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ORIGINAL ARTICLE

The pharmacokinetic behavior of the photosensitizer *meso*-tetra-hydroxyphenyl-chlorin in mice and men

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Abstract
Purpose *Meso*-tetra-hydroxyphenyl-chlorin (mTHPC) is a hydrophobic photosensitizer that binds to plasma lipoproteins after intravenous injection. In vitro experiments with human plasma have shown that mTHPC initially binds to an unknown protein and subsequently redistributes to lipoprotein fractions. It has been suggested that this might explain the unusual pharmacokinetic profile of mTHPC humans. In humans, unlike in rodents, reappearance of mTHPC has been reported, resulting in a second plasma peak after intravenous injection. However, previous studies analyzed only limited time points during the first 24 h after injection. Our aim was to determine the pharmacokinetics of mTHPC in detail, and to investigate whether the pharmacokinetic behavior of the drug is affected by binding of mTHPC to lipoproteins in vivo.
Methods Plasma of cancer patients and mice, intravenously injected with mTHPC, was analyzed for total drug content and drug distribution over the lipoprotein fractions.
Results Pharmacokinetic profiles of mTHPC in a group of human subjects showed that apparent steady state drug levels were maintained for at least 10 h. Closer examination of individual profiles showed that the initial (5 min) plasma drug levels were on average 86% of the maximal plasma concentration, which occurred at about 5 h after injection. In mice, however, plasma pharmacokinetics were described by a standard bi-exponential decline of the drug concentration. The majority (>58%) of mTHPC injected into both BALB/c nude mice and patients initially bound to the HDL plasma fraction. We extended our study to ApoE −/− mice, with highly elevated lipoprotein levels, and SR-BI −/− mice, which are lacking the main clearance pathway for HDL associated cholesteryl esters, to take into account the differences between lipoprotein levels and clearance in mice and man. Although mTHPC distribution over the lipoproteins changed in these mice, pharmacokinetic profiles of mTHPC remained the same.
Conclusions We conclude that neither lipoprotein levels nor cholesterol metabolism affects the pharmacokinetics of mTHPC in plasma.

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Introduction

Photodynamic therapy (PDT) involves the administration of a photosensitive drug, followed by illumination with light of the appropriate wavelength to activate this drug. In the presence of oxygen the ensuing photochemical reaction will generate singlet oxygen, which results in tumor destruction. PDT is now approved for the treatment of a variety of cancers (e.g., head and neck cancer, basal cell carcinoma, esophageal cancer and bladder cancer).

Meso-tetra-hydroxyphenyl-chlorin (mTHPC, Foscan®) is a second-generation photosensitizer that has been approved in Europe for the treatment of head and neck cancer. mTHPC is a potent photosensitizer with a high anti-tumor efficacy. Compared with Photofrin®, a first-generation photosensitizer, drug and light doses required for similar tumor responses are up to 100 times lower. Much of this difference can be explained by the high singlet oxygen yield and the more favorable photophysical properties of mTHPC [16].

Several studies have reported on mTHPC concentrations in human plasma after i.v. bolus injection [3, 7, 17, 18] but only one study analyzed enough samples during the first 24 h after injection to obtain meaningful pharmacokinetic profiles [7]. This study showed that plasma drug levels initially decreased and then increased until maximum drug levels were reached at 10 h, followed by a bi-exponential decline [7]. Although similar profiles were reported in hamsters and cats, in those studies only 1–3 samples were taken during the first 24 h [2, 5]. By contrast, studies in mice and rats show peak levels of mTHPC in plasma within minutes after i.v. injection, followed by a bi-exponential decline [6, 9, 20–22]. To date, no satisfactory explanation has been found for the delayed maximum plasma drug levels seen in humans. Further understanding of the pharmacokinetics of mTHPC in vivo is important with respect to determining optimal times for tumor illumination [6, 20].

The distribution of a drug over the different plasma fractions can directly influence its pharmacokinetics and tissue distribution and localization. The binding of a variety of photosensitizers has been studied (reviewed by Jori and Reddi [10]) and results show that hydrophilic sensitizers are transported by albumin and globulins, resulting in vascular stroma localization, whereas hydrophobic sensitizers, like mTHPC, are solubilized by lipoproteins, resulting in greater tumor tissue localization. Only a few studies have specifically investigated binding to and distribution of mTHPC over the lipoproteins [8, 12, 15]. Hopkinson et al. [8] showed that after addition of mTHPC to human plasma in vitro, 70% initially formed a complex with an unidentified protein. With increasing incubation time mTHPC was redistributed to the lipoproteins, of which HDL bound >50% of the drug within 2 h. Additional, but more limited, in vivo data also indicated that some mTHPC was bound to an unknown protein fraction in rat plasma immediately after i.v. injection [8].

The aim of this study was to examine whether the different pharmacokinetic profiles of mTHPC observed between rodents and humans, which have markedly different plasma lipoprotein compositions, could be explained by the in vivo binding to and distribution of mTHPC over the lipoproteins. For further elucidation of this difference, we also examined the pharmacokinetics of mTHPC in ApoE −/− mice with a lipoprotein profile comparable with that of humans, and in SR-BI −/− mice, which are lacking the main clearance pathway for cholesteryl esters. Our results show that neither lipoprotein levels nor cholesterol metabolism influenced the pharmacokinetic behavior of mTHPC.

