105

KH Moore, DSH Lam, W Lynch, E Burcher

The Pelvic Floor Unit, Department of Urogynaecology and Urology, and the School of Physiology and Pharmacology, the University of New South Wales, Sydney, Australia.

SPONTANEOUS CONTRACTILITY, ATROPINE RESISTNACE AND RESPONSE TO THE TACHYKININ ANTAGONIST SR48968 IN DIIOPATHIC DETRUSOR INSTABILITY

Aims: Previous authors have suggested that the detrusor from patients with idiopathic detrusor instability (DI) exhibits increased spontaneous contractility in vitro, compared to control (stable) muscle. Electrical field stimulation (EFS) of detrusor strips elicits contractions which are though to be abolished by atropine in normal humans, but not in animals, suggesting that the residual response (atropine resistance) is due to released of another neurochemical, such as neurokinin A.

We have measured spontaneous detrusor contractility in a specific group of chronic refracatory DI patients, using a quantitative method. In the same patients, we have examined whether responses to EFS are abolished by atropine, and whether any residual contractions are inhibited by the neurokinin A (NK-2 receptor) antagonist SR 48968.

Methods: Controls (n=19) comprised females having haematuria or check cystoscopy for previous malignacy. Refractory idiopathic DI (n=18) was defined as proven DI (>15 cm H2o pressure rise during filling/provocation cystometry) with no response to bladder training plus at least two anticholinergic drugs *for > one year*, i.e disabling urge symptoms, 10 or more voids/24h. Cystoscopy was offered, to exclude carcinoma in situ/interstitial cystitis, with cystodistension. Informed consent was obtained, with ethical committee approval.

Cystoscopy: under general anaesthesia, the bladder was filled to capacity (DI patients) or ~ 650ml (controls) (1). At refill exam (150 ml) petecchiae were sought. Cold-cup biopsies were taken at bladder base, just lateral to trigone. From the edge of the superficial (histology) site, a further specimen containing muscle was obtained, then immediately transported in iced Krebs solution gassed with carbogen (95% O_2, 5% CO_2).

The mucosa was removed; the detrusor was suspended in a microbath perfusion system at 37oC and isometric tension was recorded. Spontaneous contractility was measured by sampling a 5 min recording after 45 min equilibration. The "area under the curve" for each spontaneous contraction was summated, using a MacLab computerised recorder.

Increasing concentrations of acetycholine (Ach) (10^{-6}-10^{-2}M) were then infused to obtain concentration response curves. EFS (0.1ms, 40V) was carried out at 5, 10, 20 and 40Hz, then repeated in the presence of atropine (10^{-6}M). If an "atropine resistant" contractile response persisted, the frequency-response curve was repeated in the presence of tetrodotoxin (TTX, 10^{-6}M) or the tachykinin NK-2 receptor antagonist SR48968 (10^{-6}M). Contraction were measured in g tension and expressed as percent of maximum contraction to Ach 10^{-2}M.

Results: There was no difference in the are under the curve for spontaneous contractions between groups (Mann Whitney P=0.89). No spontaneous contractility was observed in 3/16 controls (19%) or 2/16 unstable specimens (13%).

Concentration response curves to Ach did not differ between controls and DI patients. The mean maximum tension achieved by Ach 10^{-2}M was 1.5g, SD 1.3g in controls (n=19) and 1.6g, SD 1.1g in DI patients (n=18).

Of the ~~specimens which contracted to Ach, 16/19 controls (84%) and 16/18~~ DI patients (895) also contracted in a frequency dependant manner to EFS. The mean response to 40 Hz was 0.67g, SD 0.77 for controls (45% of maximum Ach response), and 1g, SD 0.96 for DI patients (63% of maximal).

In the presence of atropine, responses to EFS were completely abolished in 8 and almost abolished in 6, for 16 control patients. Small residual contractions of the remaining 2 specimens were unaffected by TTX. Responses to EFS were completely abolished by atropine in 5 out of 16 specimens with DI. In the remaining 11/16, the responses at 20 and 40 Hz were reduced to 9% and 23%, respectively, of the responses of that specimen before atropine (Figure 1).

In 8 patients with DI who exhibited "atropine resistance", SR48968 (10^{-6}M) was applied and had no inhibitory effect on the response to EFS. Responses (expressed as % of Ach maximum) after atropine were 8% and 25% at 20 and 40 Hz: after both atropine and SR48968, responses were 7% and 19%, respectively. Subsequent exposure to TTX largely abolished this residual responses to EFS.

Conclusion: spontaneous contractility was not significantly different between patients and control. Atropine resistant contractions to EFS occurred in 69% of the DI specimens but none of the controls. These residual contractions were not abolished by SR48968, suggesting that neurokinin A is not involved in the genesis of this contractility (which we nevertheless nerve-mediated as it was abolished by TTX). A search for other pharmacological agents that might abolish this atropine resistant contractility may prove clinically useful in the treatment of refractory DI.

(1) Neurourol & Urodyn, 10, 330-331, 1991.

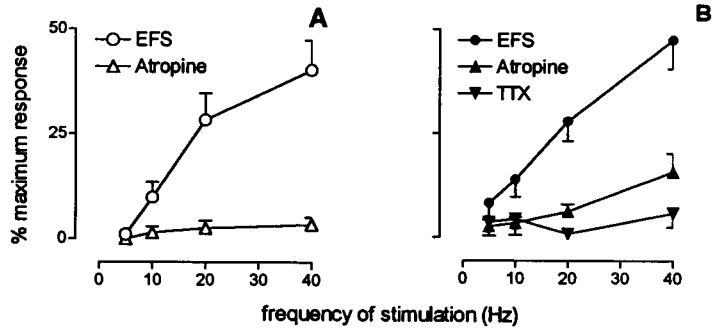

Figure 1: Frequency-response curves to EFS (A) control patients (n=16) and (B) DI patients (n=16)

106

M.B. Chancellor, G. Sathyan and S.K. Gupta.

ALZA Corporation, Palo Alto, CA 94303

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.