Pharmacokinetic Interaction Study between Ranitidine and Metoclopramide

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Abstract

The pharmacokinetics of metoclopramide in healthy volunteers was evaluated to determine if previously repeated doses of ranitidine inhibit the metabolism of the gastrointestinal prokinetic drug. Metoclopramide 20 mg (tablets) in combination with ranitidine 150 mg (tablets) were administered to 14 healthy human volunteers in a two treatment study design, separated by 5 days in which the ranitidine alone was administrated in single p.o. doses twice daily. Plasma concentrations of metoclopramide were determined during a 24 hour period following drug administration. Metoclopramide plasma concentrations were determined by a validated RP-HPLC method. Pharmacokinetic parameters were calculated with compartmental and non-compartmental analysis. In the two periods of treatment, the mean peak plasma concentrations Cmax were 44 ng/ml (metoclopramide alone) and 49.2 ng/ml (metoclopramide and ranitidine). The time taken to reach the peak, Tmax, was 1.15 hrs, and 1.21 hrs, respectively. The total areas under the curve (AUC) was 314.3 ng.hr/ml and 354.06 ng.hr/ml, respectively. The half-life (T1/2) was 5.6 hr and 6.7 hr. A statistically significant difference was observed for both AUC and half-life of metoclopramide when administered alone or after 5 days of treatment with ranitidine. The experimental data proved the pharmacokinetic interaction between ranitidine of metoclopramide, and suggest monitoring adverse effects in patients.

Key words

Metoclopramide - ranitidine - pharmacokinetics - drug interaction

Rezumat

S-a studiat farmacocinetica metoclopramidei la 14 voluntari sănătoşi, în două tratamente, după administrarea unei doze unice de 20 mg pe cale orală ca atare, sau după un pretratament cu ranitidină, de două ori pe zi câte 150 mg, timp de 5 zile, spre a vedea dacă are loc o inhibare a metabolismului medicamentului propulsor gastric. Concentrațiile medicamentoase plasmatice ale metoclopramidei s-au determinat în probele prelevate pe o durată de 24 ore în cele două tratamente, folosind o metodă validată de cromatografie de lichide de înaltă performanță. Parametrii farmacocinetici s-au calculat folosind metoda monocompartimentală şi non-compoartimentală. In cele două tratamente concentrațiile plasmatice maxime, Cmax au fost 44 ng/ml (metoclopramidă singură) and 49.2 ng/ml (metoclopramidă cu ranitidină). Timpul necesar realizării Cmax, Tmax a fost 1,15 ore şi respectiv 1.21 ore. Ariile totale de sub curba concentrațiilor medicamentoase plasmatice în funcție de timp (AUC) au fost 314.3 ng.h/ml şi respectiv, 354,06 ng.h/ml. Timpii de înjumătățire (T1/2) ai metoclopramidei au fost 5,6 ore şi respectiv 6,7 ore. Au fost observate diferențe statistic semnificative între parametrii AUC şi T1/2 după administrarea sa în doză unică singur sau după un pretratament de 5 zile cu ranitidină. Rezultatele experimentale dovedesc existența interacțiunii farmaco-cinetice între ranitidină şi metoclopramid şi sugerează monitorizarea efectelor adverse la pacienți.

Introduction

Metoclopramide is a frequently prescribed drug in adults and children as an antiemetic and for preventing vomiting induced by antineoplastic drugs, and as a gastrointestinal prokinetic drug to control symptoms of upper gastrointestinal motor disorders, such as those seen in gastroesophageal reflux disease, dyspepsia, and diabetic gastroparesis.

Romanian Journal of Gastroenterology
September 2004 Vol.13 No.3, 211-214
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Metoclopramide has been combined with both cimetidine and ranitidine in the treatment of refractory gastro-esophageal reflux disease in patients (1-4).

In view of the extensive hepatic metabolism of metoclopramide both via N-4-sulfate and N-glucuronide conjugation and the ontogeny of phase II enzymes in humans, interactions with other substrates may occur. The cytochrome P450 (CYP 450) system is a major enzyme system responsible for drug metabolism and consists of more than 20 families of enzymes that primarily are located in the hepatocytes of the liver and mucosal tract. Each CYP isoform possesses a characteristic broad spectrum of catalytic activities of substrates. Metoclopramide is a substrate for CYP2D6 (5).