Material and methods

Chemicals

The photosensitizer mTHPC (temoporfin, Foscan®) was provided by Biolitec Pharma Ltd (Breasclete, Isle of Lewis, Scotland). The drug was supplied as a 5 ml solution (4 mg/ml) in a mixture of 60/40% wt/wt propylene glycol/ethanol.

Patients

Two patients hospitalized for pleural malignancies volunteered to receive an injection of 0.02 mg/kg mTHPC. Ten patients hospitalized for treatment with PDT of multiple basal cell carcinoma (BCC) and two patients hospitalized for PDT treatment of squamous cell carcinoma of the head and neck, received 0.1 mg/kg of mTHPC; two of the BCC patients were retreated. Another 19 patients hospitalized for the treatment of malignancies in the oral cavity received 0.15 mg/kg mTHPC. In all patients the drug was given intravenously (i.v.) as a slow bolus (4 min). All patients gave written informed consent prior to inclusion in the study, which was approved by the local medical ethical committee.

Mice

Female nude BALB/c, ApoE -/- and SR-BI -/- mice were used to determine the pharmacokinetics and distribution of mTHPC over the lipoproteins. mTHPC was diluted to a concentration of 50 μg/ml in ethanol, polyethylene glycol 400, water (1:1:2, vol/vol/vol) and injected via the tail vein, at a dose of 0.3 mg/kg. All procedures were carried out according to protocols approved by the local animal welfare committee and conformed to national and European regulations for animal experimentation.

Plasma samples

Repeated whole blood samples (10 ml) were taken from patients before and up to 7 days after injection of mTHPC (i.e., were taken at one of the following timepoints; before injection, at 5, 15, 30 and 45 min, and at 1, 2, 3, 5, 7, 9, 10, 11, 12, 20, 24, 32, 48, 72, 96, 120, 144 and 168 h after injection). In total 15, 182 and 120 samples were taken during the courses of 0.02, 0.1 and 0.15 mg/kg mTHPC, respectively. Furthermore, during 12 out of 14 courses of 0.1 mg/kg mTHPC, 8–11 samples were taken during the first 12 h after injection. During the first day, whole blood samples were taken from the non-injected arm.

Whole blood samples from the mice were obtained via cardiac puncture, after brief anesthesia with methoxyflurane. Samples were taken at 0.5, 5, 10, 15, 20, 30 and 45 min, and at 1, 3, 6, 24 and 48 h. Blood samples were collected in heparin containing tubes and were centrifuged for 10 min at 1,500 *g* at 4°C to separate the plasma. For all measurements, $t = 0$ corresponded to the end of the injection.

Plasma protein separation

Plasma samples obtained from 6 BCC patients at 15 min, and 2, 3, 10, 24, 48 and 72 h after injection of 0.1 mg/kg mTHPC and from 4 head and neck cancer patients (0.15 mg/kg) at 15 min, 3 and 24 h were examined for mTHPC distribution over the lipoprotein fractions. Plasma samples from BALB/c nude and ApoE −/− mice, obtained at 15 min and 1, 3 and 6 h after injection of 0.3 mg/kg mTHPC, were also examined for mTHPC distribution over the lipoprotein fractions.

Lipoprotein fractionation was achieved by applying diluted plasma samples (1:1, vol/vol, with PBS containing 1 mM EDTA) to a Superose 6 column (3.2 × 30 mm, Smart-system, Amersham Biosciences, Freiburg, Germany) and eluted with PBS containing 1 mM EDTA. Fractions (50 × 0.1 ml) were collected and assayed for their protein content by absorption at 280 nm. The obtained protein profile was used to determine which fractions contained VLDL, LDL or HDL.

Determination of mTHPC levels in plasma and protein fractions

A mixture of CH_3OH:DMSO (4:1, vol/vol) was added to 50 μl samples of total plasma or protein fraction and centrifuged for 25 min at 14,000 rpm at 4°C; the supernatant was analyzed for mTHPC content by HPLC.

The separation of mTHPC was carried out on a Waters symmetry C18 3.5 μm 4.6 × 100 mm column, with acetonitril; 0.1% (wt/vol) TFA (50:50, vol/vol) as mobile phase, using a flow-rate of 1 ml/min. Samples were injected via a Waters 717 plus autosampler and a Waters 474 scanning fluorescence detector, set at excitation and emission wavelengths of 410 and 652 nm, was used for peak detection. Quantification of the drug was done by comparing the mean peak areas of the samples with plasma spiked with known amounts of mTHPC. The distribution of the drug was expressed as percentage of total recovered amount of mTHPC after fractionation. Recovery was determined by dividing the absolute amount of mTHPC in all fractions by the total drug amount in the plasma before fractionation.

Data and pharmacokinetic analysis

Pharmacokinetic parameters were calculated by non-compartmental analyses using the software package WinNonlin (Pharsight, version 5.0). The AUC was calculated using the trapezoidal method for which the concentration–time curve was extrapolated up to infinity for assessment of the total AUC.

All data are given by mean ± SD and student's *t*-test was used to test for difference between mean values.

