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ORIGINAL ARTICLE

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Clindamycin–paclitaxel pharmacokinetic interaction in ovarian cancer patients

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Abstract *Introduction*: Plasma protein binding is an important factor for many drugs that can influence the tissue distribution and pharmacokinetics. α_1-acid glycoprotein (AGP) is an acute-phase protein that can increase in plasma of patients with several pathological conditions including cancer. Studies performed in cultured cells indicate that paclitaxel cytotoxicity is reduced by adding AGP and the sensitivity to paclitaxel is restored by displacing its binding to AGP with clindamycin, resulting in an increased paclitaxel cell uptake. The purpose of this study was to evaluate whether clindamycin modifies paclitaxel pharmacokinetics also in cancer patients. *Patients and methods*: Sixteen patients with advanced ovarian cancer, previously treated with surgery and chemotherapy were enrolled in this study. A pharmacokinetic study of paclitaxel was performed in the first three cycles of the consolidation therapy (paclitaxel and carboplatin) in each patient. In these cycles paclitaxel was administered alone and with two different doses (600 and 1,200 mg) of concurrent clindamycin. The sequence of the three treatments was randomly assigned in each patient in order to avoid the same order of treatments. *Results*: Paclitaxel pharmacokinetics were partly modified by the concurrent administration of clindamycin. C_{max} and AUC_{0-last} of paclitaxel were significantly higher when the drug was given alone than when it was coadministered with 1,200 mg clindamycin. Moreover, AGP concentrations seem to have a small but statistically significant influence on paclitaxel pharmacokinetic, since AUC_{0-last} showed a positive significant correlation with AGP plasma concentration when paclitaxel was given alone. The linear relation was lost when paclitaxel was coadministered with 1,200 mg clindamycin. Toxicity was not influenced by the coadministration of clindamycin. *Conclusion*: The hypothesis that clindamycin could affect paclitaxel pharmacokinetics seems to be verified with this study. Nevertheless, changes induced by giving the combination of the two drugs are minimal and thus of questionable clinical relevance.

Keywords α_1-acid glycoprotein · Paclitaxel · Clindamycin · Pharmacokinetics · Ovarian cancer · Protein binding

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Introduction

In the peripheral circulation, drugs are present either as free or unbound fractions or bound to plasma protein, polysaccharides and lipids [1]. The unbound drug fraction can diffuse across biologic barriers and can interact with receptor sites in the circulation or extravascular compartment [2].

Paclitaxel, one of the most used anticancer drugs in the ovarian cancer treatment, is present in human plasma mainly as a bound fraction after infusion. There are two main explanations to this phenomenon: the first is that Cremophor EL, a castor oil derivative used to formulate this poorly water-soluble drug, decreases the unbound fraction of paclitaxel by trapping the drug in micelles composed by polyoxyethilene glycerol triricinoleate [3]. Recently, it has been demonstrated that the disposition of unbound paclitaxel increases when the drug is given as a 3-h infusion compared with the 1-h infusion, as a result of the increased clearance of Cremophor EL [4].

The second explanation is the interaction between the drug and human plasma proteins. Paclitaxel is extensively plasma-protein bound (95–98%), equally to albumin and alpha-1-acid glycoprotein.

AGP is considered as a major member of the positive acute phase protein family, but its biological functions

are poorly understood. Its concentrations in healthy subjects are within the range 0.4–1 g/l, but it is generally acknowledged that its plasma levels are increased both in many physiological states, such as pregnancy [5], and in pathological conditions, like liver cirrhosis and cancer [6, 7]. In some cases significant elevations of AGP were found in patients with active tumors; moreover, AGP levels correlated with a response to chemotherapy [8–11]. Due to its physical–chemical properties, AGP mainly binds basic and neutral drugs, while acidic drugs are mainly bound to albumin [12].

There are evidences that an increased amount of AGP, due to pathologic conditions, may reduce the efficacy of some drugs. One example is represented by the tyrosine-kinase inhibitor, STI571 (Imatinib). Human AGP in vitro inhibited the effect of STI571 in a concentration-dependent manner [13]. Adding erythromycin, which competes with STI571 in the AGP binding, the effect of the drug could be restored. These results were confirmed in vivo using a leukemia model in mice. AGP levels increased proportionally with the tumor load, and coadministered erythromycin increased dramatically the response to STI571 and the tumor-free survival [14].

