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Research paper

Pharmacokinetics of oral cyclosporin A when co-administered to enhance the oral absorption of paclitaxel

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The objective of this study was to evaluate the pharmacokinetics of oral cyclosporin A (CsA) when co-administered to enhance the oral absorption of paclitaxel. Patients received oral paclitaxel in doses of 60–360 mg/m^2 in combination with a dose of oral CsA of 15 mg/kg. Dose escalation of paclitaxel from 60 to 300 mg/m^2 resulted in a significant decrease in the area under the concentration–time curve (AUC) of CsA from 24.4 ± 9.9 to 17.6 ± 2.8 mg/l·h (p=0.03) (n=28). In conclusion, increases in the paclitaxel dose resulted in a decrease in the AUC of CsA. This observation may be explained by the increase in the co-solvent Cremophor EL of paclitaxel causing reduced absorption of CsA. [© 2001 Lippincott Williams & Wilkins.]

Key words: Cyclosporin A, oral administration, paclitaxel, pharmacokinetics.

Introduction

The oral bioavailability of the anticancer agent paclitaxel is very low, due to high affinity of the drug for the multidrug efflux pump P-glycoprotein (P-gp) abundantly present in the gastrointestinal tract.[1] Recently we demonstrated the feasibility of oral administration of paclitaxel in cancer patients by co-administration of cyclosporin A (CsA), an efficacious inhibitor of P-gp. Co-administration of oral CsA resulted in a significant increase in the oral bioavailability of paclitaxel from less than 10% without CsA up to approximately 50% in combination with CsA.[2,3] Based on these first promising results we have investigated dose escalation of paclitaxel in order to further increase the systemic exposure to oral paclitaxel.[4] Here we present the pharmacokinetic data of CsA of the latter study in order to explore an effect of different doses of paclitaxel on the pharmacokinetics of CsA.

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Patients and methods

Study design

Patients with a histologic proof of cancer for whom no standard therapy of proven benefit existed were eligible. Inclusion and exclusion criteria have been described in detail elsewhere.[4] In brief, patients had to have acceptable bone marrow, liver and renal function. Concomitant use of known P-gp inhibitors and chronic use of H2-receptor antagonists or proton pump inhibitors was not allowed. The study protocol was approved by the Medical Ethics Committee of the Institute and all patients had to give written informed consent.

Patients received oral paclitaxel in doses of 60–300 mg/m^2 in combination with an oral CsA dose of 15 mg/kg. For oral paclitaxel administration the i.v. formulation was used (Paxene®; Baker Norton Pharmaceuticals, Miami, FL). CsA (Neoral®; Novartis, Basel, Switzerland) was administered as an oral solution or as capsules, 10 and 30 min prior to paclitaxel intake, respectively. The capsules were preferred due to the

bitter taste of the solution. Standard paclitaxel premedication was given to prevent hypersensitivity reactions, and consisted of dexamethasone 20 mg orally 12 and 6 h prior to, and clemastine 2 mg i.v. and cimetidine 300 mg i.v. 30 min prior to paclitaxel administration. Three patients (300 and 360 mg/m^2 dose levels) did not receive premedication because plasma levels of Cremophor EL, the co-solvent suspected of causing the hypersensitivity reactions,[5] were undetectable after oral administration of paclitaxel. To prevent nausea and vomiting following oral intake of paclitaxel, which occurred more often at the higher paclitaxel dose levels, five patients (300 and 360 mg/m^2 dose levels) received oral granisetron (Kytril®) prior to CsA and paclitaxel administration. To further prevent nausea and vomiting, three patients (300 and 360 mg/m^2 dose levels) received a light breakfast at least 2 h prior to oral paclitaxel administration. All other patients received CsA and paclitaxel after an overnight fast.

Pharmacokinetics

Blood samples for pharmacokinetic analysis of CsA were collected in heparinized tubes, pre-dose, 15, 30, 45, 60, 75, 90 and 105 min, and 2, 2.5, 3.5, 4.5, 7.5, 10.5, 24.5, 30.5 and 48.5 h after ingestion of CsA. For CsA analysis whole blood samples were stored at 4°C and analyzed within 1 week using a specific fluorescence polarization immunoassay (FPIA) (TDxFLx cyclosporin monoclonal whole blood assay; Abbott Laboratories, Amstelveen, The Netherlands).[6]

Non-compartmental pharmacokinetic methods were applied to process the results.[7] The area under the CsA concentration time curve (AUC) was calculated by the trapezoidal rule with extrapolation to infinity using the terminal rate constant k. The terminal half-life ($t_{1/2}$) was calculated as $\ln 2/k$. The maximal plasma concentration (C_{max}) and the time to maximal plasma concentration (T_{max}) were observed measured values. Statistical analysis of the CsA data was performed using the Pearson correlation coefficient. The *a priori* level of significance was p=0.05.