Results

Plasma pharmacokinetics of mTHPC

Plasma pharmacokinetic profiles of mTHPC were determined in two volunteers, hospitalized for the treatment of pleural malignancies, who received a slow bolus injection of 0.02 mg/kg mTHPC, in 12 patients who received 0.1 mg/kg mTHPC for treatment of BCC and in 19 patients receiving 0.15 mg/kg for PDT of head and neck cancer (Fig. 1a). Calculation of the average plasma drug levels per dose group shows that apparent steady state drug concentrations

were maintained for at least 10 h after i.v. injection and that peak plasma drug levels increase in proportion to the injected dose (Fig. 1b). However, closer examination of individual profiles from the BCC patients showed an initial decrease in plasma drug levels in 10 out of 12 patients, followed by an increase to maximum levels at 2–7 h (median 5 h), which were maintained for 2–5 h (Fig. 2). These pharmacokinetic profiles in humans are in marked contrast with previously published profiles for mTHPC in mice [6, 20, 21] and rats [9], which show a bi-exponential decline of mTHPC without a plateau phase shortly after injection.

Table 1 shows the pharmacokinetic parameters obtained by analyses of the human plasma concentration–time data and of our previously published mouse data [20]. The total AUC increased proportionally to the injected dose for 0.1 mg/kg and 0.15 mg/kg mTHPC. The AUC in patients injected with 0.02 mg/kg mTHPC was disproportionately lower. However, this is difficult to interpret because the data were obtained in only two volunteers.

Distribution of mTHPC over the lipoproteins

The distribution of mTHPC over plasma lipoproteins was examined in representative samples from patients who received 0.1 mg/kg mTHPC or 0.15 mg/kg mTHPC and was compared with distribution in plasma of mice that received 0.3 mg/kg mTHPC. Initial pilot studies were carried out in human plasma samples (from untreated volunteers who were hospitalized for treatment of pleural malignancies) spiked with known quantities of mTHPC, to test whether duration of and temperature during storage influenced the distribution of mTHPC over the lipoproteins. Spiked plasma samples were either used immediately for lipoprotein fractionation or maintained at room temperature or 4°C for 4 h before separation. In addition, the plasma samples from 2 patients who had received mTHPC were split and either fractionated immediately or after 3 weeks of storage at −20°C. Neither duration of storage nor temperature during storage influenced the drug distribution over the lipoproteins (data not shown).

The relative distribution of mTHPC over the lipoproteins in patients injected with a dose of 0.1 mg/kg or 0.15 mg/kg is shown in Fig. 3. At 15 min after injection, 70 ± 9% of the drug was bound to the HDL fraction and 20 ± 6% to the LDL fraction in plasma from patients injected with 0.1 mg/kg of mTHPC. In patients who received 0.15 mg/kg mTHPC, 58 ± 7% and 31 ± 4% of mTHPC was initially bound to HDL and LDL, respectively. The distribution of the drug over

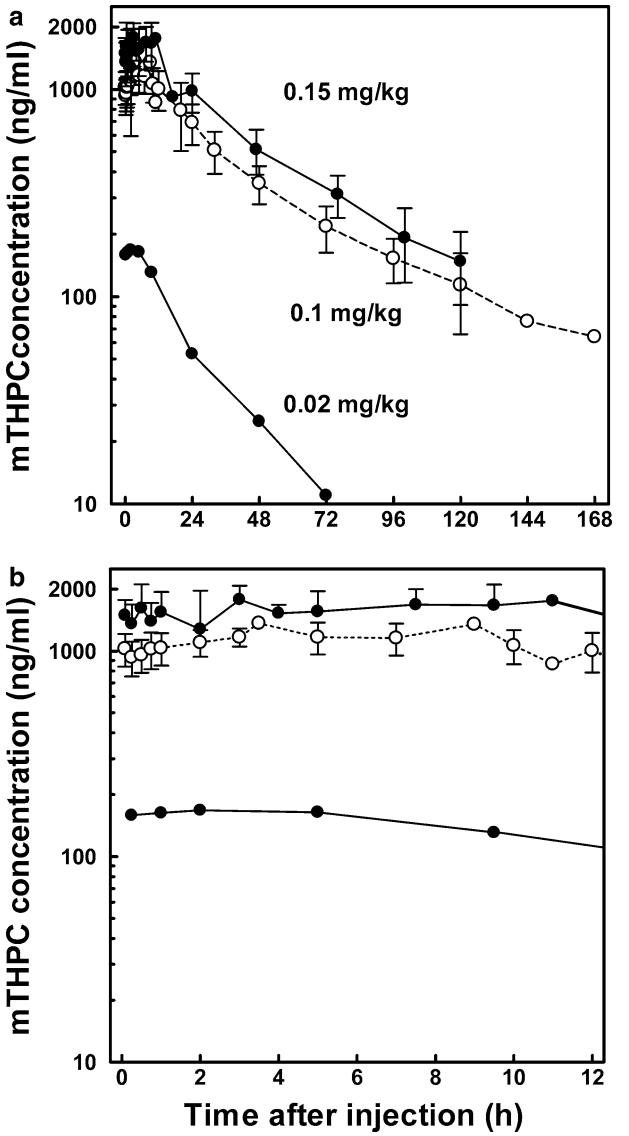

Fig. 1 **a** Pharmacokinetic profiles for mTHPC in the plasma of patients after i.v. injection of 0.02, 0.1 and 0.15 mg/kg mTHPC. In all patients the drug was given as a slow bolus (4 min). Data are expressed as mean of two courses of mTHPC (0.02 mg/kg), and means ± SD of respectively, 14 (0.1 mg/kg) or 19 (0.15 mg/kg) courses of mTHPC. **b** Pharmacokinetic profiles during the first 12 h after injection

