Effect of orally administered misoprostol and cimetidine on the steady state pharmacokinetics of diazepam and nordiazepam in human volunteers

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SUMMARY

The effects of misoprostol and cimetidine on diazepam pharmacokinetics were evaluated in order to determine whether the kinetic variables for diazepam and nordiazepam alone differ with the repeated oral administration of misoprostol and cimetidine to healthy adult volunteers. The trial was conducted as an open crossover study in 12 normal subjects, divided into two groups with all subjects receiving both regimens. Total study duration was 5 weeks. An initial clinical assessment, including blood biochemistry and assessment of subject oxidation status was carried out on study day 1. On this day, subjects began taking diazepam (10 mg) orally for one week, with pharmacokinetic studies performed at day 8, when steady state levels of diazepam were reached. This was followed by one week with active drug, misoprostol to Group I and cimetidine to Group II, with pharmacokinetic studies performed at the end of a 1-week treatment. After a 2-week wash-out period, both groups took for one week, the alternate drug, i.e. cimetidine plus diazepam to Group I and misoprostol plus diazepam to Group II. On days 8, 15 and 36, subjects were admitted to the hospital for 12 h, during which time a clinical examination was carried out and blood samples were taken at time zero and at 4, 8, 12, 24, and 36 h post-dosing for the measurement of serum diazepam and nordiazepam. The main parameters measured and evaluated were diazepam and nordiazepam pharmacokinetics at steady state (days 8, 15 and 36). These were areas under the curve in the dose intervals (AUC₀-24h), maximum plasma concentrations (Cmax), time to peak concentrations (Tmax), elimination half-life (t½), elimination constant (Kₑ), distribution volume (Vₐ), total body clearance (ClB) and clearance after oral administration (Cloral). The results demonstrated that plasma diazepam and nordiazepam concentrations had a significant increase after steady states have been reached with the simultaneous administration of 800 mg of cimetidine daily for one week. The simultaneous administration of 800 µg of misoprostol did not cause any significant change in diazepam and nordiazepam plasma levels after steady states had been reached. Comparing the pharmacokinetic parameters of Groups A and B as well as within groups on days 8, 15 and 36, a significant increase in plasma diazepam and nordiazepam levels was detected. This was due to a cimetidine-induced impairment in microsomal oxidation of diazepam and nordiazepam, which caused a decrease in total metabolic clearance and increased mean steady state plasma concentrations. A more prolonged half-life was observed for both groups taking cimetidine as well as an increase of mean maximum plasma concentrations. It was concluded that misoprostol neither inhibits nor induces drug metabolizing enzymes of diazepam in man, at least after one week treatment with 800 µg daily oral intake.

INTRODUCTION

It is important to assess the occurrence of drug interactions with new chemical entities, since drug interactions are common and may result in changes in the response to either of the drugs involved, or in potentiation of an unwanted effect that they share. The mechanism of the effect may be either pharmacokinetic or pharmacodynamic (1).
Benzodiazepines are so widely used that there can be few groups of drugs with which they have not been co-administered and precautions must be exercised when appraising drug interactions with benzodiazepines as with any other type of drug.

Pharmacokinetic interactions result from changes in hepatic oxidative metabolism (2). Since all benzodiazepines undergo phase I or phase II metabolism, it is not surprising that administration of an agent that increases or decreases liver microsomal activity might interfere with the clearance of benzodiazepines.

Enzyme-inducing drugs increase the clearance of benzodiazepines with large alkyl-groups (e.g. flurazepam, prazepam and fosazepam) and reduce the bioavailability of those with a high first pass metabolism (3, 4). Conversely enzyme-inhibiting drugs may increase bioavailability. Cimetidine binds to cytochrome P450 in hepatic microsomes and it has been shown by absorbance testing to interact with the ferri-haemoprotein in the cytochrome P450 systems (5). This binding reduces the clearance of many drugs that are eliminated by oxidative processes, including diazepam, warfarin, propranolol, chlordiazepoxide and phenytoin (6-8).

Misoprostol is a novel synthetic prostaglandin E₁ analogue with gastric antisecretory and cytoprotective properties (9). It has been shown to be a potent inhibitor of gastric secretion in animals and to prevent the development of acute upper gastrointestinal ulceration in the rat, cat and guinea pig (10-12). In the dog, it significantly strengthens the integrity of the gastric mucosa against hydrogen ion back-diffusion induced by aspirin (13, 14). In view of these actions there is a potential therapeutic use for misoprostol both as a gastric antisecretory agent in the treatment of peptic ulcer disease and as a cytoprotective agent.

Misoprostol has been proved to be a useful drug in the treatment of duodenal and gastric ulcers. The drug has been administered to approximately 6000 humans in clinical studies worldwide. Although these patients have taken more than 150 concomitant medications, there have been no reports to date of drug interactions with misoprostol (15). Misoprostol does not interfere with hepatic drug metabolizing enzymes (15) nor does it affect hepatic blood flow in animals. Even though no drug interactions have been reported for misoprostol in large scale clinical studies in humans, it is important to assess any possible pharmacokinetic interaction between misoprostol and diazepam.

The present study was performed with two main objectives: (a) to evaluate the effect of orally administered misoprostol on the steady state pharmacokinetics of diazepam and nordiazepam; and (b) to compare these data with the effect of orally administered cimetidine on the steady state pharmacokinetics of diazepam and nordiazepam.

MATERIALS AND METHODS

Trial design

The study was separated into two parts (Study I and Study II) which assessed the separate aspects of misoprostol and cimetidine activity.

The effect of misoprostol and cimetidine on diazepam pharmacokinetics was an open study conducted on 12 subjects. Total study duration was 5 weeks. An initial clinical assessment including blood biochemistry and assessment of the subjects' oxidation status using oral debrisoquine was carried out on study day 1. On this day, 12 subjects were seen at the hospital and commenced to take diazepam, 10 mg orally, for 2 weeks. On day 8, subjects were admitted to the hospital for 12 h, during which time a clinical examination was carried out and blood samples were taken at time zero and at 4, 8, 12, 24 and 36 h post-dosing for the measurement of serum diazepam and nordiazepam concentrations.

Group I (6 subjects) took additionally misoprostol, 200 μg q.i.d. orally from day 8 until day 15. Subjects were readmitted to the hospital on day 15 for the same assessments as were carried out on day 8. After a 2-week wash-out period, Group I subjects took cimetidine, 200 mg q.i.d., from day 29 until day 36. Subjects were readmitted to the hospital on day 36 for the same assessments as were carried out on day 15.

Group II (6 subjects) took cimetidine, 200 mg q.i.d., from day 8 until day 15. Subjects were readmitted to the hospital on day 15 for the same assessments as were carried out on day 8. After a 2-week wash-out period, Group II subjects took misoprostol, 200 μg q.i.d. orally, from day 29 to day 36. Subjects were readmitted to the hospital on day 29 for the same assessments as were carried out on day 15.

Study population

Sufficient subjects were enrolled to enable 12 subjects to complete the study. From 16 volunteers initially selected, twelve were included and completed the trial.