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SHORT COMMUNICATION

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Plasma alcohol concentrations in patients following paclitaxel infusion

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Abstract Paclitaxel is formulated in 50% Cremophor EL and 50% ethanol such that patients receiving paclitaxel also receive a significant amount of each of these solvents. The aim of this study was to measure the plasma alcohol levels in patients treated with paclitaxel. A total of 12 patients who were enrolled in phase II trials of non-small-cell lung cancer, breast cancer or ovarian cancer received 175 mg/m^2 paclitaxel given as a 3-h infusion. Blood samples were obtained prior to and immediately following the infusion, and plasma ethanol concentrations were measured enzymatically. The dose of ethanol delivered with the paclitaxel ranged from 20.0 to 28.9 ml. No alcohol was detected in pre-dose plasma, but 8 of 12 patients had detectable levels in post-infusion plasma, with 0.033 g/dl being the highest concentration. The elimination rate of alcohol approximates the infusion rate when paclitaxel is given over 3 h, resulting in low or undetectable levels in most patients. However, in patients receiving an equivalent dose of paclitaxel given as a 1-h infusion, the plasma alcohol levels will likely be high enough for significant pharmacological effects to occur.

Key words Paclitaxel · Drug interaction · Ethanol

Introduction

Paclitaxel is a novel microtubule-stabilising drug with significant anti-tumour activity, particularly in breast and ovarian cancers [5]. In early clinical trials, paclitaxel was given as an intravenous infusion over 1–3 h, but because of hypersensitivity reactions the infusion duration was increased to 24 h and pre-medication with corticosteroids and antihistamines was instituted. The results of a randomised trial examining the influence of the dose and schedule of paclitaxel in ovarian cancer patients have recently been reported [1]. With pre-medication, use of a 3-h infusion resulted in minimal significant hypersensitivity reactions along with less myelosuppression and with response rates equivalent to those achieved with a 24-h infusion. The greater patient convenience and lower treatment-related costs of a 3-h infusion has led to its use in routine patient care and in further clinical trials.

As paclitaxel has low water solubility, for clinical use it is formulated as 6 mg/ml in 50% ethanol and 50% Cremophor EL. In a commonly used dose of 175 mg/m^2, most patients would receive between 20 and 30 ml of each of these solvents. We have previously demonstrated that the amount of Cremophor EL in plasma obtained from patients after a 3-h infusion of 175 mg/m^2 paclitaxel is potentially capable of pharmacological effect [8]. The amount of ethanol delivered with this dose of paclitaxel is equivalent to that of approximately two standard drinks, and it is possible that some patients will achieve plasma alcohol levels above which threshold effects can occur. The potential for blood alcohol levels to exceed the legal sobriety limit for driving must also be considered if paclitaxel is given to outpatients. We therefore determined the plasma concentrations of alcohol in patients following an infusion of paclitaxel.

Patients and methods

A total of 12 patients (all Caucasians) who were receiving single-agent paclitaxel as part of phase II clinical trials for treatment of non-small-cell lung cancer, breast cancer or ovarian cancer gave

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written informed consent for blood samples to be taken for this study. The protocol was approved by the Institutional Ethics Committee. All patients received a dose of 175 mg/m^2 given over 3 h with standard anti-allergy pre-medication consisting of oral dexamethasone, intravenous promethazine hydrochloride, and intravenous cimetidine. For both the non-small-cell lung cancer and breast cancer trials, patients with a history of alcoholism were ineligible. None of the ovarian cancer patients studied had a history of alcoholism. All patients had an abdominal computerised tomography (CT) scan as part of their staging investigations prior to receiving paclitaxel, and serum levels of bilirubin and aspartate transaminase (AST) were measured prior to each cycle of treatment. Serum alkaline phosphatase was determined in all patients, but specific isoenzyme measurements to separate liver from bone or other sources were not done. Gamma-glutamyl transferase was not routinely measured.

Two brands of paclitaxel were used in these patients. Patients with ovarian cancer received Taxol (Bristol-Myers Squibb Pharmaceuticals Pty. Ltd., Melbourne, Australia), and patients with breast cancer or non-small-cell lung cancer received Anzatax (F. H. Faulding Pharmaceuticals, Adelaide, Australia). Both products contain the same amount of ethanol in the formulation (paclitaxel at 6 mg/ml in 50% ethanol and 50% Cremophor EL).

Blood (3 ml) was collected without the use of alcohol swabs into fluoride heparin tubes immediately before and at the end of the paclitaxel infusion, and the plasma was frozen until assay. Plasma alcohol was quantitated using a standard enzymatic blood-alcohol kit (Boehringer Mannheim catalogue number 123960). The lower limit of quantification of the assay is 1 mM (equivalent to 0.0046 g/dl).

