Biopharmaceutics and Pharmacokinetics of 5-Phenyl-1,2-dithiole-3-thione Complexed with Sulfobutyl Ether-7-β-cyclodextrin in Rabbits

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Abstract ☐ The biopharmaceutics and pharmacokinetics of 5-phenyl-1,2-dithiole-3-thione (5PDTT) were investigated in rabbits, after administration as a complex with sulfobutyl-ether-7-β-cyclodextrin (SBE7-β-CD) by intravenous and oral routes and as a micronized powder by oral route. 5PDTT had a rapid and large red blood cell partitioning that was not dependent on drug concentration either in vitro or ex vivo. The blood clearance was very high (354 ± 131 mL/min) suggesting extrahepatic metabolism and/or nonrenal elimination and a significant volume of distribution (67 ± 76 L). The renal clearance was 0.17% of total clearance. 5-phenyl-1,2-dithiol-3-one (5PDTO) was identified as a metabolite in blood and urine. The bioavailability of 5PDTT following administration of 5PDTT/SBE7-β-CD complex was estimated to 41% while it was close to zero when 5PDTT was given as a micronized powder.

Introduction

Some chemical agents can inhibit carcinogenesis at different stages and could be used in cancer chemoprevention. Epidemiological studies suggest that consumption of cruciferous vegetables such as brussel sprouts, broccoli, or cabbage, which are probably sources of 1,2-dithiole-3-thiones,[1] results in decreased cancer risk in humans in various localizations.[2,3] In vitro and animal studies suggest that the cruciferous vegetables and 1,2-dithiole-3-thiones protect against carcinogens by an increase in the activities of electrophile detoxification Phase II enzymes, in conjunction with an increase of intracellular glutathione level.[4] The Phase II enzymes, such as glutathione-S-transferase and quinone reductase can conjugate potential carcinogens with glutathione favoring their elimination. Glutathione is a cellular thiol, which is very important for the cellular integrity by protection against free radicals, oxidants, and electrophilic intermediates of various compounds. Animals studies have shown an inhibition of experimental carcinogenesis in liver, bladder, breast colon, lung, and skin cancer after administration of dithiolethiones such as anetholtrithione and oltipraz.[5−7] On the basis of these data, dithiolethiones appear to be promising chemopreventive agents. 5PDTT was chosen among 1,2-dithiole-3-thiones because derivatives substituted on the carbon-5 by an aryl moiety have exhibited the most interesting antioxidant properties.[8,9] Furthermore, oltipraz and anetholtrithion, which are known for their cancer chemoprevention properties, are also substituted on the carbon-5 by such a moiety.

Biopharmaceutic and pharmacokinetic studies have only been conducted with two dithiolethiones: anetholtrithione used for its scialogogue and choleretic properties, and oltipraz which has been developed for its antischistosomal activity.[10] These studies have been conducted only after oral administration in animals[11] and in humans.[5,12−14]

The goal of the current work was to study the pharmacokinetics and biopharmaceutics of 5-phenyl-1,2-dithiole-3-thione (5PDTT) after administration by intravenous and oral routes in rabbits. To study this un-ionized and highly lipophilic compound (log $P = 3.67$, intrinsic solubility 0.48 mg/L),[15] we used sulfobutyl-ether-7-β-cyclodextrin (SBE7-β-CD) that has been shown to significantly increase 5PDTT aqueous solubility[16] (480 times the intrinsic solubility at a 10% SBE7-β-CD concentration).

Materials and Methods

Materials—5-Phenyl-1,2-dithiole-3-thione and 5-phenyl-1,2-dithiol-3-one were synthesized according to A. Thuillier and J. Vialle.[17] Their chemical structure is presented in Figure 1.

The sulfobutyl-ether-7-β-cyclodextrin was supplied by Cydex L. C. (Overland Park, KS). Heptane and acetonitrile (Merck, Darmstadt, FR, Germany), ethyl acetate (Carlo Erba Reagenti, Milano, Italy), and diethylene glycol monoethyl ether (Sigma Chemical, St Louis, MO) were of analytical grade.

Analytical Method—Analysis of 5PDTT and 5PDTO was carried out by a one-step extraction procedure. 5PDTT was quantified in plasma, blood, red blood cells, and urine samples, and 5PDTO was quantified in blood and urine.