In a subsequent study the displacing effect of clindamycin, an antibiotic similar to erythromycin but more commonly used in patients, was evaluated. The coadministration in mice of this drug decreased the plasma levels of STI571 and increased its concentrations in all of the organs examined including the tumor.

In patients a linear correlation was found between AGP plasma levels and Imatinib C_{max}, and the coadministration of clindamycin reduced Imatinib plasma concentrations and the protein-bound drug from 99 to 96%.

A second example is the staurosporine analog, UCN-01. It was shown that the slow dissociation of this drug from human AGP limits its disposition and elimination [15]. Furthermore, a recent study found that the baseline AGP was the only significant predictor of docetaxel toxicity in patients with NSCLC [16]. We have recently obtained preclinical evidence that AGP concentrations influences the activity of paclitaxel in vivo and in vitro. The coadministration of clindamycin increased the cytotoxicity of paclitaxel in vitro growing ovarian cancer cells and in one ovarian carcinoma xenograft, presumably by displacing the AGP binding of paclitaxel, thus increasing the concentration of the anticancer drug in the tumor cells (R. Frapolli, personal communication). These preclinical data allowed us to perform a pilot study to evaluate whether clindamycin could affect the pharmacokinetics of paclitaxel.

Considering that a high variability of AGP plasma levels is reported in ovarian cancer patients [6], we have undertaken this study in a series of ovarian cancer patients with a design that allowed us to evaluate if there are changes in paclitaxel pharmacokinetics when the drug is given alone or in combination with clindamycin given at two dose levels.

Patients and methods

Patient selection

Women with diagnosis of ovarian epithelial adenocarcinoma that was histologically proven stage III or IV according to the criteria of International Federation of Gynecology and Obstetrics (FIGO) who had complete response to their primary treatment (surgery and platinum-based chemotherapy, no patient received paclitaxel previously) and needed to receive a consolidation therapy were candidates for this study. Median duration from prior treatment was 5 weeks (range 4–6 weeks).

Complete clinical response was defined as normal physical examination, no conclusive evidence of residual tumor by computed tomography (CT) of the abdomen and pelvis, normal chest X-ray, and normal serum CA-125 level (< 35 UI/ml). Patients must have had a performance status ≤ 2 on the Eastern Cooperative Oncology Group scale.

Exclusion criteria were compromised hematopoietic function (hemoglobin < 8 mg/l, absolute neutrophil count $< 2{,}000$ per mm^3, or platelet count $< 100{,}000$ per mm^3), significant cardiovascular, hepatic or renal abnormalities, active infection causing fever, and concurrent malignancies.

The study protocol was approved by the institutional review board of San Gerardo Hospital, Monza, and informed consent was obtained before study participation, according to institutional guidelines.

Drug administration

Paclitaxel used in the study, Taxol, was purchased from Bristol Myers Squibb. A dose of paclitaxel of 175 mg/m^2 was given as a 3 h infusion, and was followed by carboplatin AUC5 administered intravenously over 60 min. The carboplatin dose was calculated using the Calvert method, and the dose was obtained by the formula: carboplatin dose (mg): AUC $\times$ (GFR + 25). The GFR was estimated using the Jeliffe formula. Clindamycin was given as a 30 min infusion. The infusion of the antibiotic started two and a half hours after the start of paclitaxel. This schedule was chosen presuming to achieve the maximum concentration of Taxol and clindamycin at the same time [17].

All patients received premedication, in the order of reducing the risk of paclitaxel hypersensitivity, consisting of a single dose of dexamethasone (20 mg), chlorpheniramine (10 mg) and cimetidine (300 mg) administered 30 min before the start of the Paclitaxel infusion. Chemotherapy cycles were repeated every 3 weeks.

Study design

Patients were randomly assigned to one of the four treatment groups 1, 2, 3, 4 (Table 1). The cycle of che-

motherapy without the concomitant administration of clindamycin was a sort of "control" cycle, and in every group it was either the first or the second, in order to avoid an influence on paclitaxel pharmacokinetics by an eventual progression of the disease.