Results

Pharmacokinetics

Pharmacokinetic parameters of CsA (n=28) are outlined in Table 1. Dose escalation of paclitaxel from 60 to 360 mg/m^2 resulted in a significant decrease in the C_{max} and AUC of CsA (C_{max}: p=0.002, r=−0.56 and AUC: p=0.034, r=−0.40) (Figure 1). C_{max} and AUC values of CsA in combination with paclitaxel 60 mg/m^2 were 3.10±0.88 mg/l and 24.4±9.9 mg/l·h, respectively, and in combination with paclitaxel 300 mg/m^2 1.84±0.31 mg/l and 17.6±2.8 mg/l·h, respectively. At the paclitaxel dose level of 300 mg/m^2 administration of a light breakfast, premedication (dexamethasone, cimetidine and clemastine) or gran-

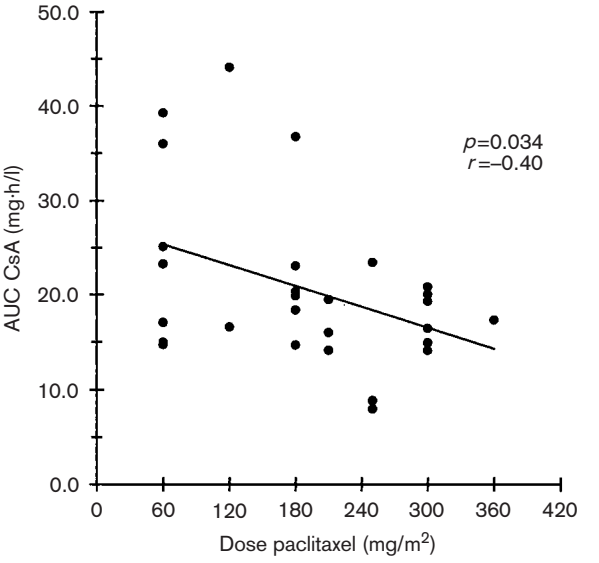

Figure 1. AUC values of oral CsA versus dose of oral paclitaxel.

Table 1. Non-compartmental pharmacokinetics of CsA when co-administered with paclitaxel (data are presented as means±SD)

Paclitaxel dose (mg/m^2)	CsA dose (mg/kg)	No. patients	AUC (mg/l·h)	C_{max} (mg/l)	T_{max} (h)	$t_{½}$ (h)
60	15	7	24.4±9.9	3.10±0.88	3.2±0.8	7.9±2.5
120	15	2	30.4±19.5	2.13±0.53	3.3±2.0	21.9±10.7
180	15	6	22.2±7.7	2.19±0.58	2.6±1.3	17.9±5.1
210	15	3	16.4±2.5	1.74±0.25	1.6±0.3	17.4±1.2
250	15	3	13.4±8.7	1.15±0.38	3.0±1.5	17.3±3.4
300	15	6	17.6±2.8	1.84±0.31	2.0±1.4	14.5±1.6
360	15	1	17.3	2.70	0.9	16.3

isetron did not result in differences in the pharmacokinetics of CsA (individual data not shown).

Discussion

The pharmacokinetics of CsA were evaluated when co-administered with different doses (60–360 mg/m^2) of oral paclitaxel.

The hypothesis of CsA co-administration to enhance absorption of orally administered paclitaxel is based on inhibition of intestinal P-gp by CsA. In addition, inhibition of paclitaxel metabolism by CsA may also be important. Both CsA and paclitaxel are metabolized by cytochrome P450 (CYP) 3A4.[8,9] Paclitaxel is along with CYP 3A4 metabolized by CYP 2C8.[9] In our proof of concept study we observed altered paclitaxel metabolism following CsA co-administration with a relative decrease in formation of the CYP 3A4 mediated metabolite 3′*p*-hydroxypaclitaxel.[3] Following the latter theory, increases in paclitaxel dose could result in relatively more competitive inhibition of CsA metabolism and thus in higher levels of CsA. However, we found that increases in paclitaxel dose resulted in significant decreases in C_{max} and AUC values of CsA. Apparently, in this study the potential effect of paclitaxel to competitively inhibit CsA metabolism is absent or negligible. In our previously published manuscript about the paclitaxel pharmacokinetics in these patients,[4] it was clearly shown that orally administered paclitaxel shows non-linear absorption pharmacokinetics with a decrease in oral bioavailability with an increase of dose. At the highest dose level of oral paclitaxel (300 mg/m^2), analysis of feces revealed data implying that the incomplete absorption of orally administered paclitaxel may be due to the co-solvent Cremophor EL.[10] We have subsequently shown in mice that increment of the amount of Cremophor EL with a constant paclitaxel dose causes a substantial reduction in the amount absorbed of orally administered paclitaxel.[11] A comparable phenomenon has been observed for vitamin K_1, which showed an increase in the oral bioavailability when the conventional Cremophor EL-solubilized formulation was replaced by a mixed-micellar formulation.[12,13] Parallel with paclitaxel and vitamin K_1, absorption of CsA might also be limited by the co-solvent Cremophor EL of the paclitaxel formulation. The decrease in CsA C_{max} and AUC values with higher doses of paclitaxel may thus be due to the increase in the amount of co-administered Cremophor EL. One way to test this hypothesis is to evaluate new formulations of paclitaxel without the co-solvent Cremophor EL.

In conclusion, increases in the paclitaxel dose co-administered with a constant CsA dose resulted in a significant decrease in the C_{max} and AUC values of CsA. This observation may be explained by the increase in the (paclitaxel) co-solvent Cremophor EL with higher paclitaxel dosages causing reduced absorption of CsA.

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