No pharmacokinetic drug–drug interaction between nevirapine and paclitaxel

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We have investigated the pharmacokinetics of nevirapine and paclitaxel in a patient who used both drugs concomitantly, as there are strong theoretical indications for a potential pharmacokinetic drug–drug interaction. Plasma concentrations of nevirapine (dose: 200 mg twice daily orally) and paclitaxel (dose: 100 mg/m^2 3-h i.v. infusion) were determined in a HIV-1-infected patient with Kaposi's sarcoma. Since both drugs are metabolized via the same cytochrome P450 isoenzymes, investigation of a drug–drug interaction was considered important. We found that the plasma concentrations of nevirapine given together with paclitaxel were similar to those given without paclitaxel. The exposures to paclitaxel ($AUC_{0-\infty}$ = 3787 h·ng/ml) and its hydroxy metabolites when co-administered with nevirapine were comparable to the mean exposure to paclitaxel and its metabolites from eight historical controls ($AUC_{0-\infty}$ = 3614 h·ng/ml) treated with the same dose. No pharmacokinetic drug–drug interaction between nevirapine and paclitaxel could be demonstrated in our HIV-1-infected patient. *Anti-Cancer Drugs* 16:627–630 © 2005 Lippincott Williams & Wilkins.

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Introduction

Kaposi's sarcoma is the most common HIV-associated malignancy [1]. Optimal anti-retroviral therapy is an essential component of Kaposi's sarcoma management, and this has reduced the incidence and prolonged the time to treatment failure in Kaposi's sarcoma [2,3]. For patients with more extensive disease or failure to respond sufficiently to highly active anti-retroviral therapy, a variety of systemic and sometimes topical therapies is used, including chemotherapy, radiotherapy and/or immunotherapy [4]. Paclitaxel has previously demonstrated impressive anti-tumor activity in patients with HIV-1-associated Kaposi's sarcoma [5]. More recently, it has been approved by the EMEA and FDA as second-line monotherapy for advanced Kaposi's sarcoma [6].

When an HIV-1-infected patient with Kaposi's sarcoma has to be treated with anti-retroviral therapy and paclitaxel, there is a considerable potential for pharmacokinetic drug interactions [7–10]. Paclitaxel is metabolized by the hepatic cytochrome P450 (CYP)3A4 and CYP2C8 isoenzymes to 3′*p*-hydroxypaclitaxel (3OHP) and 6α-hydroxypaclitaxel (6OHP), respectively [11]. Nevirapine induces CYP3A4 enzymes [12] and may thus increase paclitaxel metabolism.

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We studied the pharmacokinetics and the possible drug–drug interaction of nevirapine and paclitaxel in an HIV-1-infected patient with Kaposi's sarcoma.

Patient and methods

A 37-year-old male patient was diagnosed with Kaposi's sarcoma on the uvula and the left lower leg in the form of a sensitive and red edema with superficial injures and wound fluid. Around the swelling, small skin lesions were seen. The patient had a low cellular immunity of 170 CD4 cells/mm^3 and a high plasma viral load of 113 000 copies/ml.

The patient received anti-retroviral therapy consisting of stavudine (40 mg twice daily), lamivudine (150 mg twice daily) and nevirapine (200 mg twice daily). The extensive Kaposi's sarcoma was treated with paclitaxel, given at 100 mg/m^2 (180 mg) as a 3-h i.v. infusion.

Sampling and analyses

Samples for pharmacokinetic analysis were collected by i.v. sampling from the arm contralateral to the one in which the paclitaxel was infused. Samples were collected prior to the start of the paclitaxel infusion, at 0.5, 1 and 2 h during the infusion, at the end of the 3-h infusion, and 0.5, 1.5, 2.5 and 4.5 h after the cessation of the paclitaxel

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infusion. Paclitaxel and its metabolites 6OHP and 3OHP were quantitated by a validated and sensitive liquid chromatography–mass spectrometry (LC-MS/MS) method [13]. The area under the plasma concentration versus time curves ($AUC_{0-\infty}$) of paclitaxel and metabolites were determined using the trapezoidal rule from the concentration versus time plots with extrapolation to infinity (WinNonlin Professional, version 4.1; Pharsight, Mountain View, CA). Clearance (CL) of paclitaxel was calculated as CL = dose/AUC. Values of the pharmacokinetic parameters were compared to values from courses (100 mg/m^2 3-h infusion) from eight patients, as part of a paclitaxel dose-escalating study executed in our Institute [14].

Nevirapine, stavudine and lamivudine were given 1 h prior to the paclitaxel infusion. Samples for determination of the plasma concentrations of nevirapine were collected prior to intake, and at 0.5, 1.5, 2, 2.5, 3.5, 4.5, 5, 6, 7 and 9 h after ingestion. Concentrations were assayed by a validated and sensitive high-performance liquid chromatography assay with UV detection [15]. Plasma concentrations of nevirapine during concomitant paclitaxel use were compared with plasma concentrations of nevirapine from the same patient when no paclitaxel was used (samples were drawn at least 5 days after paclitaxel course).