One milliliter of biological sample (plasma, red blood cells, or blood) was extracted with 2 mL of a 80:20 (v/v) mixture of heptane and ethyl acetate. Extraction was performed by mixing for 5 min (horizontal shaker, model Agitelec SL 200). Then, the vials were centrifuged at 2000*g* for 5 min. The supernatant (≈1.5 mL) was poured into a polypropylene tube, containing 50 μL of a solution of diethylene glycol monoethyl ether (5 μL) and heptane-ethyl acetate (80:20, v/v, 45 μL). Diethylene glycol monoethyl ether (bp = 194 °C) was necessary to avoid the adsorption of 5PDTT and 5PDTO onto the polypropylene tubes. Then, the volatile organic phase was evaporated at room temperature under a nitrogen stream. The residue was diluted in acetonitrile (50 μL) and then stored at 4 °C until analysis.

For urine sample extraction, the volume of the samples was 5 mL, the extraction was performed by mixing for 15 min (rotary shaker Bioblock), and the vials were centrifuged at 4500*g* for 15 min.

The samples were analyzed using a HPLC system, consisting of a Waters Model 6000 A pump (Waters Assoc., Millford, MA) equipped with a Waters 717 Autosampler (Waters Assoc., Millford, MA), and a Delsi integrator, model Enica 21 (Delsi, Suresnes, France). Chromatography was performed using a Lichrospher RP-

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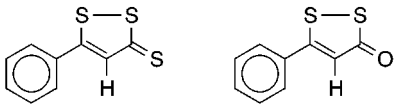

Figure 1—Chemical structure of 5-phenyl-1,2-dithiole-3-thione (left) and of 5-phenyl-1,2-dithiol-3-one (right).

SelectB column maintained at 30 °C (5 μm, 125 × 3 mm; Interchim, Montluçon, France) with a water−acetonitrile (50:50, v/v) mobile phase at a flow-rate of 0.5 mL/min.

The detection was set at 318 nm (λ_{max} of 5PDTT: 318 nm and λ_{max} of 5PDTO: 288 nm) using a Milton Roy model Spectromonitor 3100 (LDC Milton Roy, Riviera Beach, FL).

The yields of extraction of 5PDTT from whole blood and urine were 88.5 ± 2.6% and 91.0 ± 5.5%, respectively. The yields of extraction of 5PDTO from whole blood and urine were 95.5 ± 1.5% and 94.6 ± 8.3%, respectively. The selectivity factor (α) for the separation of 5PDTT and 5PDTO was 1.6. The linearity was established for concentrations up to 1000 ng/mL. The limits of quantification of 5PDTT and 5PDTO in blood were 1.3 ng/mL and 2.4 ng/mL, respectively. The limits of quantification of 5PDTT and 5PDTO in urine were 0.3 ng/mL and 0.5 ng/mL, respectively. The within-day reproducibilities, checked at a blood concentration of 200 ng/mL, were 7.8% and 4.5% for 5PDTT and 5PDTO, respectively. The within-day reproducibilities, checked at a urine concentration of 20 ng/mL, were 5.6% and 6.6% for 5PDTT and 5PDTO, respectively.

Red Blood Cell Partitioning—Red blood cell (RBC) partitioning of 5PDTT was evaluated in vitro and ex vivo in rabbits. In the in vitro experiment, the kinetics of partitioning (incubation time of 1, 5, 15, and 30 min at a blood concentration of 500 ng/mL, n = 3) and the influence of the 5PDTT concentration (blood concentration of 200, 500, and 1000 ng/mL at the incubation time of 30 min, n = 2) were investigated at 37 °C. A 30 mL blood sample maintained under gentle agitation was spiked with 20 μL of a solution of 5PDTT/SBE7-β-CD complex.

In the ex vivo experiment, the influence of 5PDTT concentration on the RBCs partitioning was checked in blood samples drawn at 1, 5, 15, and 30 min following an iv administration of a solution of 5PDTT/SBE7-β-CD complex (2 mg in 10 mL).

Blood samples (2 mL) were immediately centrifuged (9800 g for 1 min), and RBCs were lysed by freezing at −20 °C. 5PDTT concentrations in RBCs and plasma were determined as described above.

