects reported during OXY TDS treatment, as a direct reflection of substantially decreased DEO levels. Given the comparable efficacy to immediate release observed with OXY TDS, this study provides further evidence that DEO contributes significantly to anticholinergic side effects but may contribute little to antimuscarinic actions on the detrusor muscle.