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ORIGINAL ARTICLE

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Inhibition of paclitaxel elimination in the isolated perfused rat liver by Cremophor EL

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Abstract *Purpose*: Cremophor can alter the pharmacokinetics of cytotoxic drugs, including doxorubicin and etoposide. In view of its presence in the formulation of paclitaxel, the aim of this study was to investigate the influence of Cremophor on the hepatobiliary elimination of paclitaxel. *Methods*: In a recirculating isolated perfused rat-liver system the elimination of 1.7 mg paclitaxel given as a bolus into the perfusate reservoir was monitored in perfusate and bile in controls and after the administration of either 80 or 800 μl Cremophor. The higher dose of Cremophor yields clinically relevant perfusate concentrations. Paclitaxel was measured in perfusate, bile, and liver tissue by high-performance liquid chromatography. *Results*: Cremophor caused a dose-dependent inhibition of the elimination of paclitaxel, with a statistically significant mean value ± SD, $n = 3$; ($P < 0.05$ versus controls Bonferroni *t*-test) 9-fold increase in AUC (2227 ± 106 versus 245 ± 40 μg ml^{-1} min), 9-fold decrease in total clearance (0.8 ± 0.1 versus 7.0 ± 1.1 ml/min), and 5-fold increase in elimination half-life (92 ± 14 versus 18 ± 4 min) being observed after a dose of 800 μl Cremophor. With the addition of Cremophor the amount of paclitaxel remaining after 3 h increased in perfusate from none to 20%, increased in liver tissue from 4% to 18%, and remained constant in bile at 11–13%. In the control group, 86% of the paclitaxel dose was recovered in bile as five putative metabolites, which were measured in paclitaxel equivalents, with the major metabolite. M3 co-eluting with 3′-*p*-hydroxypaclitaxel. This decreased to 45% of the dose on the addition of Cremophor, and the ratio of M3 to paclitaxel in bile decreased. *Conclusions*: Cremophor inhibits the hepatic elimination of paclitaxel in the isolated perfused rat liver, primarily by preventing the drug from reaching sites of metabolism and excretion. The presence of Cremophor in the paclitaxel formulation may therefore contribute to the nonlinear pharmacokinetics and pharmacodynamics of paclitaxel.

Keywords Drug interaction · Pharmacokinetics · Cremophor · Paclitaxel

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Introduction

Cremophor (polyoxyethylenglyceroltriricinoleate 35, Cremophor EL) is a polyethoxylated castor oil derivative commonly used as a drug solubiliser. There is substantial evidence that Cremophor has inherent and varied pharmacological activities, including modulation of multidrug resistance and alteration of the pharmacokinetics of certain cytotoxic drugs [22]. We have previously shown that it increases the plasma levels of doxorubicin and its metabolite doxorubicinol in mice and cancer patients [13, 21]. Similarly, in the isolated perfused rat-liver model, Cremophor inhibits etoposide elimination through decreased total and biliary clearance from the liver [1]. Paclitaxel is a cytotoxic drug currently used widely in the treatment of many types of cancer [5]. It is formulated in Cremophor and ethanol (1:1, v:v) such that patients receive significant amounts of Cremophor in a standard dose of paclitaxel. Paclitaxel pharmacokinetics are nonlinear [3, 16], and it has been demonstrated in mice that Cremophor may contribute to this phenomenon [18], although the mechanism by which Cremophor could cause this effect has not been elucidated. In the present study we investigated the influence of Cremophor on the hepatobiliary elimination of paclitaxel using the isolated perfused rat-liver model.

Materials and methods

Chemicals

Pure paclitaxel was provided by Bristol-Myers Squibb (Melbourne, Australia). Cremophor EL was purchased from BASF Chemicals (Melbourne, Australia). Acetonitrile was of high-performance liquid chromatography (HPLC) grade (BDH Chemicals, Kilsyth, Vic., Australia); all other reagents were of analytical grade and were purchased from Sigma Chemical Co. (St. Louis, MO., USA).

