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REVIEW ARTICLE

Clinical Pharmacokinetics of Paclitaxel Monotherapy: An Updated Literature Review

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Abstract Paclitaxel is an anticancer agent efficacious in the treatment of ovarian, breast, and lung cancer. Due to a strong link between the pharmacokinetics and therapeutic efficacy of paclitaxel, we reviewed the literature on paclitaxel pharmacokinetics. Systematic data mining was performed to extract the maximum concentration (C_{max}), clearance (CL), and time of paclitaxel plasma concentration above 0.05 μmol/L ($T > 0.05$ μmol/L) following monotherapy of both the widely used cremophor-diluted paclitaxel and nanoparticle albumin-bound (nab-)paclitaxel. We identified a total of 53 studies yielding 121 aggregated pharmacokinetic profiles for paclitaxel monotherapy and extracted reported mean and median estimates of pharmacokinetic parameters. Paclitaxel has been studied formally at doses of 15–825 mg/m^2 and infused over 0.5–96 h; included studies examined both weekly and every 3-weeks dosing cycles. The most widely used dose of cremophor-diluted paclitaxel, 175 mg/m^2 given as a 3-h infusion, leads to an interstudy median C_{max} of 5.1 μmol/L [interquartile range (IQR) 4.5–5.7], CL of 12.0 L/h/m^2 (IQR 10.9–12.9), and $T > 0.05$ μmol/L of 23.8 h (IQR 21.5–26.8). Importantly, the significant interindividual variation widely reported in the literature is not reflected in these interstudy estimates of pharmacokinetic parameters. Cremophor-diluted paclitaxel pharmacokinetics are non-linear following short (<6 h) but not long (>24 h) infusions. A similar pattern of non-linearity was observed for nab-paclitaxel, although the number of studies was limited. The pharmacokinetics of paclitaxel monotherapy have been widely studied at numerous dose levels of the Cremophor EL® formulation, but are less well-characterized for the newer nab-paclitaxel formulation. In conclusion, paclitaxel pharmacokinetics are non-linear for short infusion times but not for longer infusions. Whether a similar conclusion can be drawn for nab-paclitaxel formulations requires further study.

Key Points

The time above a threshold paclitaxel plasma concentration (0.05 μmol/L) is important for the efficacy and toxicity of the drug.

Paclitaxel is administered mainly as two formulations: Cremophor EL® diluted or nanoparticle albumin bound. The cremophor-diluted formulation has been widely tested at different doses and infusion times; data are more limited for the nanoparticle formulation.

The plasma concentrations of paclitaxel do not follow linear pharmacokinetics for short infusions. This is particularly evident for cremophor-based paclitaxel.

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1 Background

Paclitaxel is a widely used drug in the treatment of breast [1], ovarian [2], and lung cancer [3]. Paclitaxel binds to and promotes the assembly of tubulin into dysfunctional microtubules, which leads to chromosome missegregation on multipolar spindles at clinically observed concentrations [4]. The consequence of microtubule dysfunction is inhibition of mitosis and cell proliferation, resulting in the death of rapidly proliferating tumor cells.

Paclitaxel is a high molecular weight drug (853.9 g/mol) with a very low solubility in water (0.7 mg/mL) [5]. It is metabolized primarily by cytochrome P450 (CYP) 2C8 to the largely inactive metabolite 6-hydroxypaclitaxel and to a lesser degree by CYP3A4 to 3′-phenyl-hydroxypaclitaxel [6]. Paclitaxel is a substrate for ATP-binding cassette (ABC) efflux transporters, including multidrug resistance protein 1 [MDR1/P-glycoprotein (P-gp), *ABCB1*] [7, 8], breast cancer resistance protein (BCRP, *ABCG2*) [9], and multidrug resistance-associated proteins 1/2 (MRP1/2, *ABCC1/C2*) [10, 11]. ABC transporter-mediated efflux of paclitaxel back into the intestinal lumen accounts for its very low oral bioavailability and requirement for intravenous administration. The influx transporter organic anion transporter (OAT) polypeptide 1B3 (OATP1B3, *SLCO1B3*) has been shown to be involved in the hepatic uptake of paclitaxel [12, 13]; paclitaxel is also a substrate for the renal OAT2 (*SLC22A7*) [14]. Activity of these hepatic and renal transporters may play an important role in the distribution and elimination of paclitaxel and may contribute to variability in the pharmacokinetics of the drug. Paclitaxel activates pregnane X receptor (PXR) [15, 16], leading to upregulation of key drug-metabolizing enzymes such as CYP3A4 [16, 17] and transporters such as ABCB1 [15]. However, the administration of paclitaxel every 1, 2, or 3 weeks has not been associated with altered metabolism over time [18–21], suggesting that autoinduction is minimal during standard dosing conditions.

Due to the hydrophobic nature of paclitaxel, it was originally diluted in the solvent Cremophor EL®, a polyoxy-ethylated oil mixed 1:1 with ethanol. This formulation solves one problem, but is associated with hypersensitivity reactions to Cremophor EL®. This was initially circumvented by using longer infusions times. However, the addition of pretreatment with prophylactic antihistamines (both histamine H_1 and H_2 receptor antagonists) and glucocorticoids has made it possible to reduce infusion times and achieve similarly low rates of hypersensitivity reactions [22]. Recently, a nanoparticle albumin-bound formulation of paclitaxel (nab-paclitaxel) was developed that does not cause infusion hypersensitivity reactions and thus eliminates the need for prophylactic treatment. Paclitaxel is highly bound (90%) to plasma proteins [23], and the free fraction of paclitaxel inversely correlates with Cremophor EL® concentrations [24, 25].