The H2-receptor antagonists, cimetidine and ranitidine inhibit the hepatic CYP450 metabolism of a number of concurrently administered drugs. Ranitidine also exerts an inhibitory effect, but to a lesser degree than cimetidine, on CYP2D6 and CYP3A4 (6). However, a structural similarity of enzymes cannot be used to predict which isoforms will be responsible for a drug's metabolism. The process of metabolic drug interaction usually begins with the first dose of the inhibitor, and onset and offset of inhibition correlate with the half-lifes of the drugs involved (8-10).

In a previous study the possibility of drug interaction between omperazole, metoclopramide and diclofenac sodium with ranitidine and fluoxetine was tested in human healthy volunteers (11).

The aim of the present study was to investigate in young healthy volunteers the effect of ranitidine on the pharmacokinetics of metoclopramide after multiple oral doses of ranitidine.

Material and methods

Subjects

Fourteen healthy, non-smoking males, aged 21-29 years (median 22.4 years) took part in a study, which was approved by the University of Medicine and Pharmacy of Cluj-Napoca Ethics Committee. All volunteers gave their written informed consent prior to study inclusion. The volunteers were healthy according to history, physical examination and laboratory tests, had no history of alcohol or drug abuse and did not take any regular medication.

Study design

The study consisted of two periods: Period 1 (Reference), when each volunteer received a single dose of 20 mg metoclopramide and Period 2 (Test), when each volunteer received a single dose of 20 mg metoclopramide and 150 mg ranitidine, after a pretreatment of 5 days with twice daily dose of 150 mg ranitidine.

Venous blood (5 ml) was drawn into heparinized tubes, in the first day of treatment (Period 1), before the drug administration as well as at 0.5, 1, 1.33, 1.66, 2, 2.5, 3, 4, 5, 6, 7, 8, 10, 12 and 24 hours after drug administration and the separated plasma was stored frozen (-20° C) until analysis. After 5 days of pretreatment with a twice daily dose of 150 mg ranitidine, metoclopramide 20 mg was give again concomitantly with the last dose of ranitidine (Period 2), and the sample collection was repeated. The number of blood samples was necessary to obtain the metoclopramide concentrations versus time profiles, for a good pharmacokinetic non-compartmental and compartmental analysis (12,13).

Analysis of samples

Metoclopramide was extracted from plasma samples. In a centrifuge tube, to 0.5 ml plasma, 100 µl NaOH 1 M and 7 ml diethyl ether were added. The tube was capped and shaken for 10 min on a vortex-mixer. After centrifugation and separation, the organic layer was evaporated at 38^0C. The residue was dissolved in 200 µl mobile phase and finally 100 µl injected in the chromatographic system.

Metoclopramide plasma concentrations were determined by a validated RP-HPLC method with fluorescence detection. The HPLC system was a HP 1100 series (binary pump, autosampler, thermostat, UV detector). A Zorbax SB-C18 column (75 mm x 4.6 mm i.d., 3.5 µm) was utilized, a mobile phase containing 20:80 (v/v) acetonitrile: 0.1% TFA in water. The flow rate was 1.8 ml/min and the thermostat temperature set at 40 °C. Fluorescence detection was in at Ex/Em = 316/359 nm.

The calibration curve was linear on range 2-206 ng/ml plasma, with a correlation coefficient r= 0.9995. The accuracy and precision were 4.3% and 6.6 % (intra-day) respectively 7.2% and 0.8% (inter-day, 3 consecutive days), as presented in Table I and II. The quantification limit was 1.3 ng/ml.

Pharmacokinetic and statistical analysis

The pharmacokinetic parameters of metoclopramide were calculated using the standard equations (12,13). The area under the plasma concentrations vs. time curve (AUC (0-24 hours) was determined by the linear trapezoidal rule and AUC (0-∞) was obtained from the equation:

$$AUC(0\text{-}\infty) = AUC(0\text{-}t) + C_{last} / K_{el}$$

where C_{last} is the last measured concentration and K_{el} is the terminal elimination rate constant (mono-compartmental analysis).

Peak plasma concentration (Cmax) and the time to reach peak (Tmax) were obtained from the plasma concentration data of each volunteer, as is stipulated in the approved Guide for bioequivalence studies (14).