The extent of RBCs partitioning ($K_{e/p}$) was determined according to Hinderling[18] as follows:

$$K_{e/p} = C_e/C_p$$

where C_e and C_p are the concentration in the RBCs and plasma, respectively.

The whole blood-to-plasma concentration ratio ($K_{b/p}$) represents an additional drug distribution parameter of interest depending on the hematocrit (H_c). $K_{b/p}$ was determined according to Hinderling[18] as follows:

$$K_{b/p} = K_{e/p} \cdot H_c + (1 - H_c)$$

Study Formulations—*Pure Drug*—5PDTT was micronized using a rotomill SRM 100 apparatus (Beckman, Nyon, Switzerland). The mean diameter, expressed by D[4,3] (Mastersizer, Malvern, Orsay, France), was 29 μm. 5PDTT was administered as a capsule containing 20 mg of the drug.

Inclusion Complex—An ethanolic solution of 5PDTT (20 mg in 10 mL) was diluted in an aqueous solution of SBE7-β-CD (11.88 g in 80 mL) to obtain a 1/10 molar ratio and a final ethanol concentration of 25%. The resulting solution was concentrated under vacuum at 60 °C using a rotavapor apparatus until elimination of ethanol. The solution was then diluted with water to obtain a 5PDTT concentration of 1 mg/mL and 0.2 mg/mL for oral and iv dosing, respectively. The solutions were checked for 5PDTT concentration by HPLC and stored protected from light at ambient temperature.

Experimental Protocol—New Zealand adult males rabbits (n = 15, mean weight 3.2 kg) were housed individually in standard cages, and were provided free access to food and water. They were fasted 12 h before each experiment. The study was approved by the Local Committee of Laboratory Animal Care in accordance with the rules and guidelines concerning the care and use of laboratory animals.

Six rabbits received 5PDTT as a complex at a dose of 2 mg (10 mL) as an iv bolus injection via the marginal ear vein. Blood samples (1.5 mL) were collected from the controlateral marginal ear vein before drug administration and at 0.5, 1, 2, 5,10,15, 20, 30, 60, 90, 120, 180, 240, 300, 360, 420, and 480 min. The samples were immediately frozen at −20 °C.

Six rabbits received 5PDTT as a complex at a dose of 20 mg (20 mL) by oral route with a gastric catheter which was subsequently flushed with water (10 mL). Three rabbits received 5PDTT as a capsule of pure drug (20 mg) and then received water (30 mL) with a syringe. Blood samples were collected before drug administration and at 15, 25, 30, 40, 45, 60, 90, 120, 180, 240, 300, 360, 420, and 480 min. The samples were immediately frozen at −20 °C.

To obtain a regular urine flow throughout the experiments, the rabbits were hydrated by a sc infusion of normal saline (250 mL over 30 min) the day before and within the hour preceding the drug administration. During the study, the animals received iterative iv infusions 20% mannitol (20 mL/h for the first hour and then for 30 min every 2 h) and normal saline (60 mL/h between the administration of mannitol). Urine was collected by miction. Samples (5 mL) were kept frozen until analysis.

Pharmacokinetic Analysis—After iv dosing, a model with two-exponential or three-exponential functions and first-order elimination from the central compartment was fitted to the individual 5PDTT blood concentrations, using weighted nonlinear least-squares regression analysis with the reciprocal of squared concentration as a weighting factor (WinNonlin version 1.5, Scientific Consulting Inc., Apex, NC). The choice between the models was judged by the distribution of residuals and comparison of the sum of squared deviations.[19] Standard methods were used to calculate the following parameters: total body clearance (CL), renal clearance (CL_r), apparent volume of distribution of the central compartment (V_c), apparent volume of distribution at steady-state (V_{ss}), distribution rate constants (K_{12}, K_{13}, K_{21}, and K_{31}), elimination rate constant (K_{10}), and apparent distribution and elimination half-lives ($t_{1/2}\,\alpha$, $t_{1/2}\,\beta$, and $t_{1/2}\,\gamma$). The extrapolated area was calculated as the ratio of the last measured whole blood concentration (C_{last}) and the slope of the terminal phase.