The paclitaxel response rate differs significantly between cancers, with ovarian cancer generally more sensitive than breast cancer [26, 27]. Efficacy and toxicity also depends on combination with other chemotherapeutic agents and even the sequence of chemotherapy administration. For example, in one study the clearance (CL) of paclitaxel was lower when administered after cisplatin compared to administration before the platinum agent [28], though this effect was not replicated in another study [29].

Significant interpatient variability is also observed for paclitaxel adverse events, although the frequency and severity is quite similar across cancer types. The most common and problematic adverse event is peripheral sensory neuropathy, with significant neutropenia also observed. Both peripheral neuropathy and neutropenia are dose limiting and lead to reduced response rates to paclitaxel. Based on a database of 812 patients with various solid tumors treated with single-agent paclitaxel, severe neutropenia ($<$500 cells/cm^3) occurred in 52% of the patients. Peripheral neuropathy was reported for 60% of the patients treated with mixed doses (135–300 mg/m^2) and infusion times (3 or 24 h), with 3% reporting severe (grade 3 or higher) neuropathy [30]; these frequencies are known to vary significantly between populations. Clinical symptoms of neuropathy range from numbness and tingling in fingers and hands to cold or heat intolerance and burning pain. Normally, neuropathy symptoms are reversible, but some patients continue to experience neuropathy up to 2 years after drug cessation, significantly impairing quality of life [31].

The reasons for variability in paclitaxel response and toxicity are multifaceted. Some studies have suggested that polymorphisms in *CYP2C8* or *ABCB1* cause pharmacokinetic variation, while others show no effect. Even when a pharmacogenetic difference in paclitaxel pharmacokinetics has been demonstrated, such as for *CYP2C8**3 (and *4), clinical relevance is limited because of the small effect size [32]. Recent genome-wide association studies (GWAS) have found a multitude of genetic variants associated with risk of peripheral neuropathy during treatment with paclitaxel [33–35]. Some findings are biologically plausible, such as variants in genes involved in neuronal repair, while others require further investigation to fully understand their relevance. These hypothesis-generating studies are of merit as they might provide new insight into the molecular mechanisms underlying the toxicities; however, substantial validation in multiple cohorts is required before their final interpretation and potential translation into clinical practice.

Drug–drug interactions (DDIs) affecting the pharmacokinetics of paclitaxel have not been systematically studied, likely because of ethical considerations of testing potentially harmful DDIs in cancer patients. Clinicians often extrapolate from case observations, in vitro data, and limited epidemiological studies to optimally manage polytherapy during cancer treatment. For example, a metabolite of clopidogrel that inhibits CYP2C8 in vitro was linked to a very low CL of paclitaxel and increased risk of neuropathy in an ovarian cancer patient [36]. This was later supported by a small case series in which seven out of eight patients treated with clopidogrel and paclitaxel experienced grade 3 neutropenia [37]. More recently, 48 patients treated with paclitaxel and clopidogrel were found to have increased rates of neuropathy compared with a control group of 88 patients using low-dose aspirin in place of clopidogrel. The study concluded that the risk of peripheral neuropathy is approximately two-fold higher in patients using clopidogrel and paclitaxel in doses of 135 mg/m^2 or greater [38].

The pharmacokinetics of paclitaxel are known to correlate with treatment response [39, 40] and adverse effects [41–44]. Thus, a comprehensive understanding may lead to improved treatment outcomes. The pharmacokinetics of paclitaxel were comprehensively reviewed by Sonnichsen and Relling [45] in 1994. However, a large number of paclitaxel pharmacokinetic studies have been published since and a new formulation, nab-paclitaxel, has been introduced to the market. These updates are captured in the current literature review, along with a systematic analysis of paclitaxel CL, maximum plasma concentration (C_{max}), and time of paclitaxel plasma concentration above 0.05 μmol/L ($T > 0.05$ μmol/L) for a range of doses of cremophor-diluted and albumin-bound paclitaxel given as single-agent therapy.

2 Methods

PubMed was searched with the following sequence: (Paclitaxel or Taxol) AND pharmacokinetics [(MESH) or (All fields)] and restricted to clinical trials in English with human subjects. The search was performed on 21 June 2016 and gave a total of 608 hits. Titles and abstracts for studies with any formulation of paclitaxel were evaluated twice by two independent reviewers and identified 322 publications for further consideration. Papers without abstracts were only included if it was clear from the title that they would be relevant. Full texts were then read by at least one reviewer and 182 publications were identified that described a minimum of 6 h of pharmacokinetic sampling for paclitaxel or nab-paclitaxel. After exclusion of studies where paclitaxel was not given as monotherapy or pharmacokinetic parameters were not available, 53 publications remained [19, 21, 46–96] and serve as the basis for this review (Fig. 1).