the lipoproteins did not change markedly over time, although the fraction bound to HDL at 3 h after injection was slightly lower (borderline significant, $P = 0.05$) for 0.1 mg/kg of drug dose. Furthermore, percentages of HDL bound mTHPC at 3 and 24 h was significantly lower in the patients injected with the high dose (0.15 mg/kg) compared with patients that received 0.1 mg/kg mTHPC ($P < 0.05$). The median drug recovery was also lower after high dose injection (i.e., 65 vs. 84%). However, absolute amounts of HDL bound mTHPC were comparable between the patients injected with different drug doses.

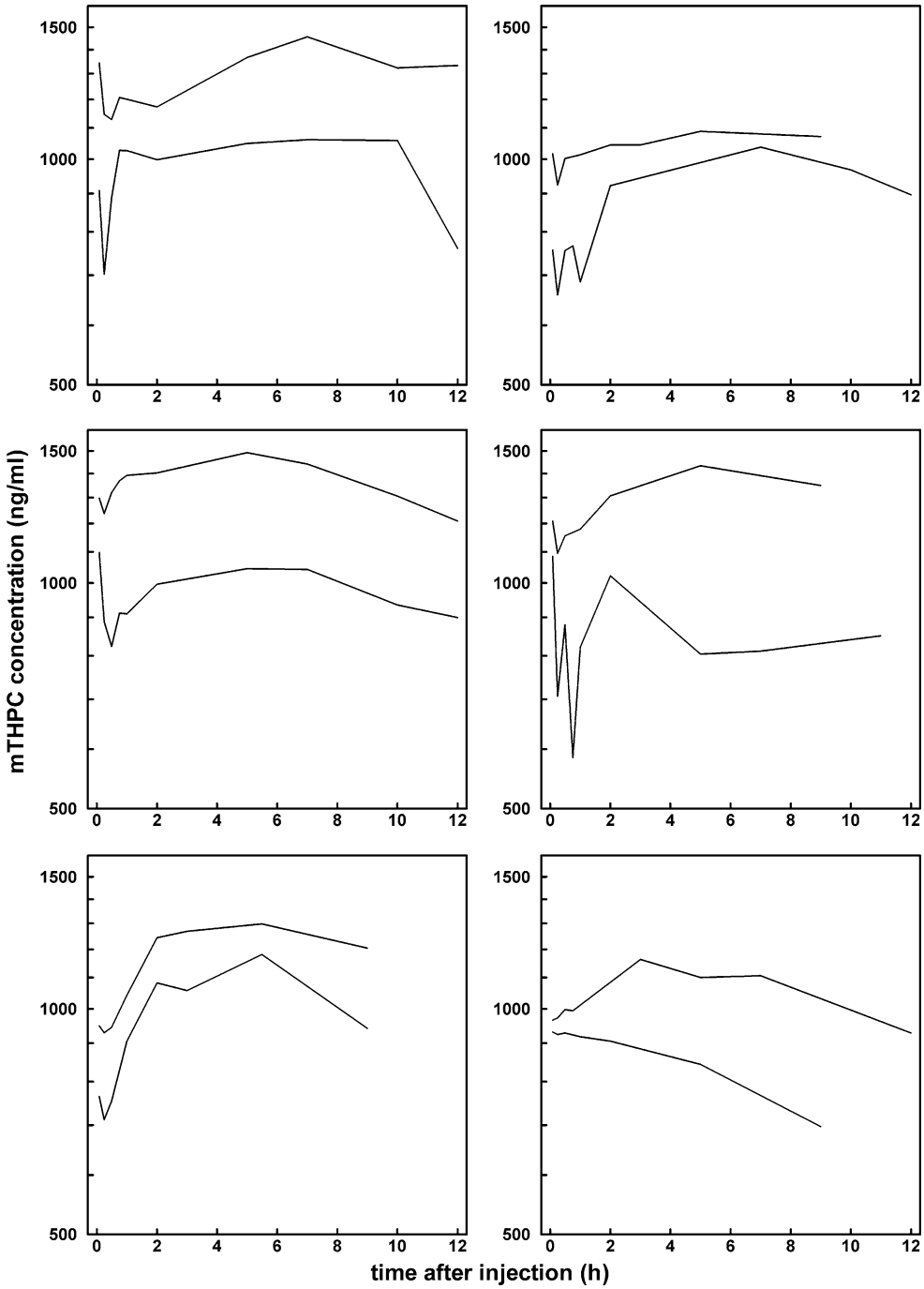

Fig. 2 Individual pharmacokinetic profiles of the BCC patients injected with 0.1 mg/kg mTHPC during the first 12 h after injection. In 10 out of 12 patients plasma drug levels initially decreased followed by an increase to maximum levels that were maintained for 2–5 h

In order to test whether these differences in drug recovery and fraction bound to HDL were the consequence of a saturation after high drug doses or of the separation method used, two patient samples and one spiked plasma sample with high dose of mTHPC (4 mg/ml) were analyzed after separation of the lipoproteins by both ultracentrifugation and our separation method using a Superose 6 column. No changes in distribution were seen after using a different separation method or adjusting drug dose (data not shown).