Liver perfusion

The experimental protocol was approved by the institutional Animal Experimentation Ethics Committee. Non-fasting male Sprague-Dawley rats (200–280 g) were anaesthetised with sodium pentobarbitone (60 mg/kg i.p.) and their livers were surgically isolated by standard techniques and perfused in a recirculating system maintained at 37°C as previously described [1]. The perfusate (80 ml) containing 20% (v/v) washed human red blood cells and 4% (w/v) bovine serum albumin (BSA, Fraction V; Commonwealth Serum Laboratories, Melbourne, Australia) was delivered through the portal vein at 15 ml/min. Sodium taurocholate (30 μmol/h) was infused into the perfusate reservoir to maintain bile flow. Liver viability for the duration of the 3-h experiment was confirmed by the normal values recorded for bile flow, perfusion back pressure, and oxygen consumption.

Drug administration and sampling

All drugs were given as a bolus dose into the reservoir of the 80-ml recirculating perfusate to simulate systemic administration. Paclitaxel was dissolved in ethanol:Cremophor:saline (1:1:10), and 1.7 mg was added to the perfusate in 720 μl of the vehicle, thus including 60 μl Cremophor. The vehicle for paclitaxel was deliberately chosen over other solvents such that it would more closely resemble the vehicle used for clinical administration, since the presence of Cremophor may influence the tissue distribution of paclitaxel. In the paclitaxel plus Cremophor experiments, additional Cremophor was added as either a low dose (80 μl) or a high dose (800 μl) 5 min prior to paclitaxel. Cremophor perfusate levels were measured following these doses in a similar study and resulted in perfusate Cremophor concentrations at 60 min of approximately 0.040 and 0.40 μl/ml, respectively [1].

Perfusate samples (750 μl) for drug estimation were taken from the reservoir prior to and at 2, 5, 10, 20, 30, 60, 90, 120, 150 and 180 min following the addition of paclitaxel. Drug amounts lost through sampling were less than 5% of the dose. Red blood cells were removed by centrifugation and discarded. Bile was collected in pre-weighed vials on ice at 30-min intervals. Livers were flushed of perfusate using 0.9% saline and then weighed. All samples were frozen at −20 °C. Prior to assay, livers were thawed and homogenised in 3 vols. (by liver weight) of cold 0.02 *M* ammonium acetate buffer at pH 5.0 using a tissue homogeniser (Polytron, Kinematica-GmbH, Lucerne, Switzerland), and homogenates were stored at −20 °C until assay.

HPLC assay of paclitaxel

Sample preparation consisted of protein precipitation with acetonitrile containing 2.5 μg cephalomannine/ml as the internal standard at the ratios (sample:acetonitrile) of 1:2 for perfusate, 1:9 for bile, and 1:4 for liver homogenate. Following vortexing and centrifugation, 20 μl supernatant was injected onto the HPLC column. The mobile phase consisted of 50:50 acetonitrile:0:02 *M* ammonium acetate buffer (pH 5.0) run at a flow rate of 2.0 ml/min. Separation was achieved on a C_8 column (Radpak–Waters Associates) with ultraviolet detection being done at 227 nm, resulting in approximate retention times of 6.2 min for paclitaxel and 5.5 min for the internal standard. Potential paclitaxel metabolite peaks were quantified as paclitaxel equivalents by comparison with the paclitaxel standard curve. Small quantities of three metabolites isolated from human faeces were kindly supplied by Dr. Alex Sparreboom (Rotterdam Cancer Institute, The Netherlands), including 6α-hydroxy-, 3′-*p*-hydroxy-, and 6α,3′-*p*-dihydroxy-paclitaxel. The limit of quantitaiton was 0.1 μg/ml (CV < 15%).