The following information was extracted from all publications: number of patients, duration of infusion (h), formulation of paclitaxel (cremophor-diluted or nab-paclitaxel), dose (mg/m^2), C_{max} (μmol/L), total CL (L/h/m^2), and $T > 0.05$ μmol/L (h). In cases where a single publication had pharmacokinetic profiles at different dose levels, every dose level was included separately. In studies with repeated pharmacokinetic profiles, only the first visit was included. Since data presentation varied among included publications, both median and mean estimates were extracted and pooled for analysis. Therefore, the summary values for all parameters reported here reflect interstudy variation and provide no indication of the significant interindividual variation in paclitaxel pharmacokinetics that is widely reported.

Correlation between dose and C_{max} was evaluated by linear and quadratic fits and r^2 was used to evaluate the best fit (STATA® 14.2, StataCorp, College Station, TX, USA).

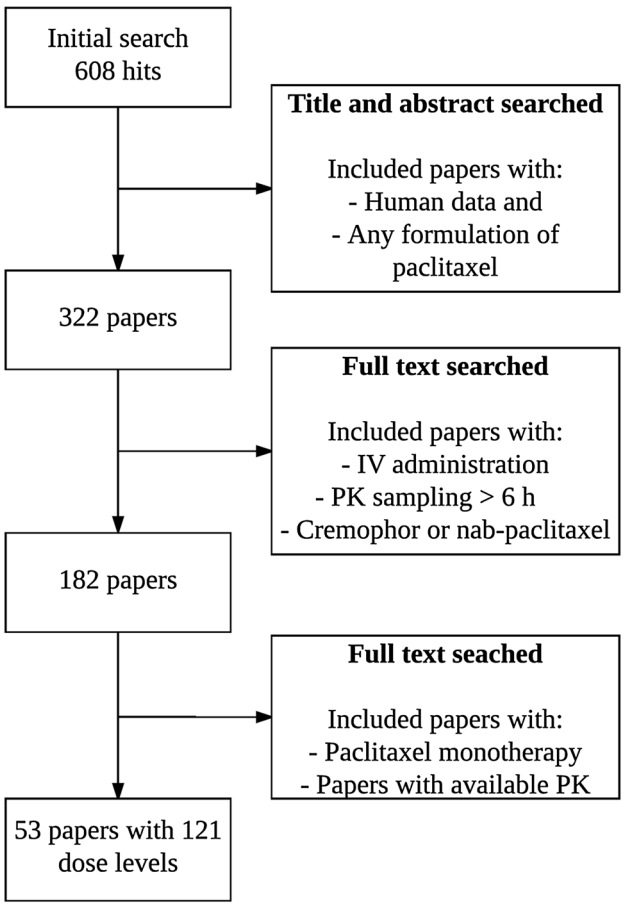

Fig. 1 Flowchart showing overview of literature search. The criteria for inclusion of papers for the final analysis are outlined as an iterative process. *IV* intravenous, *PK* pharmacokinetic

3 Results

An overview of included publications and the corresponding data extracted from these studies are provided as Electronic Supplementary Material (Online Resource 1). Briefly, 53 papers yielded a total of 121 pharmacokinetic profiles with a median number of six patients [interquartile range (IQR) 3–10 patients] in each study. Pharmacokinetic parameters presented in this paper are medians with IQRs (25th–75th percentiles), unless otherwise specified. A study with sub-therapeutic radiolabeled paclitaxel [64] was not included in the analysis due to the nature of the paclitaxel formulation. Thus, 120 profiles were included in the final analysis.

3.1 Cremophor EL® Paclitaxel

A total of 104 pharmacokinetic profiles for Cremophor EL® paclitaxel from administration of 32 different doses (15–825 mg/m^2) over six different infusion times (1, 3, 6, 24, 72, and 96 h) were evaluated. The diversity of paclitaxel dosage regimens is illustrated in Fig. 2.

Ninety-one paclitaxel CL estimates were extracted from the included studies [67 for short infusion (≤6 h) and 24 for long infusion (>6 h)]. Figure 3 shows the relationship between CL and dose for short and long infusion of Cremophor EL® paclitaxel. A single CL estimate was excluded from Fig. 3b (8.1 L/h/m^2 for paclitaxel 825 mg/m^2) to limit the range of the dose-axis and allow for more accurate representation of the majority of the data with lower doses. Paclitaxel CL decreases up to three-fold with increasing dose, which is most evident with shorter infusion times (Fig. 3a). Furthermore, for a given dose, paclitaxel CL is approximately two-fold higher when given as a long infusion than as a short infusion.

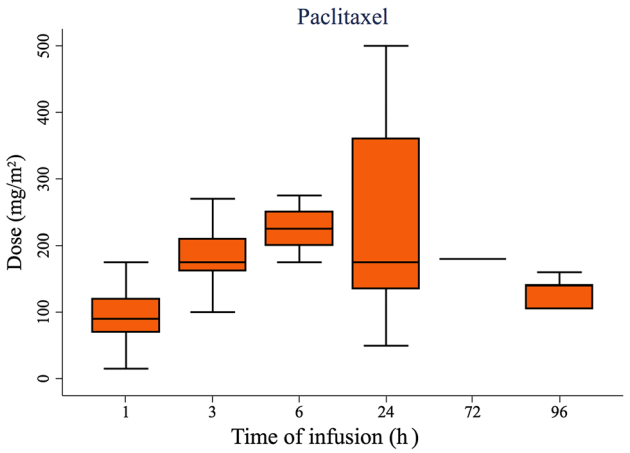

Fig. 2 Distribution of dosage regimens for cremophor-diluted paclitaxel included in this analysis. The *solid line* represents the median dose, the *box* represents the interquartile range (25th–75th percentiles), and the *whiskers* represent 5th–95th percentiles. A single outlier with a dose of 825 mg/m^2 infused over 24 h is excluded due to extension of the dose-axis and compression of the majority of the data

