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ORIGINAL ARTICLE

Pharmacokinetics of liposomal curcumin (Lipocurc™) infusion: effect of co-medication in cancer patients and comparison with healthy individuals

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Abstract

Purpose Investigation of the impact of co-medication on the plasma levels of curcumin and tetrahydrocurcumin (THC) in cancer patients and a comparison of the pharmacokinetics of curcumin and plasma levels of THC between cancer patients and healthy individuals following intravenous infusion of Lipocurc™ (liposomal curcumin).

Methods Correlation analysis was used to determine the impact of co-medication on infusion rate normalized plasma levels of curcumin and THC in cancer patients and to compare the plasma levels of curcumin and THC at different infusion rates between cancer patients and healthy individuals. In vitro hepatocyte and red blood cell distribution experiments were conducted with Lipocurc™ to support clinical findings. Plasma concentration time data were analyzed by the non-compartmental method to determine and compare the pharmacokinetic parameters of curcumin in cancer patients and healthy individuals.

Results Of 44 co-medications studied, three medications targeting the renin–angiotensin system, Lisinopril, Ramipril, and Valsartan elevated plasma levels of curcumin and THC in three cancer patients infused with Lipocurc™. Cell distribution experiments indicated that the disposition of curcumin in red blood cells may be a target for elevation of the plasma levels of curcumin. Plasma levels of curcumin in cancer patients increased to a greater extent with increased infusion rate compared to healthy individuals. Upon termination of infusion, the elimination phase for curcumin was shorter with a shorter terminal half-life and smaller volume of distribution for curcumin in cancer patients compared to healthy individuals.

Conclusion Either co-medications or health status, or both, can impact the pharmacokinetics of curcumin infusion (as Lipocurc™) in cancer patients.

Keywords Curcumin · Tetrahydrocurcumin · Pharmacokinetics · Co-medications · Cancer patients

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Introduction

The anticancer properties of curcumin (diferuloylmethane) (Fig. 1) are being extensively investigated with several studies indicating its potential for therapeutic benefit. Clinical studies [1–8] have indicated that curcumin has significant, but limited, anticancer activity following oral administration. This is a consequence of the limited solubility of curcumin, sensitivity to gut metabolism via the reductase pathway [6, 9], and chemical instability in aqueous medium at higher pH [9–13]. Upon intravenous administration, curcumin is rapidly metabolized by reductases to the major metabolite tetrahydrocurcumin (THC) and hexahydrocurcumin [13, 14] resulting in short plasma half-lives ranging from 6 to 42 min [15–19]. Hepatic metabolism is a key pharmacological deactivation step [13, 14] that contributes to the rapid elimination of curcumin. More recently, however, red blood cells have been shown to metabolize curcumin to THC in a species and pharmacokinetically relevant manner [20], providing additional pathways for the rapid elimination of curcumin from the blood. Thus, the routes available for elimination of curcumin from the plasma are numerous, increasing the potential for interactions between co-medications and curcumin.

Nanocurcumin preparations have provided an improved bioavailability for curcumin [16, 21, 22] and offer potentially better treatment outcomes in cancer patients. One such promising nanocurcumin formulation, Lipocurc™ (liposomal curcumin for infusion) has been shown to suppress pancreatic tumor growth in a mouse xenograft model [22]. Meriva®, a patented nanocurcumin formulation, decreased absolute lymphocyte count in a subset of lymphocytic leukemia patients accompanied by an increase in CD4 and CD8 T-lymphocytes and NK cells [21].

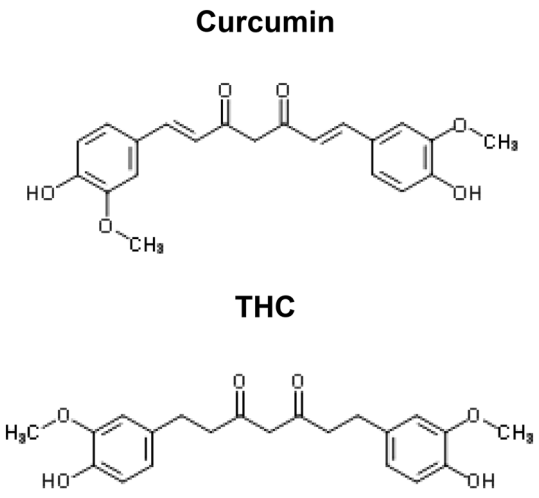

Fig. 1 Chemical structures of curcumin and tetrahydrocurcumin (THC)