Pharmacokinetic and statistical analyses

The pharmacokinetics of paclitaxel were determined by standard model-independent methods (Siphar/Win, SIMED, Créteil, France). The terminal elimination half-life was calculated by linear regression of the final four to five points on the log-linear concentration-time curve. The area under the concentration versus time curve (AUC) for paclitaxel in perfusate was calculated by the trapezoidal rule with extrapolation to infinity. Total clearance was calculated by division of the dose by the $AUC_{(0-\alpha)}$. The volume of distribution was calculated as the total clearance times the elimination rate constant. Biliary clearance was the ratio of the cumulative content in bile over 180 min to be perfusate $AUC_{(0-180\,min)}$. Statistical comparisons were made using Sigmastat version 1.01 (Jandel Corp) applying parametric analysis of variance and Bonferroni's multiple *t*-test, with $P < 0.05$ being accepted as significant.

Results

Cremophor caused a dose-dependent inhibition of paclitaxel elimination from the isolated perfused rat liver. Perfusate concentrations of paclitaxel determined in controls and in the presence of low and high doses of Cremophor are shown in Fig. 1. The associated pharmacokinetic parameters are listed in Table 1. Statistically significant increases in AUC and decreases in total clearance were observed in the presence of both doses of Cremophor. The elimination half-life increased with the

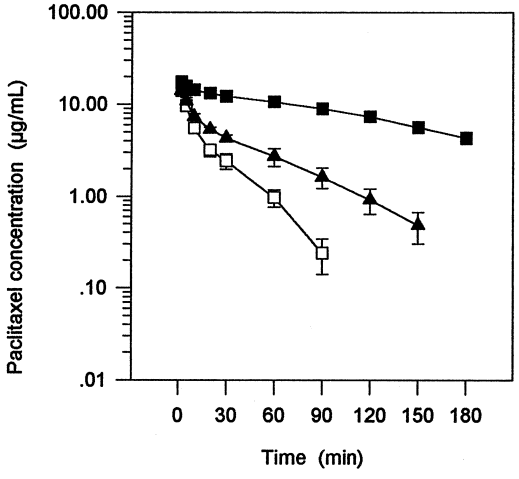

Fig. 1 Profiles of paclitaxel concentration versus time in perfusate from isolated perfused rat livers from controls (□) or following a dose of 80 (▲) or 800 μl (■) Cremophor (mean values ± SEM, $n = 3$)

Table 1 Effect of Cremophor on paclitaxel pharmacokinetics in perfusate and bile in the isolated perfused rat liver (mean values ± SD, $n = 3$). Paclitaxel in all experiments was delivered in 720 µl of a vehicle containing 60 µl Cremophor. The additional 80 or 800 µl Cremophor was added 5 min before paclitaxel

	AUC (µg ml^{-1} min)	Clearance (ml/min)	$t_{1/2}$ (min)	Vd (ml)	Biliary clearance (ml/min)
Control	245 ± 40	7.0 ± 1.1	18 ± 4	175 ± 15	0.75 ± 0.25
Cremophor (80 µl)	488* ± 127	3.7* ± 1.1	36 ± 18	179 ± 65	0.47 ± 0.12
Cremophor (800 µl)	2227* ± 106	0.8* ± 0.1	92* ± 14	101 ± 11	0.08* ± 0.01

*$P < 0.05$ compared with control, Bonferroni t-test

Cremophor dose and was significantly longer at the high dose. Biliary clearance decreased in the presence of Cremophor, with the difference also reaching statistical significance at the higher dose.

The total recovery of paclitaxel from the perfusate, liver and bile is given in Table 2. Paclitaxel concentrations detected in the perfusate circuit in the absence of a liver were close to nominal and were constant over 180 min (data not shown). In control experiments, no paclitaxel was detected in perfusate after 180 min. However, following a high dose of Cremophor, 20% of the dose remained in the perfusate as the parent drug, and the amount of paclitaxel recovered from rat liver increased to 18% from 4% in the control. Figure 2a shows the profile of biliary excretion over time, and it can be seen that high-dose Cremophor caused a delay in the biliary excretion of paclitaxel as compared with the control, but recovery apparently occurred such that the cumulative biliary excretion was similar at between 11% and 13% of the dose in all groups (Table 2).