The relationship between paclitaxel C_{max} and dose is illustrated in Fig. 4 for short ($n = 75$) and long ($n = 24$) infusion times. A quadratic equation best described the C_{max}–dose relationship for paclitaxel given as a short infusion; the data for the 1-h infusion time best fit this relationship ($r^2 = 0.99$). With a 1.7-fold increase in paclitaxel dose given as 3-h infusion the C_{max} increases three-fold (Table 1). In contrast, a linear relationship provides the best fit for data from long infusion times. C_{max} values for long infusions were approximately tenfold lower than for short infusions (Fig. 4). A single dose from the long infusion data (825 mg/m^2) was removed from Fig. 4b to better illustrate the relationship for the majority of the values.

The non-linearity in paclitaxel pharmacokinetics is also highlighted in Table 1 with data from the most commonly used infusion time, 3 h. Median values with corresponding IQR (25th–75th percentiles) for C_{max} and CL indicate a greater than dose-proportional increase in C_{max} and decrease in CL with increasing dose.

In comparison to CL and C_{max}, $T > 0.05$ μmol/L was less commonly reported for the paclitaxel pharmacokinetic studies included in this analysis. Only 28 values for $T > 0.05$ μmol/L paclitaxel were reported, 21 for short and seven for long infusion times (Fig. 5). Interestingly, increasing infusion time from 3 to 24 h does not substantially increase $T > 0.05$ μmol/L. All values for $T > 0.05$ μmol/L from a 24-h infusion are from the same study [90].

3.2 Nab-Paclitaxel

Pharmacokinetic data for nab-paclitaxel were extracted from 16 studies using nine different doses (80–375 mg/m^2). The majority of these studies ($n = 14$) used a 0.5-h infusion; a single study used a 3-h infusion and the remaining study did not indicate an infusion time and was excluded from further analysis. The relationship between nab-paclitaxel CL and dose is illustrated in Fig. 6. With nab-paclitaxel doses above 200 mg/m^2, the CL of nab-paclitaxel decreases in a similar fashion as described for the Cremophor EL® paclitaxel formulation. Non-linearity was also observed for paclitaxel C_{max} values over a >4-fold range of nab-paclitaxel doses (Fig. 7), although the increases in C_{max} were less striking than those observed with the cremophor-diluted formulation (Fig. 4).

3.3 Population Pharmacokinetic Modelling

Six population pharmacokinetic studies of paclitaxel monotherapy were identified [96–101] and these are

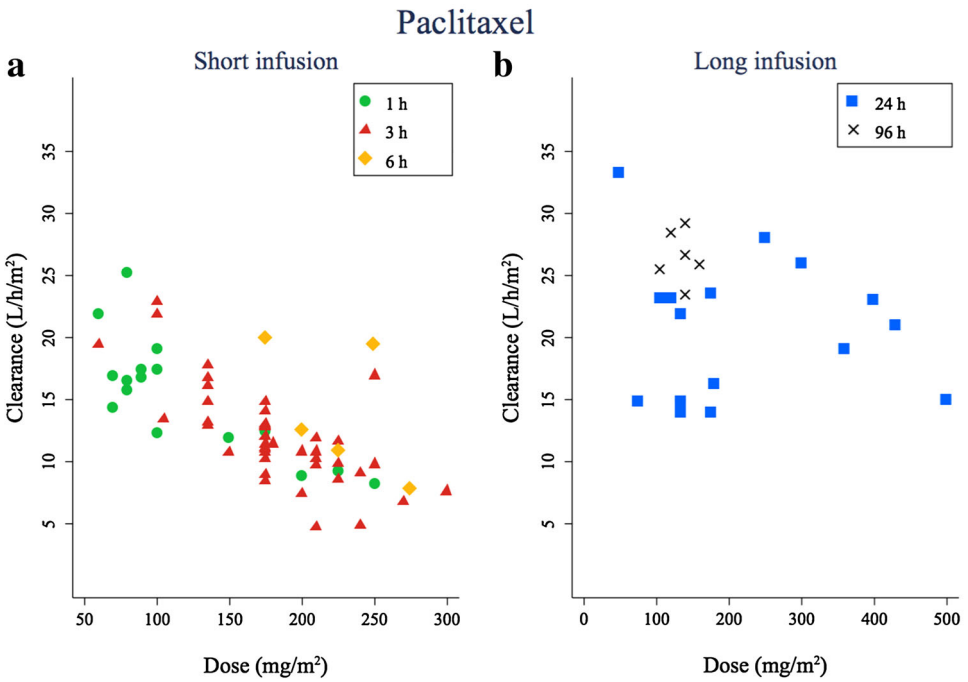

Fig. 3 Dose-dependent clearance of Cremophor-EL® paclitaxel. Paclitaxel clearance ($L/h/m^2$) plotted as a function of dose for short (≤6 h) (**a**) and long (>6 h) (**b**) infusion times