Given the rapid systemic elimination of curcumin following intravenous administration, it was of interest to assess whether or not the pharmacokinetics of curcumin were altered in cancer patients who had received five prior lines of therapy and were on co-medication compared to healthy individuals. We now report that in a Phase Ib study of Lipocurc™ in cancer patients, several patients taking angiotensin converting enzyme inhibitors (ACEI) and an angiotensin II antagonist had considerably higher plasma levels of curcumin and THC during infusion compared to other patients. We have followed up on these observations by evaluating the impact of co-medication on the plasma levels of curcumin and THC and examined the effect of ACEI on the distribution of curcumin and metabolism to THC in red blood cells and hepatocytes. In addition, the pharmacokinetics of curcumin and the plasma exposure to THC were compared between cancer patients and healthy individuals.

Materials and methods

Study materials

Lipocurc™ liposomal curcumin for intravenous administration was obtained from Polymun Scientific (Klosterneuburg, Austria). Lipocurc™ contained curcumin 6.0 mg/mL, DMPC (14:0–1,2-dimyristoyl-sn-glycero-3-phosphocholine) 72 mg/mL and DMPG (14:0–1,2-dimyristoyl-sn-glycero-3-phosphorylglycerol) 8.0 mg/mL. Lipocurc™ was stored frozen at − 10 to − 25 °C and protected from light. Ramipril and its metabolite, Ramiprilat, were obtained from Toronto Research Chemicals (Toronto, Ontario, Canada) and were stored, protected from light at − 10 to − 25 °C. Freshly isolated and washed human and Beagle dog red blood cells were obtained as previously described [20]. Cryopreserved hepatocytes obtained from Sekisui XenoTech, LLC (Kansas City, KS, USA) were used for these studies. Dog hepatocytes were obtained from male Beagle dogs. The minimum yield per vial was set at 3.5×10^6 cells with a reported viability of 81.4% upon thawing. Human hepatocytes were obtained from a male donor, who died of anoxia. The minimum yield per vial was 6.0×10^6 cells with a reported viability of 82.8% upon thawing. Hepatocytes were thawed and prepared according to the manufacturer's instructions prior to use.

Clinical studies with Lipocurc™, isolation of plasma samples and bioanalysis

Details concerning the design of the phase 1 and phase 1b clinical studies in healthy individuals and cancer patients, respectively, and collection and treatment of plasma samples are published elsewhere [19, 23]. Plasma samples were analyzed using a liquid chromatographic-tandem mass

spectrometric method developed and validated at Nucro-Technics for the determination of curcumin and THC as described previously [19, 20, 24]. Concentrations of curcumin and THC above the limit of detection were reported and used to conduct pharmacokinetic analyses.

Cell uptake of curcumin

The uptake of curcumin into red blood cells and hepatocytes in the presence and absence of a 50:50 mixture of Ramipril and Ramiprilat was investigated using methods previously described [20]. Either vehicle or the mixture of Ramipril (50 µM) and Ramiprilat (50 µM) was incubated with cells at 37 °C for 3 min prior to exposure to curcumin (in the form of Lipocurc™) and incubation for a further 15 min at 37 °C.

Data analysis and statistics

Analysis of the plasma concentration–time curves for the derivation of the pharmacokinetic parameters was performed using a non-compartmental analysis and selecting the infusion model of Phoenix WinNonlin validated Professional Software (v6.3, Certara, Princeton, NJ, USA). Plasma levels of curcumin and THC above the limit of detection were employed for the analysis. Clearance during infusion (CDI) was calculated according to the equation:

$$\text{CDI (mL/kg/h)} = [\text{Infusion rate (ng/kg/h)}] \,/\, [\text{Plasma concentration at steady} - \text{state (ng/mL)}].$$

$$\text{Infusion rate (ng/kg/h)} = [\text{Dose (mg/m}^2 \times 1{,}000{,}000) \,/\, 37] \,/\, [\text{Time of Infusion (h)}],$$

where 37 is the factor to convert the dose in weight/m^2 to weight/kg in humans. CDI was converted to L/kg/h by multiplying the CDI (mL/kg/min) by a factor of 1/1000.