After oral dosing, individual 5PDTT and 5PDTO blood concentration data were analyzed using noncompartmental analysis assuming a first-order elimination from the central compartment with the software package WinNonlin. Peak plasma concentration (C_{max}) and corresponding time to peak concentration (T_{max}) were derived from raw data. The area under the whole blood curve from zero to the last sampling point (AUC_{0-last}) and from zero to infinity (AU_{0-inf}) were calculated by linear trapezoidal method from experimental data. The extrapolated area was calculated as the ratio of the last measured whole blood concentration (C_{last}) and the slope of the terminal phase. Standard methods were used to calculate the following parameters for 5PDTT: total body clearance (CL/F), renal clearance (CL_r/F), apparent volume of distribution at pseudodistribution equilibrium (V_z/F), and apparent elimination half-lives ($t_{1/2}\,\lambda z$). Pharmacokinetic parameters were corrected by the average bioavailability (F).

Q_u is the cumulative amount of 5PDTT or 5PDTO recovered in urine during 480 min.

The average absolute bioavailability of 5PDTT (F) was determined according to: F = (mean $AUC_{0-inf(oral)}$/oral dose)/(mean $AUC_{0-inf(iv)}$/iv dose).

Statistical Analysis—All data are presented as the mean ±SD Student's t-test was used to compare individual means. A p value less than 0.05 was considered as statistically significant.

Results and Discussion

Red Blood Cell Partitioning—Most pharmacokinetic studies are derived from drug concentrations measured in plasma or in serum. To investigate 5PDTT pharmacokinetics, quantitation in whole blood has to be considered owing to the high lipophilicity of the drug.[15] Among the cellular constituents of blood, RBCs represent the largest population and drugs may bind to their membrane, to

Table 1—In Vitro and Ex Vivo Red Blood Cell Partitioning of 5PDTT[a]

	theoretical C_b (ng/mL)	duration of incubation (min)	H_c (%)	C_b (ng/mL)	C_e (ng/mL)	C_p (ng/mL)	$K_{e/p}$	$K_{b/p}$
				In Vitro Experiment				
($n = 3$)	500	30	38	512 ± 17	642 ± 30	431 ± 42	1.5 ± 0.2	1.2 ± 0.1
	200	30	35	175	266	126	2.1	1.4
	500	1	35	455	578	389	1.5	1.2
	500	5	35	462	632	369	1.7	1.3
($n = 2$)	500	15	35	482	592	422	1.4	1.1
	500	30	35	509	609	455	1.3	1.1
	1000	30	35	941	1279	759	1.7	1.4
				Ex Vivo Experiment				
	nd	1	35	1136	1380	974	2.1	1.4
	nd	5	35	332	389	301	1.5	1.2
($n = 2$)	nd	15	35	157	220	123	1.7	1.3
	nd	30	35	92	128	73	1.4	1.1

[a] n = no. of experiments.

hemoglobin, and to proteins in the cytosol. The determination of concentrations in whole blood or erythrocytes rather than in plasma should be more suitable for studying the drug disposition of lipophilic drugs that usually have a high hepatic extraction (flow-rate-limited clearance). Moreover, in case of a significant RBC distribution, measuring blood concentrations increases the sensitivity of an analytical method allowing a follow-up of the drug elimination for at least one additional half-life.[18]

The results of the in vitro and ex vivo experiments are presented in Table 1. The extent of RBC partitioning of 5PDTT, estimated by $K_{e/p}$ and $K_{b/p}$, was significant (around 50% of the drug in the RBCs). The RBC partitioning was not dependent on the concentration ex vivo in a blood concentration range from 92 to 1136 ng/mL and in vitro in a blood concentration range from 200 to 1000 ng/mL. The distribution equilibrium was obtained rapidly, 95% of the maximum RBC concentration being reached in 1 min in the in vitro experiment. The high lipophilicity of 5PDTT may account for this rapid distribution in RBCs. On the basis of these data, we choose to study the blood pharmacokinetics of this lipophilic compound.

Although RBCs contain drug-metabolizing enzymes,[20] 5PDTT was not apparently metabolized in vitro in RBCs since the recovery of the drug in RBCs and in plasma aliquots were close to the initial blood loading. Moreover, 5-phenyl-1,2-dithiol-3-one (5PDTO), which is a metabolite of 5PDTT measured in plasma and urine, was not detected in the in vitro experiments.