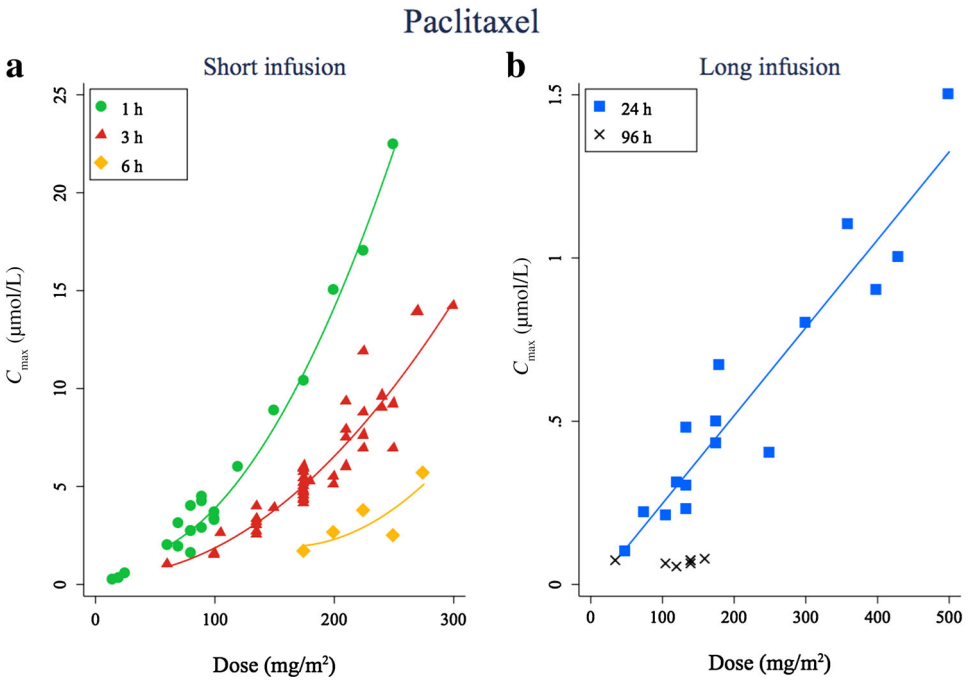

Fig. 4 Maximum paclitaxel concentrations are not dose proportional with short infusion times. Maximum concentration (µmol/L) of paclitaxel during short (**a**) and long (**b**) infusion is expressed as a function of dose and infusion time. *Solid lines* represent a quadratic fit for short infusion times and a linear fit for long infusion times. C_{max} maximum concentration

summarized in Table 2. Briefly, all but one of the studies had dense sampling with study populations ranging from seven to 150 individuals. The final models included two or three compartments with unique sets of covariates. One study developed a semi-mechanistic model with paclitaxel in four different states: peripheral or central and vehicle bound or not vehicle bound [100]. In one case, elimination was considered to be saturable and represented by Michaelis–Menten pharmacokinetics [99]. The estimates of CL and volume of distribution varied significantly across the models.

4 Discussion

In this review of paclitaxel pharmacokinetics, data were extracted from 53 papers reporting paclitaxel administration as single-agent chemotherapy with either cremophor-

Table 1 Pharmacokinetic parameters for cremophor-diluted paclitaxel following a 3-h infusion at commonly used dose levels

Dose level (mg/m^2)[a]	C_{max} (μmol/L)		CL (L/h/m^2)		$T > 0.05$ μmol/L (h)	
	n	Median (25th–75th percentile)	*n*	Median (25th–75th percentile)	*n*	Median (25th–75th percentile)
135	6	3.1 (2.7–3.3)	6	15.5 (13.1–16.7)		
175	18	5.1 (4.5–5.7)	17	12.0 (10.9–12.9)	4	23.8 (21.5–26.8)
210	4	7.7 (6.7–8.6)	5	10.1 (9.7–10.7)		
225	4	8.2 (7.3–10.3)	3	9.8 (8.5–11.6)		
240	3	9.6 (9.0–9.6)	3	4.8 (4.8–9.1)		

CL clearance, C_{max} maximum concentration, *n* number of studies, $T > 0.05$ *μmol/L* time of paclitaxel plasma concentration above 0.05 μmol/L

[a] More than three studies at a given dose were required for inclusion

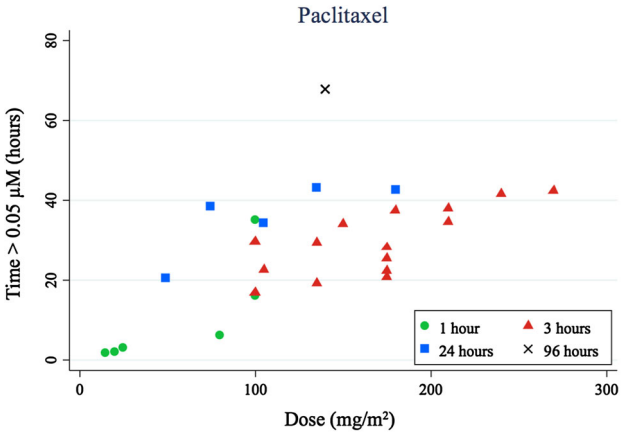

Fig. 5 The time of Cremophor-EL® paclitaxel concentration above 0.05 μmol/L plotted as a function of dose and infusion time shows that the time of paclitaxel concentration above 0.05 μmol/L is largely independent of infusion time

