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Misoprostol does not alter the pharmacokinetics of propranolol

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Summary: Twelve healthy volunteers took part in a randomised, double-blind, balanced, cross-over study to investigate the effect of misoprostol on the pharmacokinetics of propranolol. The subjects took propranolol 80 mg twice daily by mouth plus either misoprostol 400 μg twice daily or placebo by mouth for 14.5 days, followed by a 2-week washout period, followed by the alternate treatment for 14.5 days. Misoprostol had no significant effect on the t/2, C_{max} or AUC of propranolol either after a single dose or at steady state.

Introduction

Misoprostol is a synthetic prostaglandin E_1 analogue which is widely used for the treatment of peptic ulcer and for the prophylaxis and treatment of ulcer caused by non-steroidal anti-inflammatory drugs.[1] In an earlier study[2] we reported that plasma concentrations of propranolol rose both during and after cessation of concurrent misoprostol administration. These findings were unexpected and difficult to explain. An effect on hepatic enzyme activity was incompatible with our observed lack of effect of misoprostol on antipyrine clearance, and an alternative explanation was that steady state plasma concentration of propranolol had not been reached in the design used in the original study. We have repeated the study with a design that ensures the attainment of steady state conditions of dosing.

Materials and methods

The study was approved by the Bath DHA Research Ethics Committee. Twelve volunteers, 8 males, 22–29 years, 51.8–96.9 kg were studied. Each was found to be healthy by physical examination, haematological and biochemical profiles, each was a non-smoker and an extensive metaboliser of debrisoquine.[3] Each volunteer maintained a daily record of his or her intake of alcohol and caffeine-containing drinks; males limited alcohol consumption to 20 units and females to 13 units per week.

A randomized, double-blind, balanced, cross-over design was used. Each volunteer received in one part of the study propranolol 80 mg twice daily by mouth plus misoprostol 400 μg twice daily by mouth for 14.5 days and in the other part of the study propranolol 80 mg twice daily by mouth plus placebo misoprostol twice daily by mouth for 14.5 days, with a 14-day washout period between the two parts of the study. In each part of the study, blood was taken for assay of plasma propranolol on the first day of receipt of propranolol (after a single dose) and on the 15th day of receipt (at steady state) at 0, 1, 2, 3, 4, 6, 8, 10 and 12 h after dosing. Propranolol was assayed by high performance liquid chromatography.[4] Coefficients of variation of standard samples were ($n = 10$) 7% at 20 μg/l and 5% at 200 μg/l.

Plasma half-lives (t/2) were calculated by least squares linear regression analysis of the logarithm of concentration during the terminal phase, on time. Areas under the plasma concentration-time curves (AUC) to 12 h were calculated by the trapezoidal rule.[5] AUC and C_{max} values were logarithmically transformed and submitted to analysis of variance with sequence, subjects within sequence, period and treatment as factors in the model. For t/2, differences between treatments were tested using the Wilcoxon signed-rank test.

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Results

Table I gives mean values for t/2, C_{max} and AUC. After a single dose of propranolol the ratio of

Table I Effect of misoprostol on propranolol pharmacokinetics in healthy volunteers

	*t/2** *(h)*	Propranolol C_{max}* (μg/l)	*AUC** (μg/l h)
1. After single dose (propranolol 80 mg by mouth)			
a) with placebo	3.7 ± 1.0	77.3 ± 39.6	422.4 ± 174.4
b) with misoprostol 400 μg once daily by mouth	3.1 ± 1.3	65.4 ± 25.0	342.6 ± 153.3
2. At steady state (propranolol 80 mg twice daily for 14.5 days)			
a) with placebo	3.6 ± 0.6	116.1 ± 76.1	647.0 ± 281.9
b) with misoprostol 400 μg twice daily by mouth for 14.5 days	3.6 ± 1.0	118.0 ± 91.5	621.6 ± 362.6

*All values are means ± s.d.; $P > 0.05$.

misoprostol:placebo for AUC was 0.81 with the 95% confidence interval (CI) 0.60–1.10 and for C_{max} the ratio was 0.90 with the 95% CI 0.68–1.19. Mean plasma propranolol concentrations prior to the 25th, 27th and 29th (study day) doses were 29.3, 34.2 and 23.1 μg/l and are compatible with the attainment of steady state conditions of dosing. After 14.5 days the AUC for misoprostol:placebo ratio was 0.93 with the 95% CI 0.69–1.26 and for C_{max} the ratio was 0.97 with the 95% CI 0.65–1.45. There were no statistically significant differences in t/2, C_{max} or AUC between misoprostol and placebo and no evidence of a treatment sequence effect which could invalidate the cross-over design, either after a single dose or at steady state.

Discussion

Misoprostol has been co-administered in specifically designed drug interaction studies with aspirin, ibuprofen, piroxicam, diclofenac, naproxen and diazepam.[6] In an earlier study[2] we found that the AUC of propranolol increased both during and after cessation of concurrent treatment with misoprostol. Healthy volunteers took propranolol daily for 4 weeks and during the 2nd and 3rd of these weeks took misoprostol in addition. This design was selected to enable us to observe both the onset and offset of any effect of misoprostol on propranolol pharmacokinetics, although we recognized that it was open to interference from time-dependent influences. As our results could not rationally be explained we conducted the present cross-over study in which the sequence of treatments was balanced to allow for any time-related effects and the 'within subject' comparison maximized experimental precision. Our findings with the latter design indicated quite clearly that there was no significant effect of misoprostol on the pharmacokinetics of propranolol either after a single dose or at steady state.

Misoprostol does not interfere with hepatic drug metabolizing enzymes or hepatic blood flow in animals.[7] We selected propranolol as a model drug as its pharmacokinetics are affected by both these factors. Our earlier work[2] found that misoprostol did not alter hepatic mono-oxygenase activity as judged by antipyrine clearance; the present findings would suggest that neither does it affect liver blood flow in humans.

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