Results

The pharmacokinetic parameters of paclitaxel (C_{max}, $AUC_{0-\infty}$, t_{12}, CL, V and time > 0.1 μmol/l) of the HIV-1-infected patient who used concomitantly nevirapine were comparable with the results of eight courses of non-HIV-1-infected historical controls (Table 1). The pharmacokinetic profiles of paclitaxel and its metabolites are shown in Figure 1.

The concentration versus time curve of nevirapine during paclitaxel treatment is shown in Figure 2, where single concentration–time points of nevirapine, when used without paclitaxel, from our patient are also presented. The mean plasma concentrations and SDs of nevirapine with and without paclitaxel were 4.79 ± 0.56 and 4.21 ± 0.40 mg/l, respectively ($p = 0.75$).

Discussion

Optimal anti-retroviral therapy is obtained only when maximally suppressive drug concentrations during a complete dosage interval are maintained. A study exploring the association of exposure to nevirapine with virological response in anti-retroviral HIV-1-infected patients yielded a target trough concentration of 3.4 mg/l [16]. In our case it appeared that nevirapine plasma concentrations were not significantly influenced by combined use with paclitaxel and were always higher than the target trough concentration. Thus, paclitaxel and the mixture of polyoxyethylated castor oil and ethanol (50/50, v/v), which is used in the i.v. formulation of paclitaxel to improve its aqueous solubility, but causes several drug–drug interactions [17], did not influence the pharmacokinetics of nevirapine. Since adequate nevirapine levels were reached, which resulted in an increase of cellular immunity (340 CD4 cells/mm^3) and undetectable viral load (less than 50 copies/ml), dose adjustment of nevirapine when used with paclitaxel is not needed.

The pharmacokinetic parameters of paclitaxel and its metabolites 6OHP and 3′OHP in our HIV-1-infected patient were comparable with the eight non-HIV-1-infected historical controls to whom paclitaxel had been given at the same dose of 100 mg/m^2 as a 3-h infusion. To compare the pharmacokinetics of paclitaxel in our patient with those in a control group, it is of paramount importance that this group received the same dose with the same duration of infusion, since paclitaxel is characterized by non-linear pharmacokinetics [14].

Paclitaxel is metabolized into the metabolites 6OHP and 3′OHP by CYP2C8 and CYP3A4, respectively. Nevirapine induces CYP3A4. This could have led to an increased metabolism of paclitaxel into the 3′OHP metabolite and to a reduction of CYP2C8 metabolism, but was not demonstrated.

Thus, despite the strong theoretical indications for potentially clinically relevant pharmacokinetic drug–drug interactions between nevirapine and paclitaxel, the pharmacokinetic parameters of paclitaxel and metabolite profiles were comparable for our HIV-1-infected patient and the control group. Also, the plasma concentrations of nevirapine when dosed concomitantly with paclitaxel were similar to those without paclitaxel. From this case it could not be demonstrated that nevirapine affected the

Table 1 Pharmacokinetic parameters of paclitaxel

	C_{max} (ng/ml)	$AUC_{0-\infty}$ (h·ng/ml)	$t_{1/2}$ (h)	CL (l/h)	V_{ss}(l)	$T > 0.1$ μmol/l (h)
Paclitaxel 100 mg/m^2 (P)	989	3787	1.75	47.5	72.2	10.0
Paclitaxel 100 mg/m^2 (C) (mean ± SD)	967 ± 187	3614 ± 701	4.44 ± 3.85	51.2 ± 12.3	130 ± 100	6.79 ± 1.00
p[a]	1.00	0.439	0.245	1.00	0.439	0.121

[a]Mann–Whitney test.

C_{max} = maximum concentration, $AUC_{0-\infty}$ = area under the concentration–time curve with extrapolation to infinity, $t_{1/2}$ = elimination half-life, CL = clearance, V_{ss} = volume of distribution, $T > 0.1$ μmol/l = time that paclitaxel plasma concentrations are higher than 0.1 μmol/l (85 ng/ml), P = patient (also using nevirapine 200 mg twice daily), C = control group ($n = 8$) [14].