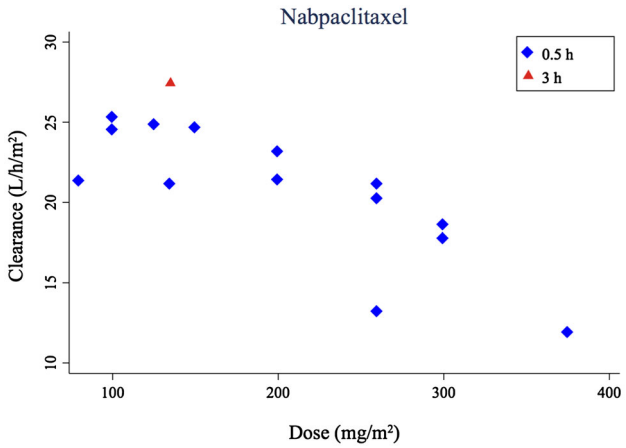

Fig. 6 Non-linear clearance of paclitaxel administered in its nanoparticle albumin-bound formulation

diluted or nab-paclitaxel-bound paclitaxel. The effect of dose and infusion time on CL, C_{max} and $T > 0.05$ μmol/L were the main outcomes analyzed. Based on 120

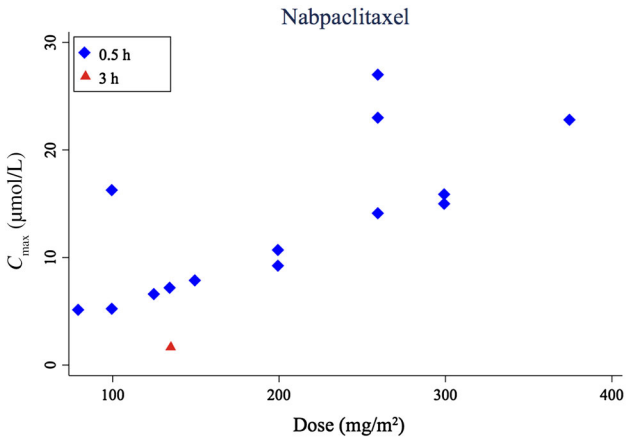

Fig. 7 Relationship between paclitaxel maximum concentration (μmol/L) values and dose following nanoparticle albumin-bound paclitaxel administration given as a function of dose and infusion time. C_{max} maximum concentration

pharmacokinetic profiles for cremophor-diluted and nab-paclitaxel, paclitaxel CL is non-linear over commonly used doses and infusion times. Non-linear paclitaxel CL results in more than dose-proportional increases in C_{max}, which is particularly apparent when paclitaxel is administered as the Cremophor EL® formulation. The most widely used dosage regimen for cremophor-diluted paclitaxel is a 3-h infusion of 175 mg/m^2. This popular dosage regimen corresponds to median values for CL, C_{max}, and $T > 0.05$ μmol/L of 12 L/h/m^2, 5 μmol/L, and 24 h, respectively. Increasing infusion time from 3 to 24 h does not significantly increase $T > 0.05$ μmol/L, and with the implementation of glucocorticoid and antihistamine pretreatment to reduce hypersensitivity reactions, there is little support for longer infusion times. While non-linear CL was also observed with high doses of the nab-paclitaxel formulation, non-linearities in C_{max} were less pronounced. The average C_{max} of the four patients who received a dose of 375 mg/m^2 in the study by Ibrahim et al. [73] was 22.6 μmol/L. Without this observation, the nab-paclitaxel

Table 2 Overview of population pharmacokinetic models describing single agent cremophor-diluted or nanoparticle albumin-bound paclitaxel therapy. All studies used the software package NONMEM®

Studied population	Sex (% male)	Paclitaxel dose (mg/m^2) and infusion time	Structural model	Clearance estimates[a]	Volume of distribution estimates[b]	Significant covariates	References
Cremophor-diluted paclitaxel							
$N = 7$ Bladder, breast, lung, and other malignancies	43	225, 175, and 135 over 3-h infusion	3-compartment	CL[c] (±SD): 71 ± 13 L/h Q1 (±SD): 30 ± 8 L/h Q2 (±SD): 34 ± 8 L/h	V1 (±SD): 41 ± 14 L V2 (±SD): 51 ± 14 L V3 (±SD): 340 ± 81 L	No covariates other than Cremophor EL® were tested	[96]
$N = 18$ Unknown malignancies	66	20–50 over 1-h infusion	2-compartment	CL_{Total}: 6.71 L/h (70%) $Q1_{Total}$: 44.7 L/h (126%)	V1: 3.64 L (79%) V2: 881 L (NA)	None	[97]
$N = 45$ Colorectal, gastric, gall bladder, breast, uterine, ovarian, and pancreas cancer	31	175 over 3-h infusion	2-compartment	$CL_{unbound}$: 343 L/h (3.5%) $Q_{unbound}$: 188 L/h (13%)	$V1_{unbound}$: 418 L (7.1%) $V2_{unbound}$: 1010 L (4.2%)	Body surface area on CL, V1, and V2, and bilirubin on CL. α-1 acid glycoprotein on B_{max}	[101]
$N = 97$[d] Breast, ovarian, esophagus, and other malignancies	41	50–225 over 1-h ($n = 42$), 3-h ($n = 49$), or 24-h ($n = 6$) infusion	3-compartment	$CL_{unbound}$: 301 L/h (4.3%) $Q1_{unbound}$: 132 L/h (6.6%) $Q2_{unbound}$: 151 L/h (6.5%)	$V1_{unbound}$: 225 L (6%) $V2_{unbound}$: 3450 L (7.8%) $V3_{unbound}$: 303 L (6.6%)	None	[98]
$N = 35$ Breast, ovarian, gastrointestinal, and other solid malignancies; multiple stages of liver dysfunction	22	70–175 over 3-h infusion	3-compartment with Michaelis–Menten elimination	V_{max}: 6.4 μmol/h (17.3%) KM_{El}: 0.06 μmol/L (35%) V_{Tr}: 161 μmol/h (13.2%) KM_{Tr}: 0.55 μmol/L (13.4%) k_{21}: 1.2 h^{-1} (12.5%) Q: 16.1 L/h (8.82%)	V1: 10.2 L (15.3%) V3: 642 L (19.7%)	Sex, body surface area, and liver function for V_{max}	[99]

