Omeprazole and lansoprazole are not inducers of cytochrome P4501A2 under conventional therapeutic conditions

Abstract. Objectives: Claims that substituted benzimidazole molecules induce cytochromes P4501A2 are still controversial. This study was undertaken to evaluate their inducing potency under conventional therapeutic conditions.

Methods: Twelve healthy non-smoking young volunteers were given 20 mg omeprazole or 30 mg lansoprazole daily, in random order, for 2 weeks, separated by a 3 week wash-out period. We evaluated the CYP1A2 activity by the ratio of the molar urinary concentrations (CUM ratio) of the three end products of the paraxanthine demethylation of caffeine over the molar concentration of a paraxanthine 8-hydroxylation product.

Results: This urinary metabolite ratio has previously been shown to be correlated with caffeine clearance. There was slight but non-significant enhancement of the CUM ratio after 2 weeks of treatment with omeprazole (3.62 (1.58) on Day 15 vs 3.09 (1.43) on Day 1), and after lansoprazole (4.26 (2.3) vs 3.65 (2.36)). Similarly, one week of treatment did not significantly alter the CUM ratio after omeprazole or lansoprazole (3.11 (1.58) and 3.28 (1.59), respectively on Day 8).

Conclusion: The results show that both omeprazole and lansoprazole in the daily recommended therapeutic doses of 20 mg and 30 mg, respectively, have no influence on the metabolism of caffeine, and therefore no influence on cytochrome CYP1A2 activity.

Key words. CYP1A2, Omeprazole, Lansoprazole; enzyme induction, caffeine

Introduction

Most drugs and foreign chemicals, including environmental pollutants and carcinogens, are metabolized by the hepatic cytochrome P450 enzyme superfamily. The past few years have brought remarkable progress in understanding of the P450 cytochromes as a gene superfamily. A common classification based on gene studies and amino acid sequences has been established for all the P450s. At least thirty families of P450 enzymes, including thirteen in mammals, have been identified. The particular cytochrome targeted in this report is cytochrome P4501A2 (CYP1A2). It belongs to the 1A subfamily, which consists of two iso-enzymes 1A1 and 1A2. The two cytochromes differ in that 1A1 is virtually absent unless induced, whereas 1A2 is present in the normal liver in a detectable amount and can be substantially augmented by inducers [1]. The best documented inducers of these enzymes are the polycyclic hydrocarbons, and 1A2 activity can be specifically inhibited by furafylline [2].

Recently, several investigators been interested in the potency of substituted benzimidazoles, specifically omeprazole, as CYP1A2 inducers [3, 4]. Omeprazole is used for its high efficiency as an inhibitor of the gastric proton pump, hydrogen-potassium adenosine triphosphatase (H+, K+, -ATPase) in parietal cells of the gastric mucosa [5, 6]. The first evidence of specific induction of cytochromes 1A1 and 1A2 by omeprazole was reported in vitro and ex vivo by Diaz et al. [7], who demonstrated that omeprazole was a CYP1A2 inducer using primary cultures of human hepatocytes from patients with hepatic cancer. They also showed enhancement of CYP1A2 activity in liver biopsies from five patients before and after they had received omeprazole 20 mg per day for 4 days. Diaz et al. concluded
that therapeutic doses of omeprazole caused significant induction of CYP1A2. Andersson et al. disagreed with this conclusion. Using caffeine urinary metabolite ratios, which reflected cytochrome CYP1A2 activity, they showed that CYP1A2 activity was not altered following one-week of omeprazole treatment of healthy volunteers at therapeutic dosage (20 mg daily) [8]. Andersson et al. concluded that omeprazole treatment had no influence on CYP1A2 activity under clinical conditions.

The aim of our study was to estimate any potential change in CYP1A2 activity in healthy volunteers following treatment with lansoprazole in comparison with omeprazole administered in the usual therapeutic doses. We evaluated CYP1A2 activity by the ratio of the molar urinary concentrations of the three end products of the paraxanthine demethylation of caffeine over the molar concentration of a paraxanthine 8-hydroxylation product. This urinary metabolite ratio (CUM ratio) has previously been shown to be correlated with caffeine clearance [9] and CYP1A2 activity [10, 11], although neither the paraxanthine 7-demethylation nor the 8-hydroxylation depends solely on CYP1A2 activity.

Materials and methods

Subjects

Twelve healthy volunteers (6 men and 6 women) median age 31 y (range 24–47 y) and median weight 65 kg (range 50–83 kg) participated in the study. They were all non smokers. The subjects were informed of the possible adverse effects of omeprazole and lansoprazole. Written informed consent was obtained from each volunteer. The study was approved by the Ethics Committee of the Ambroise Paré Hospital (Boulogne/Seine, France).