Data are presented as the group mean ± the standard deviation (SD). For the purpose of statistics, all statistical tests were performed using SigmaStat (v 3.5, Systat Software Inc., San Jose, CA, USA). Two group comparisons were performed using a Student's *t* test. Multiple group comparisons were performed using a One-Way analysis of variance with a Student Newman Keul's post hoc analysis. In either case, group differences were deemed statistically significant if they attained the $p < 0.05$ level of significance.

Results

Cancer patient and healthy individual clinical data

Details concerning the co-medications that cancer patients were taking and their clinical chemistry and hematology profiles were kindly provided by Dr. Brigitta Vcelar. An alphabetic list of the co-medications taken by cancer patients that might possibly interfere with disposition of curcumin in the liver is presented in Table 1.

Plasma levels of curcumin and THC in relationship to concurrent drug administration

The number of medications taken by patients infused with Lipocurc™ were compared with the maximal plasma levels of either curcumin or THC normalized to infusion rate for curcumin due to the different times used for infusion. For cancer patients #'s 2–6, 8 and 9–16, only 2 h during infusion blood samples were taken and the plasma concentrations of curcumin and THC were assumed to represent the maximum during infusion. The comparison is shown in Fig. 2. For the majority of patients, the number of co-medications did not produce major alterations of the normalized plasma levels

Table 1 Alphabetical list of medications taken by cancer patients in the phase 1b clinical trial and considered to possibly interfere with the pharmacokinetics of curcumin

Alprazolam	Dexamethasone	Lisinopril	Pramipexol
Amitryptyline	Dexibuprofen	Lorazepam	Progesterone
AmLodipine	Diazepam	Medroxyprogesterone	Ramipril
Atorvastatin	Diclofenac	Metformin	Risperidone
Benserazide	Dihydrocodeine	Metoclopramide	Rinatidine
Candesartan cilexetil	Escitalopram	Mitazepine	Tamsulosin
Ciprofloxacin	Fentanyl	Morphine	Tazobactam
Citalopram	Furosemide	Nebivolol	Theophylline
Cefuroxime	Glimepiride	Nitrofurantoin	Triazolam
Dronabinol	Hydromorphone	Oxazepam	Valsartan
Durotiv	Levodopa	Pantoprazole	Venlafaxin