The retention times of pure metabolites following their addition to blank bile and extraction via the usual procedure were 4.3 min for 6α-hydroxy-paclitaxel, 3.6 min for 3′-*p*-hydroxy-paclitaxel, and 2.7 min for 6α,3′-*p*-dihydroxy-paclitaxel. Five potential metabolite peaks were observed in chromatograms from bile samples following paclitaxel administration (Fig. 3), all eluting prior to paclitaxel (M1 at 2.4 min, M2 at 2.8 min, M3 at 3.6 min, M4 at 3.8 min, and M5 at 4.2 min). The major peak in bile (M3) eluted with a retention time identical to that of 3′-*p*-hydroxy-paclitaxel. The percentage of the paclitaxel dose that was recovered as potential metabolites (expressed as paclitaxel equivalents) is given in Table 2. In all experiments the content of metabolites found in liver was less than 2% of the dose, and no metabolite was detected in perfusate. In control experiments, 86% of the paclitaxel dose was excreted in bile as metabolites, but this decreased to 45% following a high dose of Cremophor. Figure 2b shows that Cremophor inhibited the biliary excretion of M3 in a dose-dependent manner, with the decrease being more evident at earlier time-points. Figure 4 compares the cumulative bile content over 180 min of each metabolite relative to that of paclitaxel. Although the profile of metabolites in bile appeared similar in all groups, Cremophor caused a significant decrease in the biliary content of M1, M3 and M5 relative to paclitaxel.

Discussion

In the present study, Cremophor inhibited paclitaxel elimination from the isolated perfused rat liver in a dose-dependent manner. Total and biliary clearance decreased, whereas the AUC and terminal elimination half-life increased. In control experiments, perfusate paclitaxel concentrations declined to undetectable levels

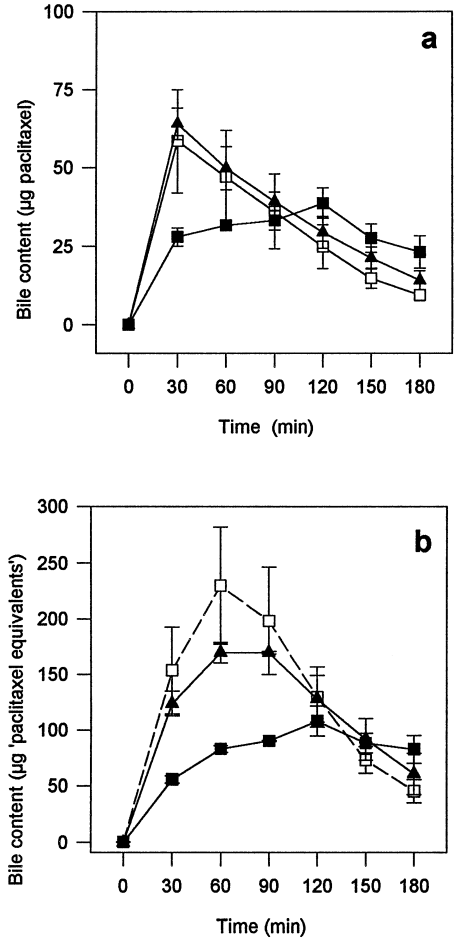

Fig. 2a,b Biliary excretion of **a** paclitaxel and **b** the major paclitaxel metabolite M3, measured as paclitaxel equivalents, in 30-min increments over 180 min following the administration of 1.7 mg paclitaxel in isolated perfused rat livers from control (□) or following a dose of 80 (▲) or 800 µl (■) Cremophor (mean values ± SEM, $n = 3$)