Results

The details of the patients studied are given in Table 1. The body surface area ranged from 1.38 to 1.99 m^2. From the total dose of paclitaxel, the amount of ethanol that each patient received was calculated and ranged from 20.0 to 28.9 ml (15.8–22.8 g; density, 0.789 g/ml). No alcohol was detected in the pre-dose plasma of any patient. In the post-infusion plasma, 8 of 12 patients had detectable levels (Table 1), and the highest concentrations were 0.033 and 0.017 g/dl.

Four patients had hepatic metastases on their CT scan. Two of these patients had elevated AST levels (> 40 U/l). These two patients were those with the highest plasma alcohol concentrations (patient 7–AST, 50 U/l, patient 11–AST, 206 U/l). The other two patients with liver metastases had normal AST levels and their plasma alcohol concentrations amounted to 0.009 g/dl and were not detectable (patients 4 and 2). None of the patients without liver metastases had an elevated AST level. All patients had a normal serum bilirubin value (< 17 μmol/l).

Discussion

The elimination of ethanol in women and most men who are not chronic alcohol misusers follows zero-order kinetics [7] with an elimination rate constant of approximately 120 mg kg^{-1} h^{-1}, or 8.4 g/h per 70 kg

Table 1. Patients characteristics and plasma alcohol levels following a 3-h infusion of 175 mg/m^2 paclitaxel (*NSCLC* Non-small-cell lung cancer, *ND* Not detectable)

Patient	Sex	Age	Tumour type	Paclitaxel dose (mg)	Ethanol dose[a] (ml)	Post-paclitaxel plasma alcohol (g/dl)
1	F	73	Ovary	270	22.5	ND
2	F	67	Ovary	288	24.0	ND
3	F	63	NSCLC	240	20.0	0.006
4	M	73	NSCLC	343	28.6	0.009
5	F	54	Ovary	243	20.3	0.005
6	F	56	Ovary	292	24.3	0.006
7	F	52	Breast	280	23.3	0.033
8	F	60	Ovary	273	22.8	0.005
9	F	56	NSCLC	333	27.7	0.006
10	M	49	NSCLC	347	28.9	ND
11	F	36	Breast	312	26.0	0.017
12	F	45	NSCLC	290	24.2	ND

[a] Ethanol dose as calculated from the actual paclitaxel dose

[4, 7]. The patients included in this study received a constant intravenous infusion of 16–23 g ethanol over 3 h, or 5.3–7.7 g/h. Therefore, the infusion rate was very similar to the expected elimination rate, resulting in low or undetectable plasma alcohol concentrations at the end of the infusion in the majority of patients. The influence of hepatic metastases on the metabolism of ethanol has not been investigated, but the two patients who had plasma alcohol levels of > 0.01 g/dl had hepatic metastases along with elevated AST levels, suggesting that in such patients the elimination of ethanol may be reduced.

One "standard drink" is generally defined as 10 g alcohol (given orally), as this is the alcohol content in 30 ml (1 oz) spirits; this is also equivalent to 375 ml low-alcohol [3.3% (v/v) alcohol] beer, whereas the same volume of regular beer (4.9%, v/v) contains 15 g and 200 ml of table wine (10% v/v) contains 16 g. Although a blood alcohol concentration of 0.02–0.03 g/dl is generally accepted as the threshold for pharmacological activity [4], the legal sobriety limit for newly licensed drivers in the state of Victoria, Australia, is zero, and for other drivers, 0.05 g/dl is the legal limit. The legal limits in other countries in Europe and North America are in the range of 0.05–0.08 g/dl. The depressant effect of alcohol on the central nervous system is increased by concurrent intake of antihistamines [9], resulting in potentially greater impairment of motor performance. Consequently, the use of such medication as routine prophylaxis against hypersensitivity reactions from paclitaxel is likely to increase the effect of the ethanol in the formulation.

The sensitivity of persons to alcohol is partially genetically determined; orientals in particular may experience unpleasant symptoms after ingesting small amounts of alcohol. This reflects polymorphisms of the

alcohol and aldehyde dehydrogenase genes [3] resulting in higher blood acetaldehyde levels. Such patients may be more likely to experience subjective symptoms due to the ethanol in paclitaxel.

The ethanol delivered with paclitaxel may lead to higher blood alcohol levels if other schedules are used. With granulocyte colony-stimulating factor support, the dose of paclitaxel given over 3 h can be increased to 250 mg/m^2 [6], which would correspond to an ethanol infusion rate of 11 g/h for a patient with a body surface area of 2.0 m^2. Studies examining the administration of paclitaxel over 1 h have used doses as high as 200 mg/m^2 [2]. This dose requires an ethanol infusion of 26 g/h for a 2.0-m^2 patient, with the end-infusion ethanol load being 18 g at average elimination. This situation would be analogous to the consumption of two to three standard drinks over 1 h, with the alcohol being delivered intravenously, and would likely result in significant plasma alcohol levels in patients.

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