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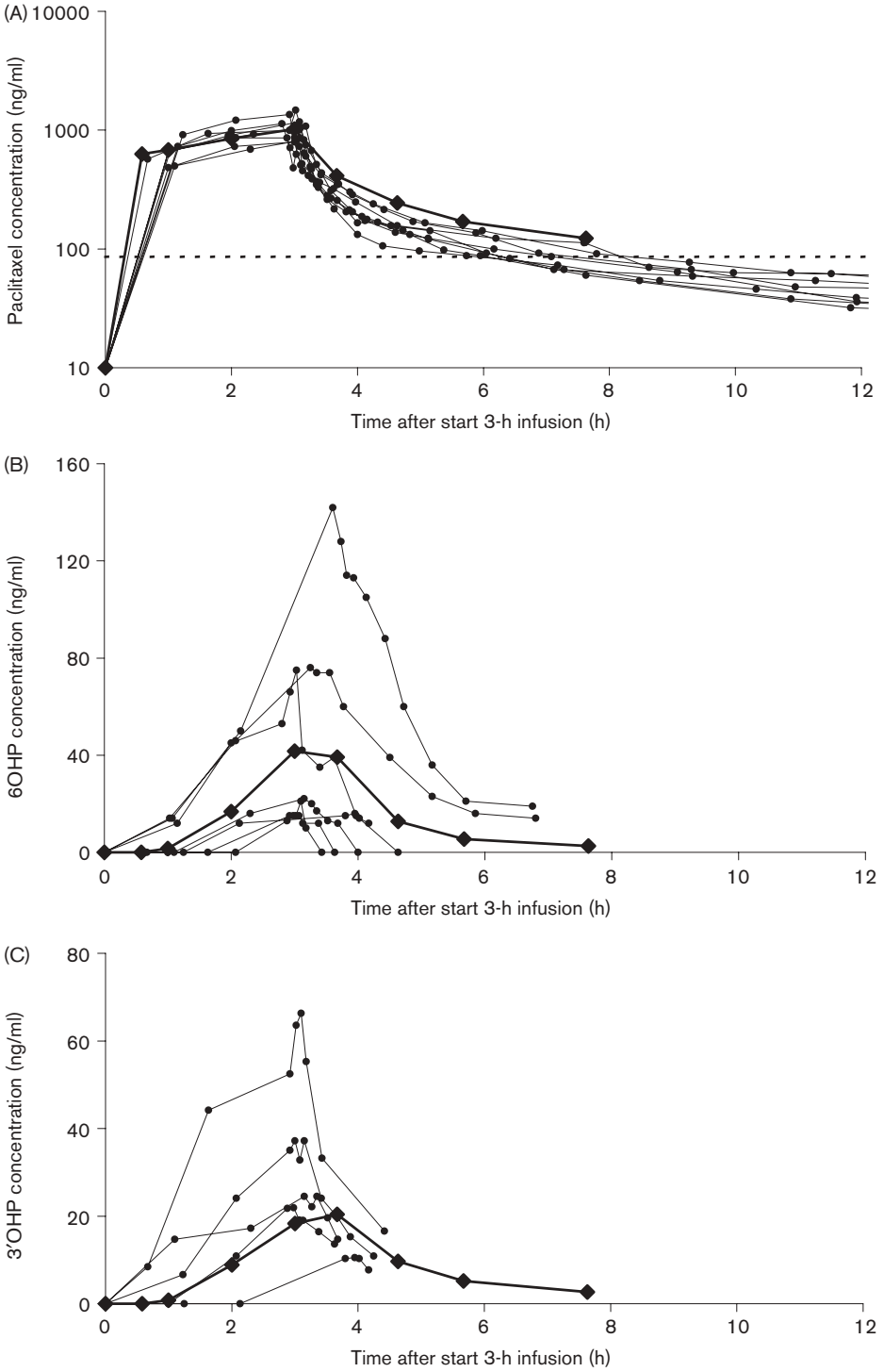
Fig. 1



Plasma concentration–time curves of paclitaxel (A), metabolite 6OHP (B), metabolite 3′OHP (C). Dots represent the paclitaxel curves of control patients. Diamonds represent paclitaxel concentrations with concomitant use of nevirapine. The horizontal dotted line in (A) represents the threshold concentration of 0.1 μmol/l (85 ng/ml) [14].

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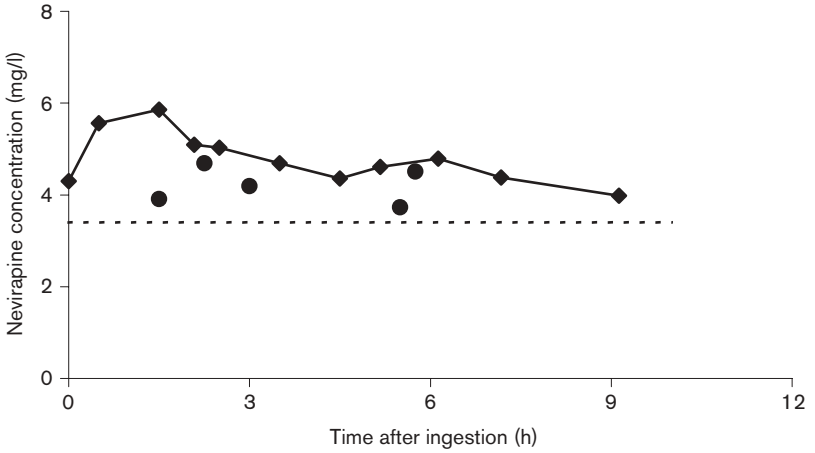
Fig. 2



Plasma concentration–time curve of nevirapine. Diamonds represent the nevirapine curve during paclitaxel treatment. Dots represent single nevirapine concentrations without concomitant use of paclitaxel. The horizontal line represents the target trough concentration of 3.4 mg/l.

pharmacokinetics of paclitaxel or its metabolic pathway, or *vice versa*.

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