Table 2 Percentage of the paclitaxel dose recovered as the parent drug and as the sum of all metabolites (quantitated as paclitaxel equivalents) from isolated perfused rat livers after administration of 1.7 mg paclitaxel alone or in combination with low or high doses of Cremophor (% of dose, mean values ± SD, $n = 3$). Paclitaxel in all experiments was delivered in 720 µl of a vehicle containing 60 µl Cremophor. The additional 80 or 800 µl Cremophor was added 5 min before paclitaxel (*ND* Not detected)

	Paclitaxel			Metabolites[a]			Total
	Perfusate[b]	Liver	Bile[c]	Perfusate	Liver	Bile	
Control	ND	4.1 ± 1.4	11.2 ± 5.5	ND	1.4 ± 1.1	86.4 ± 38.3	103.2 ± 24.9
Cremophor (80 µl)	1.0 ± 1.8	14.8* ± 2.9	12.8 ± 2.1	ND	1.2 ± 1.3	70.6 ± 2.4	100.4 ± 5.8
Cremophor (800 µl)	20.2* ± 1.7	18.0* ± 4.4	10.7 ± 2.0	ND	0.3 ± 0.3	45.2 ± 3.2	94.4 ± 6.4

*$P < 0.05$ compared with control, Bonferroni *t*-test (calculated from the total content in µg)
[a] Represents the sum of all 5 metabolites quantitated as paclitaxel equivalents
[b] Percentage of the dose remaining in perfusate at 180 min
[c] Cumulative amount excreted in bile over 180 min as a percentage of the dose

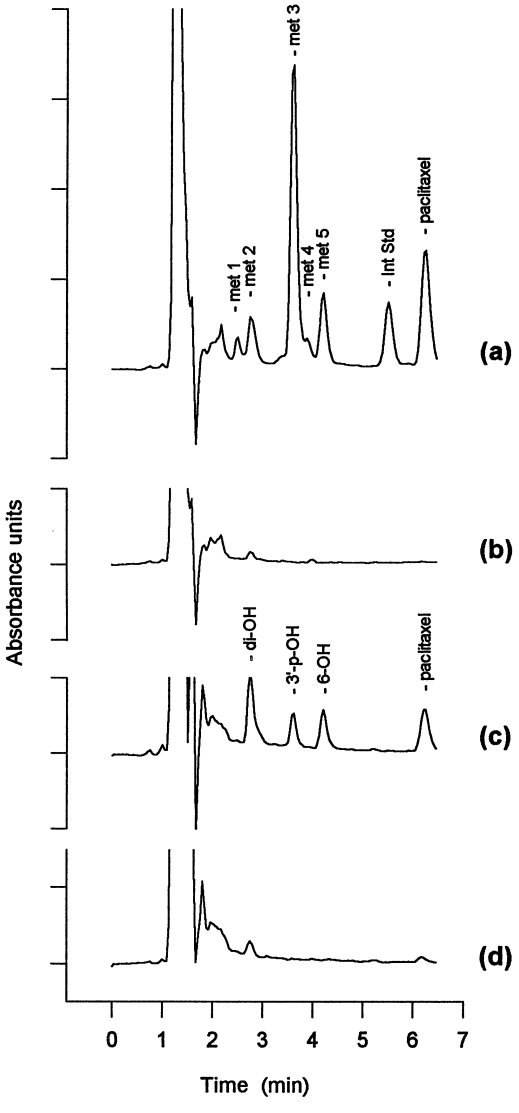

Fig. 3a–d Representative chromatograms of bile samples from **a** a paclitaxel control liver at 180 min, showing peaks of potential metabolites *(1–5)*, of the internal standard (*Int Std*) and of paclitaxel, and **b** a paclitaxel control liver at 0 min, or pooled bile from a vehicle control liver **c** with and **d** without the addition of 6α,3′-*p*-dihydroxy-paclitaxel (*di-OH*),3′-*p*-hydroxy-paclitaxel (*3′-p-OH*), 6α-hydroxy-paclitaxel (*6-OH*) and paclitaxel