Table 2 continued

Studied population	Sex (% male)	Paclitaxel dose (mg/m^2) and infusion time	Structural model	Clearance estimates[a]	Volume of distribution estimates[b]	Significant covariates	References
$N = 38$ Advanced or metastatic solid tumors	NA	175 over 3-h infusion	Semi-mechanistic model with 4 compartments	CL (90% CI): 101.0 L/h (83.8–113.4) Q1 (90% CI): 10.9 L/h (8.3–14.3) Q2 (90% CI): 0.6 L/h (0.1–7.4) Q3 (90% CI): 42.0 L/h (33.3–50.0)	V1 (90% CI): 24.8 L (18.2–32.1) V2 (90% CI): 271.0 L (183.1–447.8) V3 (90% CI): 16.5 L (0.4–56.9) V4 (90% CI): 178.0 L (146.3–319.1)	None	[100]
Nanoparticle albumin-bound paclitaxel							
$N = 150$ Advanced or metastatic breast, melanoma, or other solid tumors	40	80–375 over 30-min infusion, infusion time was 3 h in 1 individual	Semi-mechanistic model with 4 compartments	CL (90% CI): 260 L/h (226–307) Q1 (90% CI): 39.4 L/h (32.7–46.3) Q2 (90% CI): 7.2 L/h (1.7–12.0) Q3 (90% CI): 49.6 L/h (44.4–55.6)	V1 (90% CI): 11.8 L (10.5–13.5) V2 (90% CI): 270.6 L (192.8–367.0) V3 (90% CI): 169.6 L (133.5–195.0) V4 (90% CI): 399.1 L (300.8–507.6)	None	[100]

B_{max} maximal non-linear binding to plasma components, *CI* confidence interval, *CL* clearance, CL_{total} total clearance, $CL_{unbound}$ unbound clearance, KM_{EL} plasma concentration at half of the maximal elimination rate, KM_{Tr} plasma concentration at half V_{Tr}, k_{21} transfer rate constant (first-order) from the peripheral to central compartment, *NA* not available, *Q* intercompartmental clearance, $Q1_{total}$ total intercompartmental clearance in compartment 1, $Q1_{unbound}$ unbound intercompartmental clearance in compartment 1, $Q2_{unbound}$ unbound intercompartmental clearance in compartment 2, $Q_{unbound}$ unbound intercompartmental clearance, *RSE* relative standard error, *SD* standard deviation, *V1* volume of compartment 1, *V2* volume of compartment 2, *V3* volume of compartment 3, *V4* volume of compartment 4, $V1_{unbound}$ unbound volume of compartment 1, $V2_{unbound}$ unbound volume of compartment 2, $V3_{unbound}$ unbound volume of compartment 3, V_{max} maximum rate, V_{TR} maximaltransport rate from the central to the first peripheral compartment

[a] Data are shown as mean (RSE%) unless otherwise specified

[b] Data are shown as population estimate (RSE%) unless otherwise specified

[c] Overall CL based on unbound (non-micellar) paclitaxel

[d] 15 of 82 (18%) were also treated with carboplatin

C_{max} approached a non-linear pattern similar to that of cremophor-diluted paclitaxel. Further studies are needed to fully understand the relationship between nab-paclitaxel dose and C_{max}.

The main limitation of this analysis is the exclusion of papers where paclitaxel was given concomitantly with other chemotherapeutics. This limitation was necessary to limit variability in paclitaxel pharmacokinetic parameters and to identify robust dose-dependent changes in paclitaxel elimination. The strong correlation between C_{max} and dose for a given short infusion time (Fig. 4a) supports the study design that was utilized. Furthermore, data regarding interindividual variability in paclitaxel pharmacokinetics were not widely available for the included studies. Both medians and means from pooled data in each study were used for the analyses described in this review. Thus, all measures for variability presented in the current study reflect interstudy variability rather than interpatient variability.

The main strength of this study is the number and diversity of paclitaxel pharmacokinetic profiles that were analyzed. Data were included for more than 30 different doses and six different infusion times, representing the most extensive analysis to date of single-agent paclitaxel pharmacokinetics. This allows for the detection of strong

correlations between paclitaxel dose and C_{max} and clearly illustrates that paclitaxel CL is dose dependent, with CL decreasing with increasing dose. The robustness of the analyses is even more striking, considering that the data was from more than 50 studies performed between 1991 and 2015 that employed a wide range of drug assays and dosage regimens. Patient heterogeneity with respect to age, ethnicity, co-morbidities, and treatment indication was also significant. The conclusions drawn from the current analysis can therefore be applied broadly across diverse patient populations and a broad range of paclitaxel dosage regimens. Due to the nature of the data mining implemented in this study, the results do not provide insight regarding interpatient variability.