Study design

The study was of open, randomised, two-period crossover design. Each subject was given 20 mg omeprazole every morning for 2 weeks, and 30 mg lansoprazole every morning for 2 weeks, in random order. The treatment periods were separated by a 3-week washout period. Urine was collected 3 h after the ingestion of each period.

Subjects were not allowed to consume medication for 2 weeks before or during either treatment period. They were also told to eat a normal diet and to avoid broccoli, white cabbage and charcoal-broiled meat, as well as heavy physical exercise during the study, since these factors have previously been shown to alter CYP1A2 activity [12, 13]. Except during the three hours of each caffeine test, when it was strictly forbidden, subjects were allowed to consume moderate amounts of caffeine-containing food and beverages.

Study medication

Omeprazole was given as MOPRAL® tablets (Astra) and lansoprazole as LANZOR® tablets (Houdé). Caffeine was administered as two 100 mg caffeine monohydrate capsules (Coopérative Pharmaceutique Française, France).

Chemicals

1-Methyluric acid (1U), 1-methylxanthine (1X) and 1,7-dimethyluric acid (17 U) were obtained from the Sigma Chemical Co (St Louis, MO, USA). We used an analytical sample of 5-acetyl-amino-6-formylamino-3-methyluracil (AFMU) supplied by Dr. Galteau (Centre du Médicament, Nancy, France). Methanol and isopropyl alcohol (all from Farmitalia Carlo Erba, Milano, Italia) were HPLC grade. Reagent grade chloroform was obtained from Prolabo (Paris, France). All other chemicals were reagent grade and came from Sigma Chemical Co. (St Louis, MO, USA).

Analytical procedure

Urine was collected and 20 ml aliquots were immediately acidified to pH 3 and stored at −20°C until analysis. Under these conditions, AFMU is stable and quantitative determination by HPLC can be performed [14]. Levels of the caffeine metabolites AFMU, 1X, 1U and 17U were measured using a modified version of the HPLC method described by Grant et al. [15]. Briefly, 1/2 diluted urine 500 μl was added to a tube containing 100 μl internal standard solution (240 μg/ml N-acetyl-p-aminophenyl). After addition of 120 mg ammonium sulphate, the metabolites were extracted in 2×8 ml chloroform/isopropyl alcohol (80:20, vol:vol) by vortexing for 2 min. Phases were separated by centrifugation at 3000 g for 10 min. The organic phase was transferred and dried under a nitrogen stream at 45°C. The dry extracts were dissolved in 0.05% acetic acid 50 μl and 20 μl was injected onto a C8 column (Ultrasphere ODS Beckman, 5 μm, 150×4.6 mm). The mobile phase was acetic acid 0.05%/methanol (92:8, vol:vol) with a constant flow of 0.8 ml·min−1. The metabolites were detected by absorbance at 280 nm and quantified by comparison with blank urine, spiked with pure standards. Recovery was 67%, 65%, 92% and 95% for AFMU, 1U, 1X and 17U, respectively. The limit of quantification was 1 mg·l−1 for AFMU and 1U, and 2 mg·l−1 for 1X and 17U. The intersay coefficients of variation were 9.6% (2 mg·l−1) 5.0% (5 mg·l−1) 5.0% (10 mg·l−1), 3.3% (5 mg·l−1) 7.7% (10 mg·l−1) 7.6% (25 mg·l−1), 9.9% (5 mg·l−1) 14% (20 mg·l−1) 4.0% (50 mg·l−1), and 5.2% (5 mg·l−1) 3.8% (20 mg·l−1) 6.7% (50 mg·l−1) for AFMU, 1U, 1X and 17U, respectively. Bias was less than 10% for each compound.

Determination of P450 1A2 activity: CUM ratio

The CYP1A2 activity was evaluated by the caffeine urinary metabolite ratio (CUM ratio) calculated by dividing the sum of the molar concentrations of the three end products of the paraxanthine demethylation of caffeine over the molar concentration of a paraxanthine 8-hydroxylation product: 1-7-dimethyluric acid (17 U), i.e. AFMU + 1U + 1X/17U.

Statistical analysis

The results are given as mean (SD). The effect of treatment with lansoprazole was tested by comparing the urinary caffeine metabolite ratio on Day 8 versus Day 1 and Day 15 versus Day 1 using a test based on pair-wise differences, the non-parametric Wilcoxon paired test. The effect of omeprazole was tested in the same way. P < 0.05 was taken as the statistically significant level.