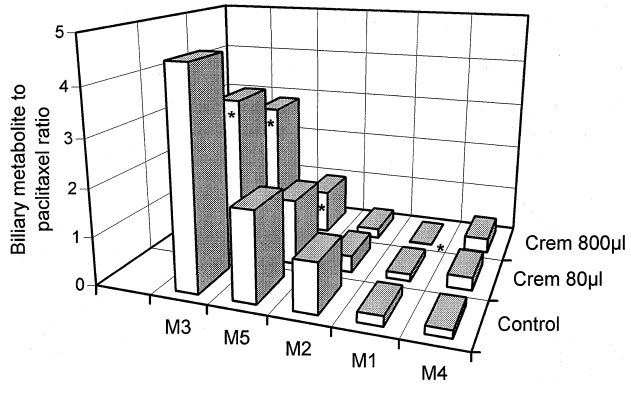

Fig. 4 Comparison of total biliary excretion of individual metabolites relative to paclitaxel, expressed as the ratio of total cumulative bile content over 3 h of metabolite (in µg "paclitaxel equivalents") to paclitaxel (mean of 3 in each group; *$P < 0.05$ as compared with control, Bonferroni *t*-test)

by 120 min, whereas in the presence of Cremophor, up to 20% of the dose of paclitaxel remained in the perfusate at 180 min. The amount of paclitaxel remaining in liver tissue increased significantly, although this may have included some contamination from drug remaining in the hepatic sinusoids, since progressive peripheral ischaemia may have reduced the effectiveness of the flushing procedure. Although the biliary excretion of paclitaxel was delayed, the total cumulative amount excreted was unaffected. Biliary excretion of apparent metabolites was lower by approximately 41%, but this could almost be accounted for by the increases in concentrations of the parent drug in perfusate and liver. Thus, the major effect of Cremophor in this study appears to be that of preventing paclitaxel from reaching sites of metabolism and excretion.

These results are consistent with other in vitro studies reporting a possible effect of Cremophor on drug distribution, including decreased uptake of paclitaxel into human liver slices [16] and by human tumour cell lines [9]. Also in agreement with the present study is the investigation by Sparreboom et al. [18], whereby the presence of Cremophor caused an increase in paclitaxel plasma levels in mice that was more than proportional to

the dose. More importantly, this group showed that tissue levels of paclitaxel increased only linearly with dose [17], suggesting that higher plasma levels of paclitaxel do not necessarily reflect higher tissue levels and supporting the hypothesis that Cremophor causes drug retention within the plasma compartment.

Despite a relatively small difference in the absolute amounts of Cremophor present in the control and low-dose studies, there was a significant effect on the perfusate pharmacokinetics of paclitaxel. However, there was a 5-min gap between the 80-μl low dose of Cremophor and the subsequent dose of paclitaxel given in a vehicle containing 60 μl Cremophor. It is likely that this time was sufficient to allow Cremophor to equilibrate in the tissues and perfusate, which, in turn, may have contributed to its effect on drug distribution.

There are several potential mechanisms for the effect of Cremophor on drug distribution and excretion [1, 22], including Cremophor-induced drug-micelle formation [7], altered binding of drugs to serum albumin [8], and changes in the plasma lipoprotein profile causing paclitaxel to bind preferentially to low-density lipoproteins, which persist longer in the circulation [19]. Our previous study using isolated perfused rat liver showed the possible uptake or binding of Cremophor to liver, and this may also affect the influence of Cremophor on paclitaxel disposition in the liver [1]. Since Cremophor modulates the multidrug resistance (MDR) phenotype [15, 23], which is primarily mediated by increased expression of the plasma-membrane export pump P-glycoprotein (P_{gp}), it is also possible that Cremophor inhibits P_{gp}-mediated biliary excretion of drugs. Many MDR modulators, including Cremophor, affect the pharmacokinetics of cytotoxic drugs that are also P_{gp} substrates, such as etoposide, doxorubicin and paclitaxel, in both animals and clinical studies [2, 22]. In addition, co-administration of paclitaxel with doxorubicin results in altered doxorubicin pharmacokinetics, which may be due to the presence of Cremophor in the paclitaxel formulation [4].