Sample collection

Blood specimens (5 ml) were drawn from a peripheral vein in the arm opposing that used for drug administration, and collected directly in plasma collection tubes containing freeze-dried sodium heparin. Patency of the catheter was maintained with the use of a heparin lock. Sample tubes were mixed and centrifuged (2,500 rpm, 10 min, 4°C) within 15 min. Plasma was transferred into polypropylene cryovial, covered with polyester protective label tape and stored until assayed.

Blood samples were collected before infusion of paclitaxel, at midpoint of infusion, 1–2 min after the end of the infusion, and 15 and 30 min and 1, 2, and 3 h after the end of the infusion.

Analytical methods

The total concentration of paclitaxel in plasma specimen was determined by high-performance liquid chromatography with UV detection (Waters Associates, Milford, MA, USA, model 2487 Variable Wavelength Detector, Wavelength: 230 nm).

Analytical reference samples of paclitaxel was generously provided by Indena SPA, Settala (MI), Italy and the internal standard docetaxel was generously provided by Aventis Oncology, Vitry-sur-Seine, France. One milliliter of study samples was spiked with 50 µl of docetaxel as IS and 1 ml of 0.2 M ammonium acetate buffer pH 5 were added. After vortex for 10 s, samples were kept at 4°C for 30 min and centrifuged at 3,000 rpm for 5 min. Supernatant were processed automatically by using a Bench Mate Workstation, with Sep-Pak cartridges for solid-phase extraction (Waters Associates, Milford, MA, USA). Paclitaxel was eluted from the columns into glass tubes with 1 ml of 0.1% triethylamine in CH_3CN. The eluents were dried under nitrogen. The residues were reconstituted in 120 µl of mobile phase, transferred into HPLC vials and 100 µl were injected into the HPLC system. The chromatography column was a Novopack C18 (3.5 µm, 4.6×150 mm) proceeded by a precolumn (5 µm, 4.6×20 mm).

Table 1 Treatment groups: dose of clindamycin administered (mg)

	First cycle	Second cycle	Third cycle
Group			
1	600	0	1,200
2	0	600	1,200
3	1,200	0	600
4	0	1,200	600

Mobile phase was composed of CH_3COONH_4 0.01 M pH 5.5 (59%), CH_3CN (34%), CH_3OH (6%) and THF (1%) and the flow rate was 1.3 ml/min. Each study sample was assayed together with a series of six plasma calibration standards containing paclitaxel at concentrations ranging from 0.1 to 5 µg/ml.

AGP determination method

AGP levels have been determined in all patients using TT4 Turbitimer Dade-Behring for the quantitative determination of the plasma proteins. The method is based on the kinetic turbidimetric measurement of the precipitation reaction between proteins and their corresponding specific antibodies. The obtained measuring data are converted into concentrations by means of a calibration standard curve made in the range of 0.4–5.5 mg/ml, which at the upper level corresponds to more than five times the normal physiological value of AGP present in plasma. Standard samples of 0.5, 0.8 and 1.0 mg/ml are processed together with unknown samples.

The procedure necessitates the dilution of 5 µl of plasma sample for 21 times with saline; 50 µl of the obtained solution is mixed to 500 µl of the antibody reagent and loaded into the Turbiquant instrument to measure the originated turbidity.

Data analysis

Actual sample times were calculated from the beginning of the drug infusion to the sample collection time. Plasma concentration–time profiles of paclitaxel were analyzed by non-compartmental methods using the software package WinNonlin Version 4.0.1 (Pharsight Corporation, Mountain View, CA). AUC was estimated using the logarithmic–linear trapezoidal algorithm to the last data point.

In order to evaluate the effect of the concomitant administration of clindamycin with paclitaxel, we divided the 48 cycles into three groups of 16 cycles each based on the dose of clindamycin coadministered. Mean values of pharmacokinetic variables were calculated for the three treatment groups marked as A, B and C (0, 600 and 1,200 mg of clindamycin, respectively) as the geometric mean of the individual patient values. SDs for the geometric mean values were estimated with the jackknife method.