The difference between plasma concentrations and pharmacokinetic parameters of metoclopramide when administered as a single dose alone and a single dose in combination with ranitidine after treatment with ranitidine for 5 days, were evaluated using ANOVA test. Differences in Tmax were evaluated by the Friedman non-parametric test.

The pharmacokinetic and statistical calculations were made with Kinetica 4.02 software (Inna Phase, U.S.A.).

Table I The precision, accuracy and recovery for metoclopramide validation (intra day)

Added concentration (ng/ml)	Measured concentration (ng/ml)	(SD)	Precision (C.V.%)	Accuracy (%)	Recovery (%)	(SD)
1.032	1.1	0.0	4.3	6.6	95.3	3.9
2.065	2.2	0.2	9.3	6.7	89.8	8.1
4.129	3.9	0.3	8.0	-6.0	76.2	6.0
8.258	8.2	0.3	3.6	-0.9	77.6	2.8
16.517	17.4	0.5	2.6	5.3	83.1	2.2
33.034	34.1	1.1	3.4	3.2	80.5	2.7
264.269	263.0	12.2	4.6	-0.5	77.1	3.6

Table II The precision, accuracy and recovery for metoclopramide validation (inter day)

Added concentration (ng/ml)	Measured concentration (ng/ml)	(SD)	Precision (C.V.%)	Accuracy (%)	Recovery (%)	(SD)
1.032	1.0	0.1	7.2	0.8	90.4	6.2
2.065	2.1	0.2	9.7	3.5	87.2	8.3
4.129	3.9	0.4	10.1	-6.4	75.9	7.5
8.258	8.1	0.3	4.1	-2.5	76.4	3.1
16.517	16.2	1.3	8.0	-2.0	77.3	6.1
33.034	33.5	2.5	7.5	1.4	79.1	5.9
264.269	261.9	9.8	3.7	-0.9	76.8	2.9

Results

The mean plasma concentrations of metoclopramide when administered alone or in combination with ranitidine after 5 days treatment with ranitidine twice daily are shown in Fig.1.

Pharmacokinetic parameters such as Cmax, Tmax, AUC (0-24), AUC (0-∞) and T1/2 are given in Table III.

Apparently similar concentrations of metoclopramide were observed after administration alone or with 150 mg ranitidine after 5 days ranitidine treatment 2x150 mg daily (Fig.1). Only in the first sampling points during the absorption period were the great intersubject variations observed. However, the difference between means values for the parameters which characterize the absorption, Cmax and Tmax, were not significant. Peak plasma concentrations (Cmax) of metoclopramide before and after the ranitidine multiple doses of treatment (44.02 ng/ml vs. 49.19) did not differ significantly between the two treatments (p=0.065), nor did the time to attain peak plasma concentrations (Tmax) (1.15 h vs. 1.21 h), (p=0.679).