Injection of 0.3 mg/kg mTHPC in BALB/c nude mice resulted in an initial binding of 75 ± 12% to the HDL fraction (Fig. 4a). Once again there was no significant change in drug distribution over the lipoproteins over time, although there was a large experimental variation in data from the 1 h sampling time. The median recovery of mTHPC for these mouse plasma samples was 76% of total plasma drug levels.

Since the majority of mouse strains (including BALB/c nudes) have extremely low LDL levels,

Table 1 Pharmacokinetic parameters of mTHPC in the plasma of patients and BALB/c nude mice

Patients				BALB/c nude mice
Injected dose (mg/kg)	0.02	0.1	0.15	0.3
AUC (h*mg/l)	4	55 ± 11	81 ± 23	21
Cl (l/h)	0.367	0.166 ± 0.05	0.143 ± 0.05	0.00036
V_d (l)	8.5	7.3 ± 2.2	5.5 ± 1.8	0.005
$t_{1/2}$ elimination (h)	17	33 ± 4	32 ± 7	13
MRT (h)	23	44 ± 5	40 ± 10	15

Parameters were obtained by using non-compartmental analyses for patients injected with 0.02, 0.1 and 0.15 mg/kg mTHPC. The AUC was calculated with the trapezoidal method for which the concentration–time curve was extrapolated up to infinity. Parameters are expressed as mean of two courses of mTHPC (0.02 mg/kg), and means ± SD of respectively, 14 (0.1 mg/kg) or 19 (0.15 mg/kg) courses of mTHPC *AUC* area under the plasma concentration–time curve, *Cl* clearance, V_d distribution volume, *MRT* mean residence time

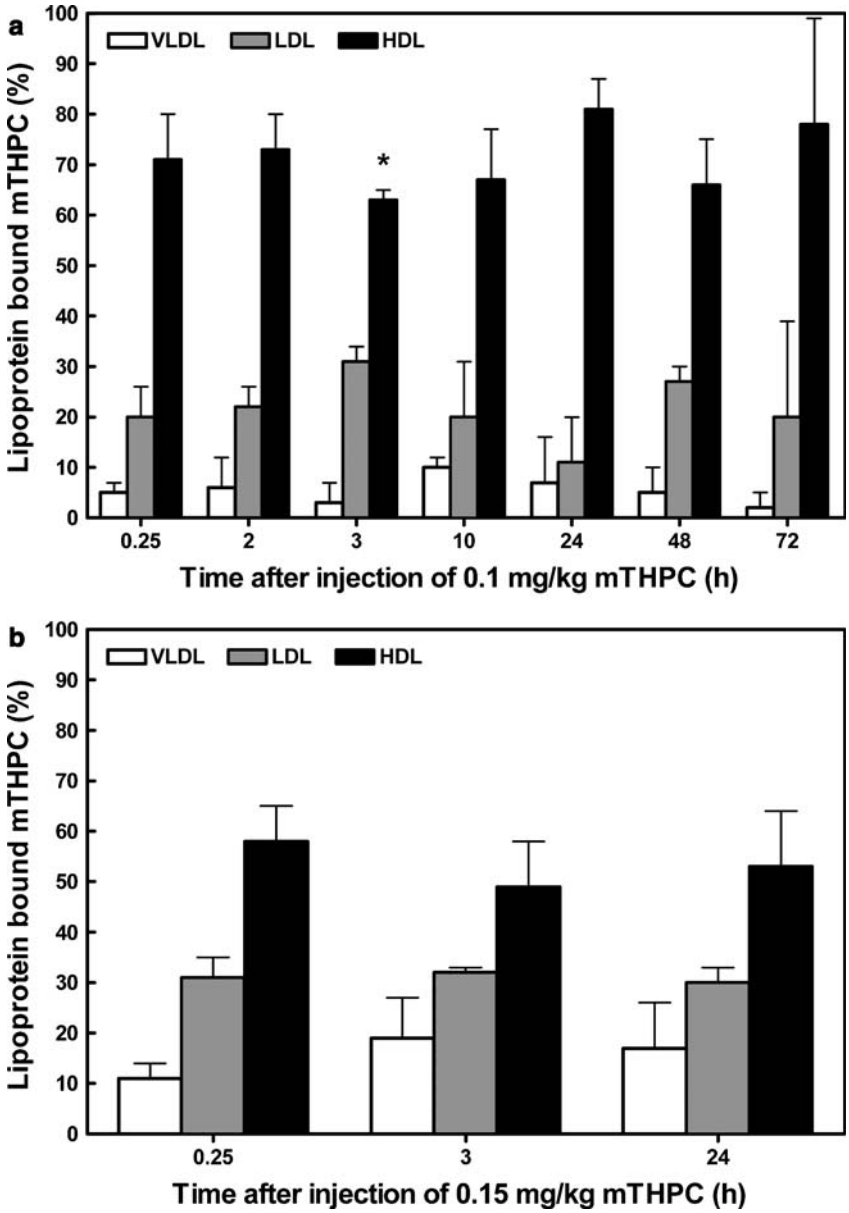

Fig. 3 The relative distribution of mTHPC over the lipoproteins in the plasma of patients, who received 0.1 mg/kg (**a**) or 0.15 mg/kg mTHPC (**b**). Data are expressed as means ± SD and $n = 3$ or 4 per time point. The *asterisks* indicates the drug levels bound to HDL that were significantly lower, $P = 0.05$