Statistical comparison between the three groups was performed using the *t*-test paired for means. The correlation between AGP plasma levels and PK parameters was evaluated using a linear regression model.

Results

Sixteen patients were enrolled in this trial, and they were divided in four groups, depending on the sequence of the

concomitant dose of clindamycin given at each cycle of chemotherapy. The 16 women with advanced ovarian cancer enrolled and treated in this study ranged in age between 45 and 70 years. The majority of the patients had stage III disease (87%) with serous histopathology (Table 2).

All 16 patients received paclitaxel 175 mg/m^2 with or without clindamycin (dose of 600 and 1,200 mg) in each cycle, following the study design described in the Patients and methods section. In all the 48 cycles the duration of paclitaxel infusion was 3 h.

Mean paclitaxel plasma concentration–time profile for each treatment group is in Fig. 1. Similar paclitaxel plasma profiles were observed in the presence or absence of concomitant clindamycin. Mean C_{max} in group A is 3.25 μg/ml, in group B is 3.02 μg/ml and in group C is 2.87 μg/ml. The mean of the last sample (3 h after the end of the infusion) measured in the three groups is similar (0.59 ± 0.24 μg/ml in group A; 0.60 ± 0.24 μg/ml in group B; 0.57 ± 0.27 μg/ml in group C).

AGP levels were measured in the pretreatment sample of every cycle of chemotherapy, and they ranged between 0.4 and 1.21 mg/ml. The mean AGP value considering all the 48 cycles was 0.63 mg/ml; there were no statistically significant differences between the AGP plasma levels of the three treatment groups (mean values shown in Table 3).

All the patients enrolled in the study were analyzed for PK and mean PK parameters for the three groups are shown in Table 3. Comparing paclitaxel pharmacokinetic variables of the treatment groups A and C (patients treated with 0 and 1,200 mg of clindamycin, respectively) using a paired *t*-test, we found a statistically significant difference for C_{max} (*P*: 0.01) and AUC_{last} (*P*: 0.01). Comparison of these two groups with group B did not show a statistically significant difference of any of the pharmacokinetic variables considered.

Figure 2 shows the correlation between AGP levels and paclitaxel AUC_{last} in patients receiving paclitaxel alone (panel A) in combination with clindamycin, 600 mg (panel B) and 1,200 mg (panel C). A weak yet significant correlation is seen only in patients receiving paclitaxel alone (r^2: 0.28, *P*: 0.03), while linearity is lost in patients receiving concomitant clindamycin 600 mg (r^2: 0.24, *P*: 0.06) or 1,200 mg (r^2: 0.02, *P*: 0.6).

Finally we evaluated the effect of the coadministration of different doses of clindamycin on the occurrence and on the grade of toxicity of paclitaxel. There were no differences in the three treatment groups, as summarized in Table 4. High-grade hematological toxicity occurred in 9, 10 and 10 courses and weeks of treatment delay were 12, 11 and 12 in groups A, B and C respectively. Low-grade sensory neuropathy occurred in 6, 7 and 5 courses in the three groups.

Table 2 Patient Characteristics ($n = 16$)

	No. of patients	Percentage
Age (years)		
Median	62	
Range	45–70	
ECOG performance status		
0	15	93
1	1	7
2	0	0
Stage		
III	14	87
IV	2	13
Primary tumor grade		
1	2	13
2	4	25
3	10	62
Histological diagnosis		
Serous adenocarcinoma	14	87
Mucinous adenocarcinoma	1	7
Other	1	7

Discussion

There are some evidences that AGP is an important determinant of pharmacokinetics for several drugs [13–16]. Moreover, as an acute-phase protein, its concentration can rise in all pathologies with an inflammatory component, like neoplasia. The variable levels of AGP may affect the drug-free fraction, thus influencing the pharmacological activity. This can be particularly relevant for anticancer drugs, because they generally have a narrow therapeutic range.

Growing evidence exists that AGP levels can influence the pharmacokinetics of some anticancer drugs, such as UCN-01 and Imatinib. For the latter, recent data have supported that it is possible to displace the binding of this drug with AGP by erythromycin and clindamycin, thus modifying its pharmacokinetics.