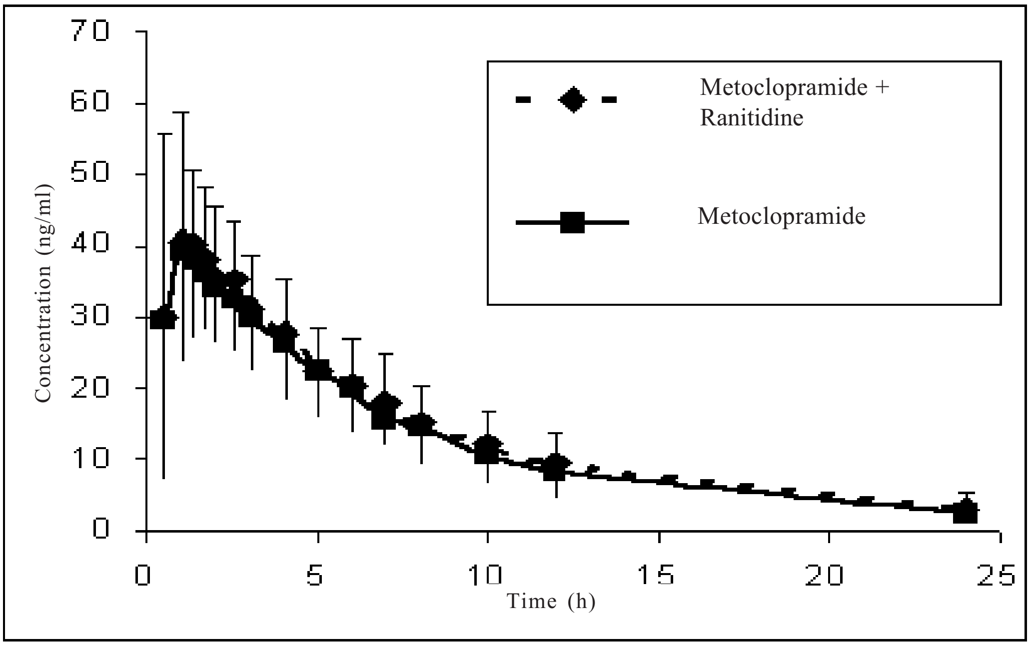

Fig.1 Mean (±S.D.) plasma levels of metoclopramide (20 mg p.o.) when alone or in combination with ranitidine (2x150 mg, p.o.) after treatment with ranitidine for 5 days (2x150 mg p.o. b.i.d.), n=14.

Table III Pharmacokinetic parameters of metoclopramide

Parameter	Metoclopramide alone	Metoclopramide + ranitidine after ranitidine b.i.d for 5 days	p* value, t-test
Cmax (ng/ml)	44.02	49.19	0.065, NS
Tmax (hrs)	1.15	1.21	0.679, NS
AUC (0-24) (ng.hr/ml)	291.95	332.1	0.002, S
AUC (0-Ą) (ng.hr/ml)	314.34	354.06	0.001, S
T1/2 (hrs)	5.62	6.72	0.010, S

* significance for p<0.05

However, for the terminal half-life (T1/2) (5.62.h vs. 6.82 h), the differences between values were statistically significant (p=0.01) (Table I).

The AUC of metoclopramide is different between the two treatments until the last sampling time (291.95 ng.hr/ml vs. 332.1 ng.hr/ml) (p=0.002) and also for AUC to the infinity (314.3 ng.hr/ml vs. 354.06 ng.hr/ml) (p=0.001) (Table I).

The treatment with multiple doses of ranitidine had a significant effect on metoclopramide pharmacokinetics regarding both drug exposure (AUC) and half-life (T1/2).

Discussion

The present study showed that a b.i.d treatment with ranitidine for 5 days influences the pharmacokinetics of a single oral dose of metoclopramide co-treatment with ranitidine. This implies that there is the possibility of interaction between the two drugs in the pharmacokinetics' phases. The fact that Tmax and Cmax values of metoclopramide were not significantly altered by ranitidine, indicates that the measured pharmacokinetic parameters for the rate of absorption were not affected. The increase in metoclopramide bioavailability (AUC) after the pretreatment with ranitidine is probably due to decreased metoclopramide elimination by alteration of metabolisation (ranitidine is a weak CYP2D6 inhibitor).

Metoclopramide metabolism in man is mediated through CYP2D6. The metabolism of a number of compounds has been shown to be inhibited by cimetidine and ranitidine (6,7). Like cimetidine, ranitidine binds to CYP450 in the liver where it appears to exert an inhibitory effect, but to a lesser extent than cimetidine. Both H2-receptor antagonists may also reduce hepatic blood flow. Several interactions between ranitidine and some drugs have been established, which may be attributed to an effect of ranitidine on hepatic metabolism (warfarin, metoprolol, nifedipine, theofylline, fentanyl) or to an effect on the absorption of concomitantly administered drugs (midazolam, procainamide). However some of the pharmacokinetic interactions are unlikely to be of clinical significance (7).

The pharmacokinetic interaction between metoclopramide and ranitidine was assessed and proved by the differences in both half life (19% increased after ranitidine) and drug exposure (12% increased after ranitidine). Owing to the known extrapyramidal effects of higher doses of metoclopramide in clinical treatments, these observations might be of importance in clinical monitoring of patients under treatment with this co-medication.

Conclusions

A pretreatment with ranitidine until the steady state plasma concentrations will significantly influence the pharmacokinetic parameters of metoclopramide co-administered as a single dose in human healthy volunteers, namely half-time and area under the curve. This extended residence time of metoclopramide in patients by co-administration with ranitidine may be of clinical importance, because the known extrapiramidal effects of metoclopramide at higher doses and elevated plasma concentrations could determine adverse effects.

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