unlike humans, we also examined mTHPC distribution in the plasma of ApoE −/− mice, which have elevated total cholesterol levels and a HDL:LDL ratio more comparable with humans (Fig. 5). The distribution of mTHPC over the lipoproteins in plasma from ApoE −/− mice was markedly different to that in

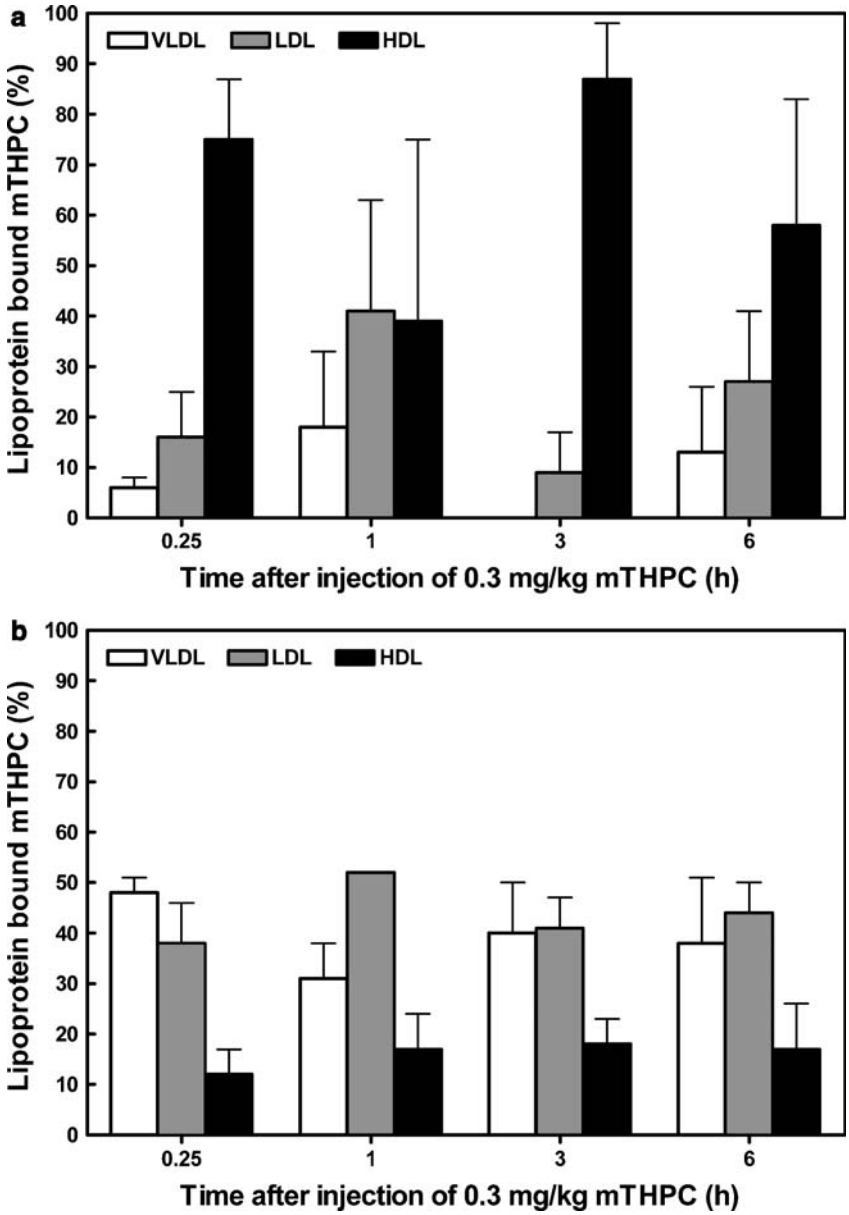

Fig. 4 Relative distribution of mTHPC over the lipoproteins in the plasma of BALB/c nude (**a**) and ApoE −/− mice (**b**) injected with 0.3 mg/kg. Data are expressed as means ± SD and $n \geq 3$ per time point

BALB/c nude mice or humans, with >80% bound to either VLDL or LDL and <20% bound to HDL (Fig. 4b). However, pharmacokinetic profiles for clearance of mTHPC in ApoE −/− mice were identical to BALB/c nude mice (Fig. 6).