Preclinical data showed that by increasing AGP concentrations in culture medium, the intracellular uptake of paclitaxel in ovarian cancer cells in vitro decreases with consequent reduction of drug cytotoxicity. Cell sensitivity to paclitaxel and intracellular uptake could be restored by adding erythromycin or clindamycin (unpublished data).

If AGP influences the distribution of paclitaxel this can be relevant for ovarian cancer patients, considering that literature data indicate that AGP levels in ovarian cancer patients are higher than healthy subjects [6].

Although in our cases we found a relatively limited increase in AGP levels—much lower than increases reported in literature—we found a statistically significant correlation between AGP levels and AUC_{0-last} in patients treated with paclitaxel alone.

The same correlation was not found in patients treated with the two doses of clindamycin, and the explanation could be that the antibiotic displaces the drug from its AGP binding, therefore removing the effect of the protein. In order to evaluate the effect of clindamycin on paclitaxel pharmacokinetics, we compared pharmacokinetic parameters of the three treatment groups.

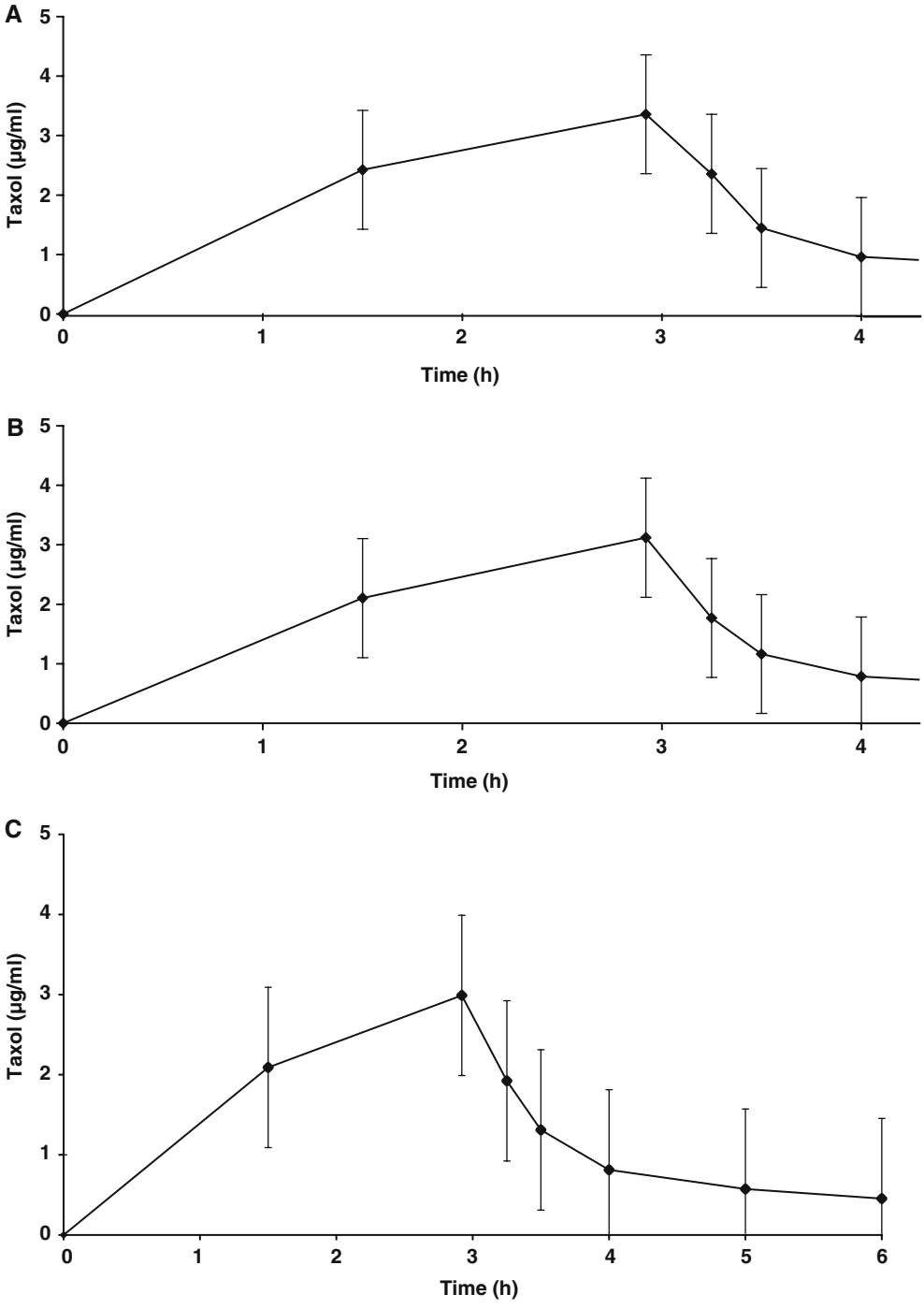

Fig. 1 Mean paclitaxel pharmacokinetic profile without clindamycin (*Panel A*), with 600 mg (*Panel B*) and 1,200 mg (*Panel C*) clindamycin

Each patient received two different doses of clindamycin and a cycle without antibiotic was also monitored. The highest dose administered, 1,200 mg, is common in clinical use, and allowed us to reach plasma levels that, according to preclinical observations, could possibly displace paclitaxel from AGP.

Table 3 Mean pharmacokinetic parameters for paclitaxel

Group	Clindamycin dose (mg)	No. of cycles	C_{max} (µg/ml)	AUC_{last} (µg h/ml)	AGP (mg/ml)
A	0	16	3.25 ± 1.22	8.40 ± 2.88	0.58 ± 0.16
B	600	16	3.02 ± 0.81	7.49 ± 1.94	0.59 ± 0.18
C	1200	16	2.87 ± 0.89	7.45 ± 2.24	0.65 ± 0.19