The non-linearity of paclitaxel pharmacokinetics, which is easily visible for both C_{max} and CL (Figs. 3, 4), was first recognized in the 1990s [67]. Initial reports suggested saturation of CYP-mediated metabolism of paclitaxel, but the non-linear CL is now largely attributed to the formulation of paclitaxel. Because of the high hydrophobicity of paclitaxel, it requires dilution in Cremophor EL®, a polyoxy-ethylated oil mixed 1:1 with ethanol. Free concentrations of paclitaxel are inversely correlated with Cremophor EL® concentrations [102], which means that less paclitaxel is available for distribution at higher doses. As a result, tissue distribution and pharmacodynamics are largely assumed to be linear. In this review, we see indications of non-linear CL of nab-paclitaxel at higher doses, which could indicate saturation of metabolism at high paclitaxel concentrations. Gemfibrozil, another CYP2C8 substrate, is known for non-linear pharmacokinetics [103, 104] at higher concentrations. Although gemfibrozil non-linear pharmacokinetics have no apparent implications for its clinical use, CYP2C8 saturation could clinically affect nab-paclitaxel elimination.

Population pharmacokinetic modeling is a useful tool to describe and investigate the effect of covariates in drug variation. A number of population pharmacokinetic models have described the pharmacokinetics of paclitaxel monotherapy and have provided important insight into paclitaxel pharmacokinetics and pharmacodynamics. Hempel et al. [97] estimated the total paclitaxel plasma CL to be 6.7 L/h for 13 predominantly male patients treated with 20–50 mg/m^2 as a 1-h infusion. This is in agreement with the reported values for non-compartmental analyses of higher doses of paclitaxel. While this study did not report pharmacokinetic non-linearity, this is likely due to the low paclitaxel doses that were analyzed. Zuylen et al. [96] were elegantly able to demonstrate that both non-linear distribution and elimination could be explained by micelle encapsulation of paclitaxel by Cremophor EL®. Henningsson et al. [98] concluded that the *CYP2C8* genotype did not impact CL of unbound paclitaxel, a finding disputed by Bergmann et al. [32] who found a small effect of the *CYP2C8**3 variant on paclitaxel CL that may depend on the *ABCB1* genotype [105]. A direct relationship between liver impairment and paclitaxel elimination was linked to susceptibility to paclitaxel-induced neutropenia by Joerger et al. [99]. A model proposed by Li et al. [100] demonstrated that the similar paclitaxel concentration–time profiles of nab-paclitaxel and cremophor-diluted paclitaxel mask discordant paclitaxel tissue concentration profiles. Based on these findings, the authors conclude that the paclitaxel plasma profile is a poor marker for clinical outcome.

Paclitaxel is rarely given as monotherapy, but often administered in combination with a platinum (cisplatin, carboplatin) or doxorubicin. There are no reported pharmacokinetic interactions between paclitaxel and cisplatin [106–108] or carboplatin [109–111], although the toxicities of the drugs may be affected by the sequence of their administration [28]. When doxorubicin and paclitaxel are administered within a short time interval, the exposure to doxorubicin is significantly increased [112], which results in dose-dependent cardiotoxicity [67, 113]. Furthermore, a number of relevant pharmacokinetic interactions with paclitaxel have been reported, largely due to inhibition of the major paclitaxel efflux transporter, P-gp. Recent evidence also indicates that a metabolite of the widely used anticoagulant drug clopidogrel reduces CYP2C8-mediated paclitaxel metabolism and can lead to neurotoxicity [36, 38, 114].

Accumulation of paclitaxel in the peripheral nervous system has been associated with its toxicity. In mice, paclitaxel accumulates in the dorsal root ganglia and sciatic nerve following both single and multiple doses [115]. Paclitaxel was still detectable up to 72 h after a single dose, which was significantly after the drug could be detected in the systemic circulation. Following six doses of paclitaxel, the drug was measurable in these peripheral sites for up to 2 weeks. While such accumulation is not expected to be reflected in the plasma, these findings in mice are consistent with the observation that cumulative exposure to paclitaxel is highly correlated with the risk of paclitaxel-induced sensory neuropathy. Further exploration into the mechanisms underlying accumulation of paclitaxel in the peripheral nervous system may lead to better prediction of an individual patient's risk for developing sensory neuropathy.

5 Conclusion

The data presented in this review demonstrates non-linearity in paclitaxel pharmacokinetics when administered as a short infusion of ≤6 h. This is largely a result of the

dilution of paclitaxel in Cremophor EL® [24], and possibly to a lesser extent by saturation of CYP2C8-mediated metabolism. A strong correlation between paclitaxel C_{max} and CL values and dose is also demonstrated. The limited data available for paclitaxel $T > 0.05$ μmol/L do not allow for an accurate prediction of its relationship with dose.

Compliance with Ethical Standards

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Conflicts of interest Tore B. Stage, Troels K. Bergmann, and Deanna L. Kroetz have no conflicts of interest.

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