We also examined the effect of HDL metabolism on pharmacokinetics of mTHPC in SR-BI −/− mice, which lack the main clearance pathway for HDL associated cholesteryl esters. The pharmacokinetic profile for mTHPC in these mice was very similar to that observed in wild type BALB/c nude and ApoE −/− mice (Fig. 6), although plasma drug levels in the SR-BI −/− mice where slightly higher at the 1 h time point ($P \leq 0.02$).

Discussion

The pharmacokinetic profile for mTHPC in plasma following an i.v. bolus injection has been reported for several species. In mice and rats, mTHPC shows a classic bi-exponential decline with $t_{1/2}$ values of 0.5–1.3 h for the initial decline and 6.9–20.9 h for the elimination phase [6, 9, 20, 21]. Few studies have investigated mTHPC levels in the plasma of humans [3, 7, 18] and only one study analyzed enough time-points in the first 24 h to optimally describe the pharmacokinetics [7]. Our results reveal that mTHPC levels in plasma decreased immediately after slow bolus injection, reaching an initial trough within 45 min, after which

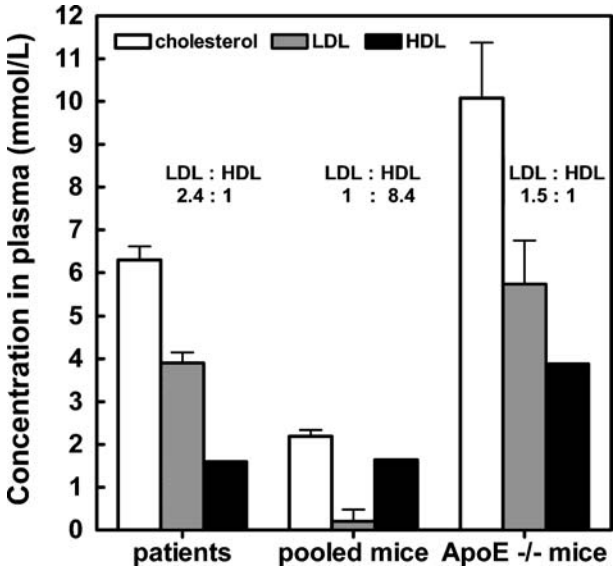

Fig. 5 Lipoprotein levels and LDL:HDL ratio in plasma of the patients used for analysis of mTHPC distribution over the lipoproteins, of a pool of different mouse strains and of the used ApoE −/− mice

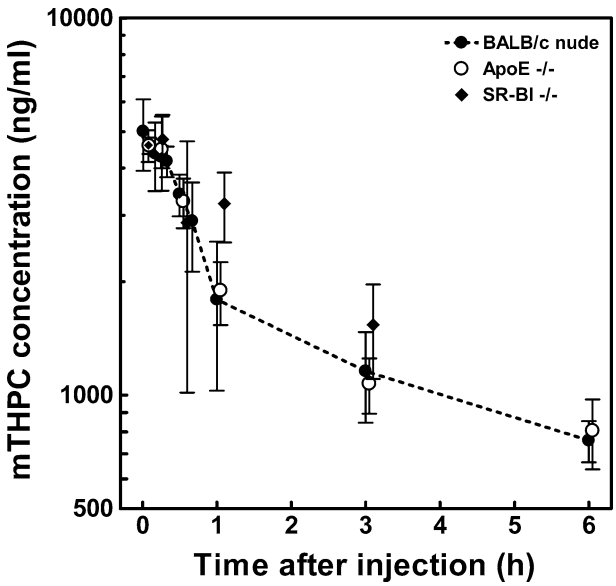

Fig. 6 Pharmacokinetic profiles for mTHPC in the plasma of BALB/c nude, ApoE −/− and SR-BI −/− mice after IV injection of 0.3 mg/kg. Data are expressed as means ± SD ($n \geq 3$ per group) and the previously published average of nude mice is plotted as *dotted line* [20]. The pharmacokinetic profile of mTHPC was identical in all three mice strains

drug reappeared in the plasma resulting in peak values as late as 10 h after injection. Similar delayed peak profiles were also seen for mTHPC administered intravenously to cats and hamsters, although these studies had very limited sampling over the first 24 h, making it difficult to obtain accurate pharmacokinetic information [2, 4, 5].

For further elucidation of the pharmacokinetics of mTHPC in humans we sampled plasma for 168 h after bolus i.v. injection, with extensive sampling during the first 24 h. The mean plasma drug levels for groups of 12–19 patients were near maximum immediately after injection and remained in steady state for at least 10 h. Closer examination of 118 plasma concentration-time points taken from 12 patients within the first 24 h, after injection of 0.1 mg/kg, revealed a similar delayed peak as described before [7], but with a less pronounced initial decrease immediately after injection. In our study these initial trough values were about 90% of the initial concentration, compared with initial trough values of 55% in the study of Glanzmann et al. [7]. It should be noted that in the previously reported study, mTHPC was dissolved in a mixture containing water (50% of total volume), whereas in our study the drug was already supplied as a solution in a mixture of 60/40% wt/wt propylene glycol/ethanol. The presence of water could affect drug aggregation and consequently its pharmacokinetics, as described below.