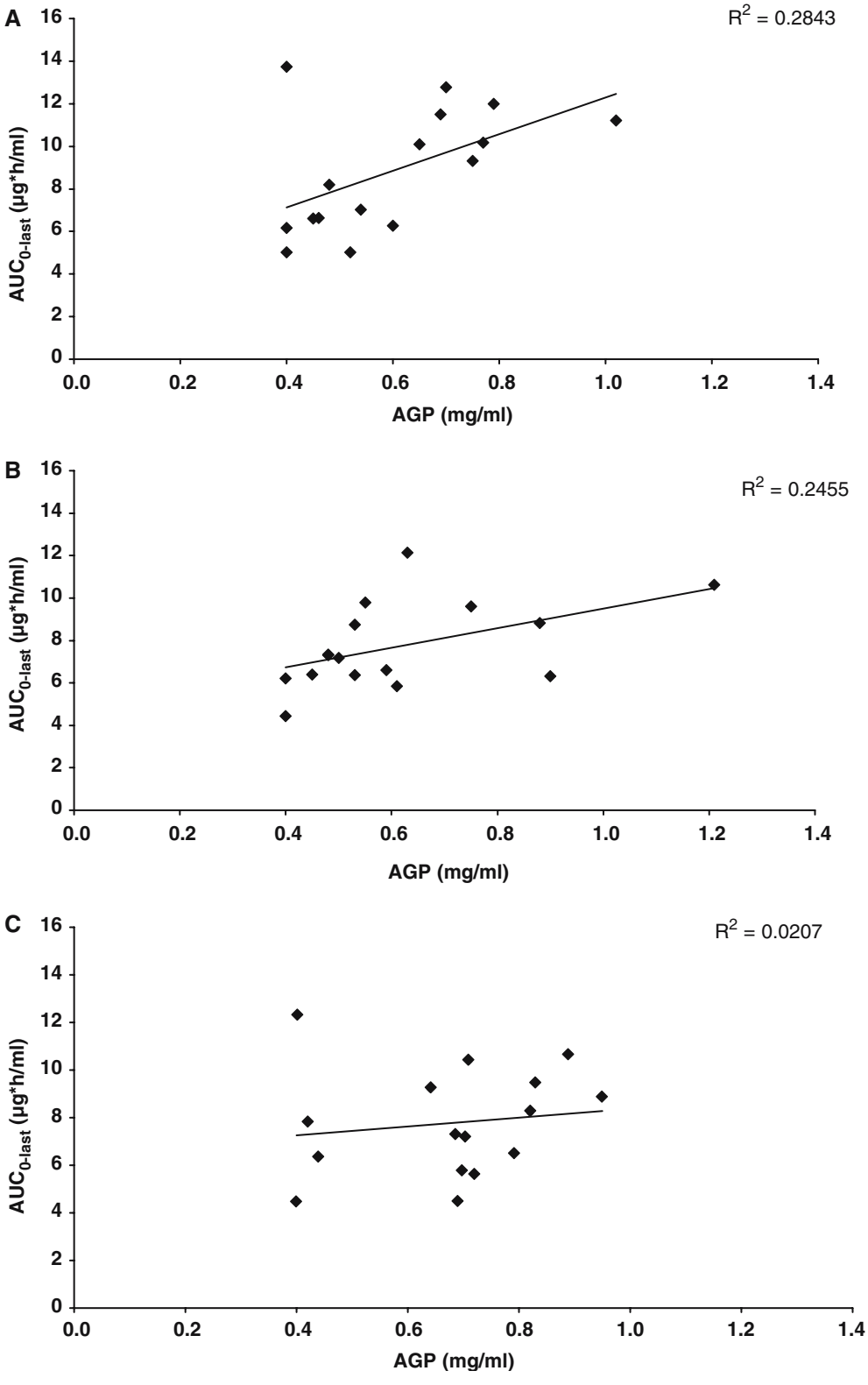

Fig. 2 Correlation between plasmatic AGP concentrations and $AUC_{0\text{-last}}$ of paclitaxel alone (*Panel A*) and in combination with 600 mg (*Panel B*) and 1,200 mg (*Panel C*) clindamycin

Moreover, giving each patient different doses of clindamycin, we could evaluate the intrapatient variability of pharmacokinetic variables. Because of the rapid decay from its plasmatic peak [17], we administered clindamycin as a rapid infusion during the last 30 min of paclitaxel infusion, in order to have the peaks of the two drugs concomitantly. Our hypothesis was that the displacing phenomenon, if present, could have been maximized if a large amount of antibiotic was present in blood concomitantly to paclitaxel C_{max}, which corre-

Table 4 Main toxicities of each treatment group

	Grade 1–2 neutropenia	Grade 3–4 neutropenia	Grade 1–2 neuropathy	Grade 3–4 neuropathy	Grade 1–2 alopecia	Grade 3–4 alopecia	Weeks of treatment delay
Clindamycin 0 mg	7 (44%)	9 (56%)	6 (37%)	0	0	16 (100%)	12
Clindamycin 600 mg	6 (37%)	10 (63%)	7 (44%)	0	0	16 (100%)	11
Clindamycin 1,200 mg	6 (37%)	10 (63%)	5 (31%)	0	0	16 (100%)	12

sponds to the largest amount of paclitaxel bound to AGP. This justifies why we have focused our pharmacokinetic sampling to relative early time points.

Our results showed that paclitaxel kinetic is different in the group of patients receiving the highest dose of clindamycin when compared with the group of patients who did not receive it. There were no statistically significant differences when comparing pharmacokinetic parameters of the group of patients who received 600 mg clindamycin with both the other groups. The lack of statistical difference might be related to the relatively low number of patients investigated.

Is this statistical significance clinically relevant? We are inclined to think that it is not. In fact, we found no differences whatsoever in the degree or in the occurrence of toxicity. If we analyze all the pharmacokinetic data we could detect relatively low changes in paclitaxel plasma levels, too low to account for marked changes in drug toxicity or activity.

It should be pointed out, however, that the presence of Cremophor EL has presumably reduced paclitaxel protein binding, thus reducing the extent of paclitaxel–clindamycin interaction. It is plausible that with a paclitaxel Cremophor EL-free formulation the interaction between paclitaxel and clindamycin could be more evident.

In conclusion, these data support the hypothesis that AGP can influence paclitaxel pharmacokinetics. The clindamycin-induced pharmacokinetics changes of paclitaxel, although reached a statistically significant value, appeared too limited to provide a rationale for undertaking clinical trial with this combination.

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