There is also some evidence from our study that Cremophor inhibited paclitaxel metabolism. In both humans and rodents, paclitaxel is eliminated primarily by microsomal hydroxylation followed by biliary excretion, with 3′-*p*-hydroxy-paclitaxel being a major rat metabolite [10] and 6α-hydroxy-paclitaxel being the major human metabolite [11].

In the present study the major metabolite M3 in bile co-eluted with 3′-*p*-hydroxy-paclitaxel, and when normalised to biliary paclitaxel concentrations the biliary excretion of M3 as well as of M1 and M5 was decreased by Cremophor. The absence of a concomitant increase in these metabolites in either perfusate or liver suggests that formation rather than excretion of these metabolites was inhibited. There is little information on the effect of Cremophor on microsomal metabolism, although in one study it did prevent the metabolism of paclitaxel to 6α-hydroxy-paclitaxel in human liver microsomes [6].

Patients receiving a standard paclitaxel dose of 175 mg/m^2 also receive between 20 and 30 ml Cremophor, resulting in plasma levels after a 3 h paclitaxel infusion in the range of 1–2 μl/ml Cremophor [20], which are at the upper range of the perfusate Cremophor concentrations reached following the higher dose in the present study. Since plasma Cremophor levels vary according to the duration of paclitaxel infusion [14], a decrease in the tissue uptake of paclitaxel induced by Cremophor might partially explain the different toxicities and higher maximum tolerated dose reported following shorter infusions in clinical trials [12]. Furthermore, increased plasma Cremophor concentrations achieved with shorter paclitaxel infusions and higher doses may contribute to the nonlinear pharmacokinetics of paclitaxel [3, 16].

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References

1. Ellis AG, Webster LW (1996) Inhibition of etoposide elimination in the isolated perfused rat liver by Cremophor EL and Tween 80. Cancer Chemother Pharmacol 38: 81–87
2. Fisher GA, Lum BL, Hausdorff J, Sikic BI (1996) Pharmacological considerations in the modulation of multidrug resistance. Eur J Cancer 32A: 1982–1088
3. Gianni L, Kearns CM, Capri G, Vigano L, Locatelli A, Bonadonna G, Gianni A, Egorin MJ (1995) Nonlinear pharmacokinetics and metabolism of paclitaxel and its pharmacokinetic/pharmacodynamic relationships in humans. J Clin Oncol 13: 180–190
4. Gianni L, Vigano L, Locatelli A, Capri G, Giani A, Tarenzi E, Bonadonna G (1997) Human pharmacokinetic characterization and in vitro study of the interaction between doxorubicin and paclitaxel in patients with breast cancer. J Clin Oncol 15: 1906–1915
5. Huizing MT, Sewberath Misser VH, Pieters RC, Ten Bokkel Huinink WW, Veehof CHN, Vermorken JB, Pinedo HM, Beijnen JH (1995) Taxanes. A new class of antitumour agents. Cancer Invest 13: 381–404
6. Jamis-Dow C, Klecker R, Katki A, Collins J (1995) Metabolism of taxol by human and rat liver in vitro: a screen for drug interactions and interspecies differences. Cancer Chemother Pharmacol 36: 107–114
7. Kessel D (1992) Properties of Cremophor EL micelles probed by fluorescence. Photochem Photobiol 56: 447–451
8. Kongshaug M, Cheng LS, Moan J, Rimington C (1991) Interaction of Cremophor EL with human plasma. Int J Biochem 23: 473–478
9. Liebmann J, Cook J, Lipschultz C, Teague D, Fisher J, Mitchell J (1994) The influence of Cremophor EL on the cell cycle effects of paclitaxel in human tumor cell lines. Cancer Chemother Pharmacol 33: 331–339
10. Monsarrat B, Mariel E, Cros S, Gares M, Guenard D, Gueritte-Voelelein F, Wright M (1990) Taxol metabolism: isolation and identification of three major metabolites of Taxol in rat bile. Drug Metab Dispos 18: 895–901
11. Monsarrat B, Alvinerie P, Wright M, Dubois J, Gueritte-Voelelein F, Guenard D, Donehower R, Rowinsky E (1993) Hepatic metabolism and biliary excretion of taxol in rats and humans Monogr Natl Cancer Inst 15: 39–46
12. Ohtsu T, Sasaki Y, Tamura T, Miyata Y, Nakanomyo H, Nishiwaki Y, Saijo N (1995) Clinical pharmacokinetics and pharmacodynamics of paclitaxel: a 3-h infusion versus a 24-h infusion. Clin Cancer Res 1: 599-606