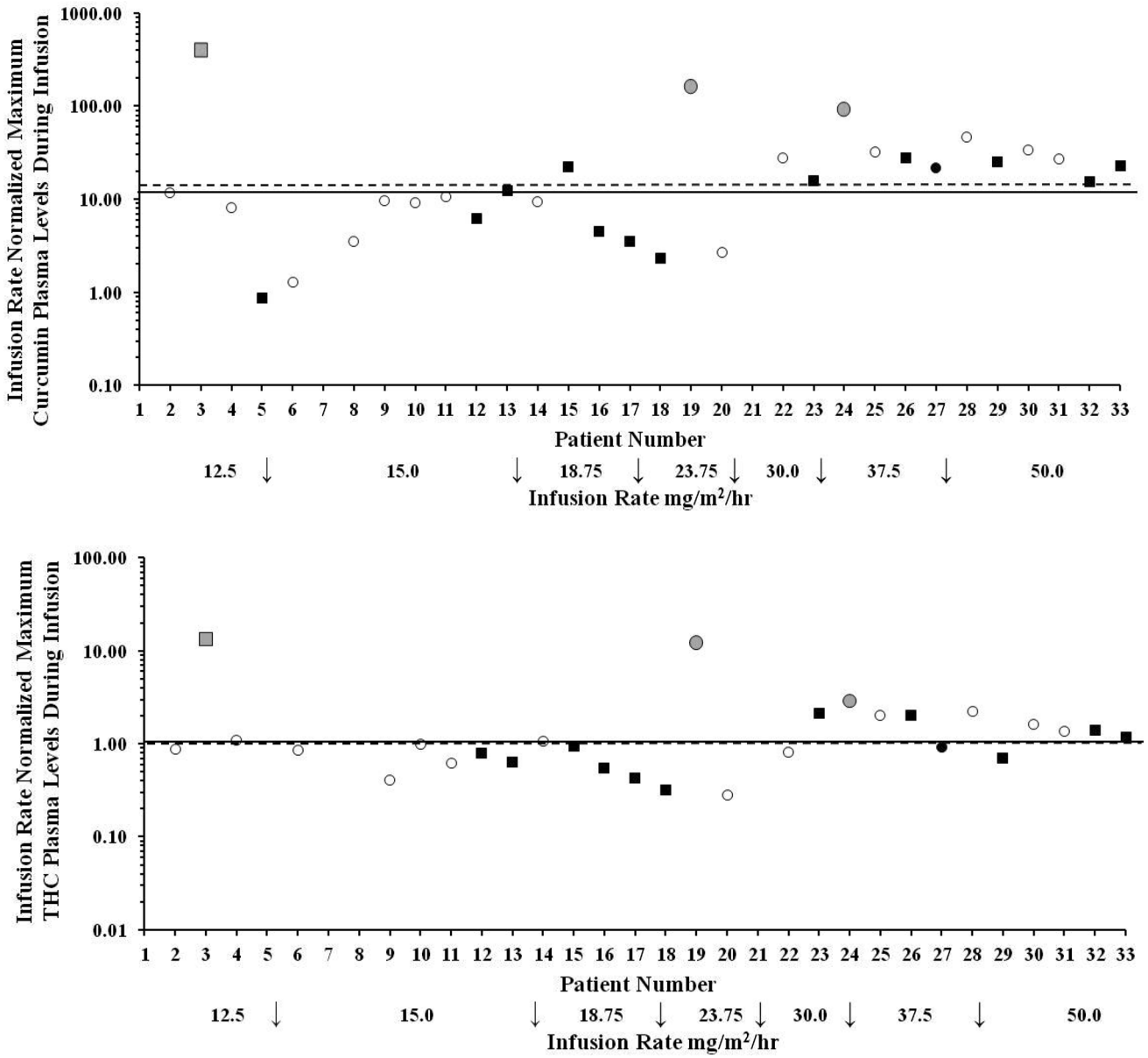

Fig. 2 Relationship between the number of medications used by cancer patients and infusion rate normalized maximum plasma levels of curcumin and THC. Patient number versus infusion rate normalized maximum plasma levels of curcumin and THC are presented. Symbols represent the following number of medications taken by the patients and listed in Table 1: open circles and larger grey shaded circles, patients taking less than or equal to 5 medications; closed black and larger grey shaded squares, patients taking greater than 5 but less than or equal to 10 medications; closed black circles, patients taking greater than 10 medications. Larger grey shaded symbols, patients taking in addition to other medications, medications acting on the renin–angiotensin system. Maximum rate normalized plasma levels of curcumin (ng/mL)/(mg/m^2/h) during infusion were 397, 164 and 93 for patients, #'s 3, 19 and 24, respectively, compared to 15 ± 12 for all other patients. Maximum normalized plasma levels of THC (ng/mL)/(mg/m^2/h) during infusion were 13.4, 12.3, and 2.9 for patients, #'s 3, 19 and 24, respectively, compared to 1.0 ± 0.5 for all other patients

of curcumin even as the infusion rate increased and normalized plasma levels of curcumin rose at higher infusion rates. Plasma levels of THC displayed a similar pattern. For three cancer patients #3, #19 and #24, normalized plasma curcumin levels were much higher compared to other patients (Table 2); a similar pattern of higher normalized plasma levels of THC was also observed for these three patients. After consideration of clinical chemistry and hematological parameters, the difference for these three patients was related to use of co-medications that targeted the renin–angiotensin system. Patient #3 was taking the ACEI Lisinopril at a dose of 30 mg, once per day, patient #19 was taking the ACEI

Table 2 Mean and individual 2 h and maximum plasma levels of curcumin and THC during infusion of Lipocurc™ in cancer patients and healthy individuals

Patient or subject #	Infusion rate (mg/m^2/h)	Mean 2 h plasma levels of curcumin (ng/mL)	Mean C_{max} curcumin (ng/mL)	Mean 2 h plasma levels of THC (ng/mL)	Mean C_{max} THC (ng/mL)
Cancer patients					
8 h infusion					
2, 4, 5	12.5	87 ± 70	ND	10 (4)	ND
3[a]		4960	ND	168	ND
6, 8, 9–12, 13	15	101 ± 60	ND	10 (4)	ND
14–16, 17	18.75	175 ± 168	ND	14 (6)	ND
18, 20	23.75	54 ± 1	60 (6)	7 (1)	7 (1)
19[b]		414	3885	123	396
21–23	30	324 ± 17	476 (344)	34 (26)	36 (24)
24[c]	37.5	3484	3484	108	108
25–27		587 ± 128	1026 (199)	60 (19)	63 (21)
6 h infusion					
28–33	50	1198 (318)	1484 (540)	66 (29)	70 (25)
Healthy individuals, 2 h infusion					
6–8	10	87 (70)	97 (61)	4 (3)	9 (1)
10–12	20	237 (75)	317 (13)	12 (5)	13 (3)
13,15,16	40	425 (125)	775 (360)	30 (14)	30 (12)
17,18,20	60	618 (125)	1235 (813)	65 (27)	107 (21)
21, 23–27, 29	90	1091 (344)	1697 (661)	73 (23)	109 (32)
30–34, 42, 43	120	1268 (507)	1355 (382)	98 (41)	107 (37)
35–38	160	2170 (745)	2578 (453)	147 (43)	159 (39)