Several theories have been suggested to explain the delayed maximum plasma drug levels in humans. The drug could be sequestered in excretory organs like the liver or the kidneys immediately after injection and thereafter slowly released. Our data in human subjects are consistent with the formation of a drug depot after injection of mTHPC with subsequent release back into the circulation. The initial decrease and reappearance of the drug followed by near steady state levels would then be the consequence of equilibrium between drug clearance and the new supply from the putative depot. The duration of equilibrium was independent of the injected drug dose.

Several studies in mice and rats have shown that internal organs, such as the liver, kidneys, heart and lung retain high amounts of mTHPC for at least 2–5 days after injection [6, 9, 22]. Although the organ drug concentrations remained fairly constant for at least 2 days, this cannot be interpreted as evidence for drug depot formation, since plasma concentrations in these species did not show a plateau at early times after injection. Measurement of mTHPC concentrations in the internal organs of patients is rather difficult, therefore definitive proof for drug depot formation is lacking. Our pharmacokinetic analysis showed a distribution volume ranging from 5.5 to 8.5 l, which suggests that mTHPC is localized in or near the blood compartment, rather than in another deep tissue compartment in one of the organs. The photosensitizer however, does leave the plasma compartment, because increasing tissue levels have been reported, using spectroscopy [3], during the first 10 h in human skin and superficial tumors.

Another possible explanation for the observed plateau and delayed plasma peak is aggregation and precipitation of mTHPC directly after injection [8, 14, 19]. Drug aggregation in the vascular compartment could explain the apparent initial decrease in drug levels in the plasma, followed by increasing levels when mTHPC interacts with plasma proteins and disaggregates. The possibility of a vascular depot was supported by our clinical observations of discoloration of the vein in which the drug was injected (data not published). This occurred in several patients from 2 weeks up to 6 months after injection.

From experiments with human plasma spiked with mTHPC in vitro, it was postulated that the unusual pharmacokinetics of this drug could be the result of aggregation and binding to an unknown protein followed by redistribution to the lipoproteins [8]. Therefore, it was suggested that early plasma pharmacokinetics are a reflection of the plasma lipoprotein profile [9]. Since mice do not show a prolonged plateau phase after i.v. injection of mTHPC, a direct comparison of the distribution of mTHPC over plasma lipoproteins in humans and mice was made to test this hypothesis. The drug distribution in plasma obtained from patients and mice was very similar, with 50–80% of mTHPC bound to HDL and no change in relative distribution over time after injection. This is consistent with other published results, which show that hydrophobic photosensitizers like photofrin, mTHPC and BPD-MA, bind preferentially to HDL [1, 8, 11, 13, 15,]. The constant absolute amounts of mTHPC bound to each lipoprotein fraction during the plateau phase in humans, together with the lack of depletion of mTHPC in one of the fractions over time, suggests a continuous redistribution between the lipoproteins with replenishment from an unknown depot during the first hours after injection.

Although no significant differences were observed between humans and mouse in drug distribution over plasma proteins, there are major differences in the levels of plasma lipoproteins and cholesterol metabolism. The major cholesterol component of human plasma is LDL (3.9 ± 0.25 mmol/l), whereas mice generally have extremely low levels of LDL (0.2 ± 0.28 mmol/l). Therefore, we performed additional studies in ApoE −/− mice, with a lipoprotein profile more comparable with that of humans. The distribution of mTHPC in plasma of ApoE −/− mice with elevated LDL levels (5.73 ± 1.02 mmol/l) was markedly different, since most of the drug was bound to VLDL and LDL. However, this did not result in altered pharmacokinetic profiles for the drug and strongly suggests that binding of mTHPC to specific plasma protein fractions is not responsible for differences in pharmacokinetic profiles seen in mice and humans.

Rapid redistribution of mTHPC between the lipoproteins could mask the importance of one lipoprotein in particular. In cholesteryl transfer protein (CETP)-expressing animals, including humans, HDL cholesteryl esters can be transferred to other lipoproteins and subsequently metabolized via receptor mediated endocytosis. Mice lack CETP and their main clearance pathway for cholesteryl esters involves specific uptake via SR-BI at the liver, without metabolizing the HDL particle. Both mTHPC and cholesteryl esters are strongly hydrophobic and accumulate in the core of the HDL particle. We therefore examined the pharmacokinetics of mTHPC in mice deficient for SR-BI, to determine whether cholesterol metabolism influences the pharmacokinetics of mTHPC. Although at 1 h after injection plasma drug levels were significantly higher than that observed in nude mice ($P \leq 0.02$), the similar levels at other time points suggests that there is no substantial difference in clearance of mTHPC between SR-BI −/− and BALB/c nude mice. Therefore it is unlikely that mTHPC clearance is dependent of cholesterol metabolism.

In conclusion, we explored the role of mTHPC binding to lipoproteins in relation to drug disposition in an attempt to elucidate the difference in pharmacokinetic profiles seen between humans and mice. This study showed that neither drug distribution over the lipoproteins nor metabolism of lipoproteins influenced the plasma pharmacokinetics of mTHPC. The most likely explanation for the prolonged plateau in drug concentrations seen in human plasma over time after i.v. injection is the formation of a drug depot, possibly in the vascular compartment, immediately after i.v. injection. Clearly, rodents do not predict human pharmacokinetics as the long initial plateau in the concentration–time curve of mTHPC observed in humans is not seen in rodents.

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