Biopharmaceutics and Pharmacokinetics—The mean concentration−time profiles of blood 5PDTT and 5PDTO in rabbits following iv and oral dosing of 5PDTT are presented in Figure 2. The pharmacokinetic parameters of 5PDTT after iv and oral dosing are listed in Tables 2 and 3, respectively.

The 5PDTT blood concentration−time curves following iv administration were best described using a tricompartmental model. The extrapolated area averaged 7.2 ± 5.4% indicating that the sampling schedule was suitable.

Due to its high lipophilicity and significant RBC partitioning, 5PDTT was expected to have a high tissue distribution. The volume of distribution (V_{ss}(iv)) was high, suggesting a large distribution. However, the volume of distribution was highly variable compared to other pharmacokinetic parameters. Considering the respective values of the distribution rate constants (K_{12} plus K_{13}) compared to the elimination rate constant (K_{10}), 5PDTT has, from a statistical point of view, more chance to be distributed in tissues than to be eliminated, even though the systemic clearance of 5PDTT was high. The tissue affinity of 5PDTT

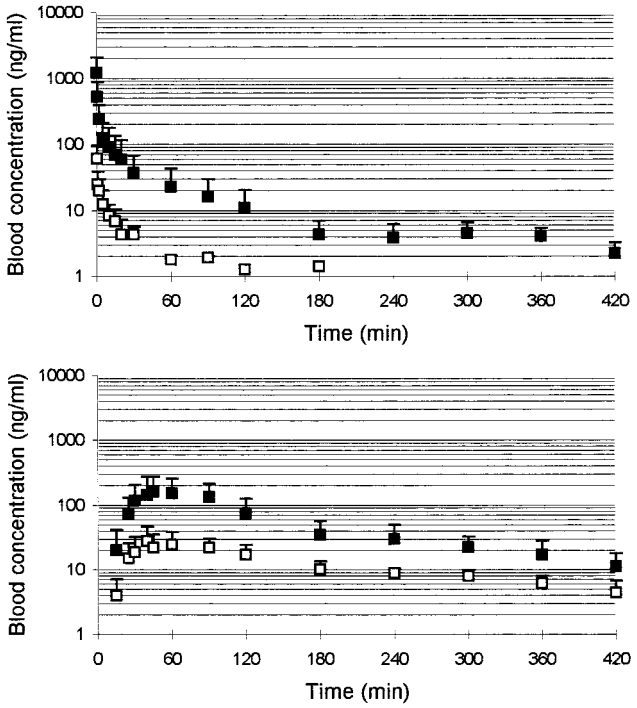

Figure 2—Mean (±SD) whole blood concentrations of 5PDTT and 5PDTO after administration of 5PDTT as a complex with SBE7-β-CD at a dose of 2 mg by intravenous route (top) and at a dose of 20 mg by oral route (bottom) in rabbits. 5PDTT (filled square); 5PDTO (empty square).

can be illustrated by the rapid distribution half-lives. Moreover, the values of the redistribution rate constants (K_{21} and K_{31}) were on average five to six times lower than the corresponding distribution rate constants (K_{12} and K_{13}), also suggesting the affinity of 5PDTT for tissue components. It should be noticed that a very slow redistribution back into the central compartment cannot be ruled out. However, the LOQ of our assay precluded such investigation.

The total blood clearance was three times higher than the hepatic blood flow described in rabbits (around 120 mL/min),[21] suggesting a significant extrahepatic metabolism and/or extrarenal excretion. However, the omission of a very slow redistribution might have led to an underestimation the AUC, leading to an overestimation of the clearance. Considering this assumption, a terminal half-life of around 35 h will lead to a clearance close to the liver blood flow.