13. Rischin D, Millward M, Webster L, Tinnelly K, Toner G, Bishop (1994) Phase I trial of Cremophor EL and doxorubicin in patients with advanced cancer. Anticancer Drugs 5 [suppl 1]: 43–44
14. Rischin D, Webster LK, Millward MJ, Linahan BM, Toner GC, Woollett AM, Morton CG, Bishop JF (1996) Cremophor pharmacokinetics in patients receiving 3-, 6-, and 24-h infusions of paclitaxel. J Natl Cancer Inst 88: 1297–1301
15. Schuurhuis GJ, Broxterman HJ, Pinedo HM, Heijningen THM van, Kalken CK van, Vermorken JB, Spoelstra EC, Lankelma J (1990) The polyoxyethylene caster oil Cremophor EL modifies multidrug resistance. Br J Cancer 62: 591–594
16. Sonnichsen D, Relling M (1994) Clinical pharmacokinetics of paclitaxel. Clin Pharmacokinet 27: 256–269
17. Sparreboom A, Tellingen O van, Nooijen WJ, Beijnen JH (1996) Tissue distribution, metabolism and excretion of paclitaxel in mice. Anticancer Drugs 7: 78–86
18. Sparreboom A, Tellingen O van, Nooijen WJ, Beijnen JH (1996) Nonlinear pharmacokinetics of paclitaxel in mice results from the pharmaceutical vehicle Cremophor EL. Cancer Res 56: 2112–2115
19. Sykes E, Woodburn K, Decker D, Kessel D (1994) Effects of Cremophor EL on distribution of Taxol to serum lipoproteins. Br J Cancer 70: 401–404
20. Webster L, Linsenmeyer M, Millward M, Morton C, Bishop J, Woodcock D (1993) Measurement of Cremophor EL following Taxol: plasma levels sufficient to reverse drug exclusion mediated by the multidrug-resistance phenotype. J Natl Cancer Inst 85: 1685–1690
21. Webster LK, Cosson EJ, Millward MJ, Stokes KH (1996) Effect of the paclitaxel vehicle, Cremophor EL, on the pharmacokinetics of doxorubicin and doxorubicinol in mice. Br J Cancer 73(4): 522–524
22. Webster LK, Woodcock DM, Rischin D, Millward MJ (1997) Cremophor pharmacological activity of an ''inert'' solubiliser. J Oncol Pharm Pract 3: 186–192
23. Woodcock DM, Jefferson S, Linsenmeyer ME, Crowther PJ, Chojnowski GM, Williams B, Bertoncello I (1990) Reversal of the multidrug resistance phenotype with Cremophor EL, a common vehicle for water-insoluble vitamins and drugs. Cancer Res 50: 4199–4203