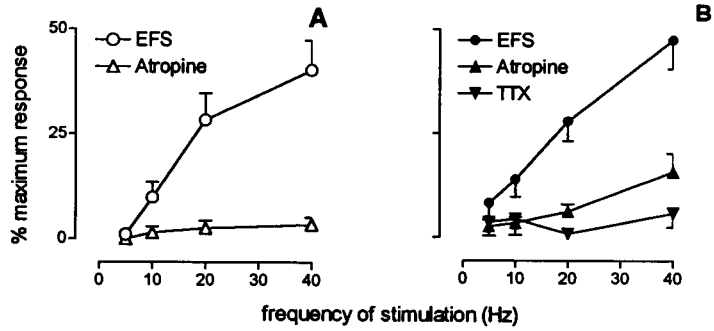

Figure 1: Frequency-response curves to EFS (A) control patients (n=16) and (B) DI patients (n=16)

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EFFECT OF KETOCONAZOLE ON THE PHARMACOKINETICS OF OXYBUTYNIN: COMPARISON BETWEEN AN EXTENDED RELEASE OXYBUTYNIN AND CONVENTIONAL OXYBUTYNIN.

Aims of Study: Oxybutynin (OXY) has been reported to be mainly metabolized by the cytochrome P-4503A4 (CYP3A4) enzyme system. Ketoconazole (KET), an anti-fungal agent, is a potent CYP3A4 inhibitor. The objective of this study was to investigate the effect of ketoconazole on the pharmacokinetics of extended-release oxybutynin (ER-OXY) and conventional OXY (Conv-OXY). Additionally, the effect of KET co-administration on dry mouth produced by ER-OXY and Conv-OXY (most common side effect) was investigated.

Methods: This was an open label four-treatment, four-period crossover study in 18 healthy volunteers (18-45 years). In period 1 and 2, subjects received either Treatment A or B. Three days prior to Period 3, the subjects were started on KET 200 mg twice-a-day until the end of period 4 and subjects received either Treatment C or D in these two periods.

A. Conv-OXY 5 mg, 2-doses 8-hours apart B. ER-OXY 10 mg, single dose

C. Conv-OXY 5 mg, 2-doses 8-hours apart + KET D. ER-OXY 10 mg, single dose + KET

Blood samples to measure the R-and S-isomer of OXY and its active metabolite, desethyloxybutynin (DES) were taken prior to and up to 48 hours post treatment initiation at serial scheduled time points. The subjects also rated dry mouth severity on a 100 mm visual analog scale prior to and every hour for 14 hours post treatment initiation . Pharmacokinetic parameters, C_{max} (maximum concentration), T_{max} (Time to maximum concentration) and AUC (area under the plasma concentration-time curve) were estimated. Dry mouth severity was evaluated as a function of time among the four treatments. Treatment comparison was done using an analysis of variance model (ANOVA).

Results: The mean pharmacokinetic parameters estimated for all four analytes are summarized in Table 1. The plasma concentrations were much higher for the drug (R- and S-OXY) when Conv-OXY was administered with KET than Conv-OXY alone; C_{max} and AUC were about 3-4 fold higher. In contrast, the effect of KET on ER-OXY was much smaller; increase in R- and S-OXY C_{max} and AUC was only 2-fold. The effect of KET on the metabolite enantiomers was similar for both Conv-OXY and ER-OXY.

Dry mouth severity was significantly ($p<0.05$) lower for ER-OXY than Conv-OXY regardless of whether it was administered alone or with KET. For both formulations, KET did not have significant effect on dry mouth.

Table 1: Mean C_{max} and AUC Values

Parameter	Analyte	ER-OXY	ER-OXY+ KET	x-fold	Conv-OXY	Conv-OXY + KET	x-fold
AUC_{inf}	R-OXY	41	82	2	29	84	2.9
(ng.h/mL)	S-OXY	82	159	1.9	44	184	4.2
	R-DES	334	413	1.2	462	517	1.1
	S-DES	256	449	1.8	282	571	2.0
C_{max}	R-OXY	1.9	3.9	2.1	6.1	17.9	2.9
(ng/mL)	S-OXY	3.7	7.8	2.1	12.8	44.7	3.5
	R-DES	18.5	19.0	1.0	68.3	53.3	0.8
	S-DES	12.1	18.4	1.5	38.1	51.3	1.4

With ER-OXY, the metabolite formation is lower (R-DES 75%; S-DES 90%) and the bioavailability of OXY is higher (R-OXY 154%; S-OXY 190%) than Conv-OXY. The difference in metabolism between the two formulations may be due to differences in the presystemic intestinal metabolism because with ER-OXY, the drug is mainly absorbed in the colon, whereas the small intestine is the absorption site for Conv-OXY. The intestinal metabolic enzymes are less prevalent in the colon compared to the small intestine. Literature reports suggest metabolites are responsible for dry mouth (1). Thus lower metabolite formation, especially R-DES may account for lower dry mouth severity with ER-OXY compared to Conv-OXY. This would explain the lack of effect of KET on dry mouth for either formulation, even though there is a 2-4 fold increase in R-and S-OXY concentration and also a 2-fold increase in S-DES concentration. R-DES concentration however does not change significantly, paralleling the lack of increased dry mouth for either ER-OXY or Conv-OXY when administered with KET. In vitro literature studies (2,3) have shown that the antimuscarinic activity lies with the R-isomer (both OXY and DES) and DES has a higher affinity for the parotid gland than OXY (OXY and DES have similar affinity for the bladder antimuscarinic receptors). Thus, it appears that R-DES may be responsible for dry mouth observed in OXY therapy.

Conclusions: Enzyme inhibition by KET has less effect on ER-OXY pharmacokinetics and dry mouth severity is lower with ER-OXY compared to Conv-OXY. Dry mouth does not seem to be affected by KET for either formulation. Formation of the metabolite, R-DES, is significantly lower with ER-OXY than Conv-OXY and it appears that R-DES may play a major role in dry mouth observed in OXY therapy.

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PLACEBO-CONTROLLED, RANDOMISED, DOUBLE-BLIND, MULTICENTRE CLINICAL TRIAL ON THE EFFICACY AND TOLERABILITY OF 1 X 40 mg AND 2 X 40 mg TROSPIUM CHLORIDE (SPASMO-LYT®) DAILY FOR 3 WEEKS IN PATIENTS WITH URGE-SYNDROME

OBJECTIVE: Evaluation of the efficacy and tolerability of 1 x 40 mg and 2 x 40 mg trospium chloride (TCI) daily in patients with urge-syndrome.

METHODS: Until the first interim analysis of this placebo-controlled, randomised, multi-centre clinical trial with an adaptive design 175 patients received either 40 mg TCI once daily or 2 x 40 mg daily or placebo for 3 weeks. Primary efficacy variables were the micturition frequency in 24 hours assessed by data from the patients' micturition diaries