The contribution of the renal clearance to the overall clearance was very low, 0.2% of the administered dose

Table 2—Pharmacokinetic Parameters of 5PDTT after Intravenous Administration as a Complex with SBE7-β-CD at a Dose of 2 mg in Rabbits

	$AUC_{0-inf(iv)}$ (ng·min/mL)	CL (mL/min)	Q_u (μg)	CL_r (mL/min)	V_c (L)	V_{ss} (L)	K_{12} (min^{-1})	K_{21} (min^{-1})	K_{13} (min^{-1})	K_{31} (min^{-1})	K_{10} (min^{-1})	$T_{1/2}$ α (min)	$T_{1/2}$ β (min)	$T_{1/2}$ γ (min)
R1	3834	522	3.3	0.9	5.5	200	0.414	0.185	0.106	0.032	0.095	0.9	13.6	472
R2	4899	408	0.4	0.1	0.3	8	1.030	0.162	0.305	0.017	1.230	0.3	7.2	51
R3	5915	338	1.8	0.3	1.5	50	1.195	0.209	0.264	0.210	0.228	0.4	11.5	165
R4	4867	411	4.3	0.9	1.1	11.4	0.586	0.169	0.635	0.006	0.386	0.4	6.6	301
R5	15123	132	8.1	0.5	0.3	5	1.020	0.246	0.428	0.048	0.393	0.4	5.7	36
R6	6437	311	5.0	0.8	0.7	26	1.671	0.184	0.351	0.013	0.440	0.3	11.4	102
mean	6846	354	3.8	0.6	1.6	67	0.986	0.193	0.348	0.054	0.462	0.4	9.3	188
SD	4155	131	2.7	0.3	2.0	76	0.448	0.031	0.177	0.078	0.398	0.2	3.2	169

Table 3—Biopharmaceutic and Pharmacokinetic Parameters of 5PDTT after Oral Administration as a Complex with SBE7-β-CD at a Dose of 20 mg in Rabbits

	C_{max} (ng/mL)	T_{max} (min)	$AUC_{0-inf(po)}$ (ng·min/mL)	CL (mL/min)	Q_u (μg)	CL_r (mL/min)	V_z (L)	$T_{1/2}$ λ-z (min)
R7	200	45	17586	466	9.3	0.2	177	263
R8	46	90	7153	1146	10.2	0.6	255	154
R9	119	90	33703	243	16.1	0.2	236	672
R10	299	60	39026	210	15.2	0.2	51	169
R11	261	60	46164	177	26.6	0.2	42	163
R12	333	40	25114	326	114.3	1.9	57	122
mean	210	64	28124	428	31.9	0.5	136	257
SD	110	22	14390	367	40.8	0.7	98	209

being excreted in urine. The high RBC partitioning may account for such a low contribution. A low renal excretion (less than 1% of the dose) has also been shown for oltipraz after oral administration in mouse, rat, monkey, and humans.[11,14]

The use of cyclodextrins to solubilize drug administered by the iv route raises the problem of a potential alteration of the drug pharmacokinetics by an incomplete or a delayed release of the drug from the cyclodextrin.[22] This problem should be considered for 5PDTT given the magnitude of the stability constant obtained with SBE7-β-CD (10 705 M^{-1}).[16] The answer to this problem would be given by a comparative pharmacokinetic study of the drug with a control formulation providing that the excipient(s) used (e.g., organic solvent, surfactant in case of lipophilic drugs) are themselves devoid of any effect on drug kinetics. The influence of complexation on 5PDTT pharmacokinetics cannot be ruled out in the current study since we did not compare the drug disposition to that obtained with a control formulation. However, 5PDTT can be expected to be quickly released from its complex as a result of (i) the dilution of the study formulation in the blood circulation, (ii) the rapid and significant distribution of 5PDTT in RBCs, and (iii) the extensive distribution of 5PDTT that further dilutes the complex. Furthermore, competitive displacement of the drug from its complex by lipophilic plasma components may also favor the drug release. Moreover, in an in vitro study comparing the RBC partitioning from a solution of SBE7-β-CD complex to that of obtained from an ethanol−DMSO solution of 5PDTT, it appeared that the RBC partitioning were similar. The RBC and plasma concentrations of 5PDTT (687 ± 11 ng/mL and 374 ± 31 ng/mL, respectively) were close to those obtained with the SBE7-β-CD complex (Table 1), suggesting that the complexation between 5PDTT and SBE7-β-CD was not a limiting factor for 5PDTT partitioning and should not be a limiting factor for 5PDTT disposition.

5PDTO was identified as a metabolite of 5PDTT. The urinary excretion of this metabolite represented around 0.025% of the dose of 5PDTT administered. A metabolic investigation is in progress to identify other metabolites, the structures of which are not so far determined. Following iv administration of 5PDTT, it was not possible to delineate the metabolite kinetics since 5PDTO blood concentrations were below the LOQ in five of the six animals after 90 min postdosing. However, following oral administration, 5PDTO blood concentrations were measured until 420 min with a C_{max} (209 ± 110 ng/mL) and a T_{max} (64 ± 22 min) being close to those of the parent drug. The apparent terminal elimination half-life of 5PDTO ($T_{1/2}$ λ-z = 190 ± 89 min) was close to that of 5PDTT, suggesting a formation rate-limited metabolite kinetics.

Given that dithiolethiones have a chemopreventive potential against solid tumors,[7] a more precise investigation of the distribution of 5PDTT should be performed to specify if the drug has a selective distribution in particular organs and tissues. In this respect, the evaluation of the distribution in the colon, breast, skin, bladder, and lung should be investigated. In an autoradiographic study in mice, ^{14}C-anetholtrithione given orally displayed high concentrations in intestine, liver, gall-bladder, kidney, and urinary bladder.[23] The study of the organ and tissue distribution of ^{14}C-oltipraz orally administered in mice showed that, during the 6 h postdosing, the highest levels were found, in a decreasing order, in stomach and intestine contents, in gall-bladder, in bladder, and at a lower level in brown fat, liver, and kidney.[11]

Individual concentration−time profiles of complex 5PDTT-SBE7-β-CD following oral dosing displayed a distribution-nose, indicating the multicompartmental pharmacokinetic pattern of 5PDTT. However, concentration−time profiles could not be suitably fitted according to a pharmacokinetic model so that a noncompartmental analysis was performed. With the exception of one animal, whose concentration−time profile was rather unusual and displayed some scattering, the extrapolated area averages 10.3 ± 3.0%, indicating that the sampling schedule was suitable. T_{max} was much smaller and less variable that described for oltipraz in humans[13] (mean 2.8 h, range: 0.5 to 8 h). Following oral administration, the volume of distribution (V_z/F) also indicated a large distribution but the difference was less pronounced than after bolus regimen. The apparent elimination half-life of 5PDTT was slightly higher than that observed following iv dosing ($p = 0.54$) and lower than

that described for oltipraz in humans (4.2 to 11.1 h with increase in dose). The contribution of the renal clearance to the overall clearance of oral 5PDTT was very low, 0.16% of the administered dose being recovered in urine.

In two of three rabbits receiving 5PDTT as a micronized powder, 5PDTT was not detectable during the study period (until 8 h). In the third animal, 5PDTT was detected only at 7 h (100 ng/mL). These data suggest that the absorption of 5PDTT given as a powder did not occur, highlighting the need of a particular oral formulation for such lipophilic drugs. The optimization of the formulation of the complex between 5PDTT and SBE7-β-CD is currently in progress in order to reduce the amount of cyclodextrin (11.88 g of cyclodextrin by 20 mg of 5PDTT in the formulation studied) and to obtain a solid-state complex.[16]

Biopharmaceutic data on dithiolethiones are scarce and have only be obtained for oltipraz following oral dosing in animals[11] and humans.[5,12−14] These studies have shown that the pharmacokinetics of oltipraz was dose-dependent, suggesting a increased oral bioavailability with increasing doses that may result from a saturable first-pass effect.[5,10,11] Since 5PDTT was not administered by iv and oral routes in the same animals, the oral bioavailability could not be determined individually. The average absolute oral bioavailability of 5PDTT complexed with SBE7-β-CD was estimated to 41% while its was close to zero when administered as a micronized powder.

The current study has shown that 5PDTT had a rapid and significant red blood cell partitioning. After administration by intravenous and oral routes in rabbits, 5PDTT had a very high clearance, suggesting extrahepatic metabolism and/or nonrenal elimination, and a large volume of distribution. 5PDTO was identified as a metabolite of 5PDTT in plasma and urine. The bioavailability of 5PDTT after administration as complex 5PDTT/SBE7-β-CD was estimated to 41% while it was close to zero when it was given as a micronized powder.

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