Values are presented ± SD of the number of subjects or patients shown

ND not determined

[a]Patient on a full dose of the angiotensinogen converting enzyme inhibitor lisinopril

[b]Patient on a full dose of the angiotensinogen converting enzyme inhibitor ramipril

[c]Patient on a full dose of the angiotensin II receptor blocker valsartan

Ramipril at a dose of 2.5 mg/kg twice per day and patient #24 was taking the angiotensin II antagonist Valsartan at a dose of 160 mg once per day. Multiple plasma samples were taken for patient #19 during and after infusion and for this patient, plasma levels of curcumin and THC rose during infusion from levels of 414 ng/mL at 2 h to 3885 ng/mL at 6 h. Patient #26 who was taking 5 mg of Ramipril every second day had maximal plasma levels of curcumin and THC which did not increase during infusion and were similar to other patients in the same dose group.

Effects of ACEI inhibitor ramipril on red blood cell and hepatocyte levels of curcumin and THC

Both human and dog hepatocytes and red blood cells were employed in these studies, as the distribution of curcumin and cell levels of THC displayed species selectivity [20]. The results are presented in Table 3. Incubation of either dog or human hepatocytes with a combination of 50 μM Ramipril and 50 μM of its active metabolite, Ramiprilat, had no impact on the cell distribution of curcumin and no effect on THC levels. A significant increase of THC levels in dog hepatocytes was observed. In human red blood cells, ACEI produced a non-significant decrease (38%) of curcumin levels, while in dogs it caused a significant increase (51%) in curcumin levels. THC levels in red blood cells were not significantly changed by treating with the ACEI combination, however a non-significant 42% increase in THC levels was observed in dog red blood cells upon treatment with ACEI.

Medium levels of curcumin and THC were also evaluated (Table 3). In the medium from human red blood cells, the levels of curcumin remained high and the presence of ACEI reduced the medium levels of curcumin by 69%. THC levels in the medium were not changed by ACEIs. For dog red blood cell medium, levels of curcumin were increased significantly by 2.3-fold, while THC levels were reduced significantly by 54%.

Table 3 Distribution of curcumin and THC in red blood cells and hepatocytes and levels of curcumin and THC in red blood cell medium

Cell	Curcumin		THC	
	Control	+ACEI[a]	Control	+ACEI[a]
Human (ng/g w.w.)				
Red blood cells	150.9 ± 60.2 (4)	94.1 ± 38.0 (4)	14.0 ± 5.6 (4)	8.8 ± 3.6 (4)
Hepatocytes	831.5 ± 30.9 (3)	819.5 ± 14.7 (3)	231.0 ± 15.4 (3)	231.8 ± 8.7 (3)
Beagle dog (ng/g w.w.)				
Red blood cells	52.0 ± 3.2 (7)	78.7 ± 21.7 (7)**	112.0 ± 20.4 (7)	158.5 ± 57.2 (7)
Hepatocytes	414.3 ± 34.6 (3)	457.2 ± 13.5 (3)	71.7 ± 8.0 (3)	110.0 ± 7.8 (3)**
Red blood cell medium (ng/mL)				
Human	311.9 ± 65.0 (4)	96.8 ± 50.6 (4)**	0.9 ± 1.8 (4)	1.0 ± 1.9 (4)
Beagle dog	68.3 ± 15.0 (4)	158.8 ± 17.0 (4)**	604.0 ± 7.2 (4)	275.1 ± 10.8 (4)**

Values are presented as the mean ± SD with the number of determinations shown in parenthesis

Significantly different from control, *$p < 0.05$, **$p < 0.010$, Student's t test

[a]Cells were incubated in the presence of 50 μM ramipril + 50 μM ramiprilat

Pharmacokinetics of curcumin in cancer patients and healthy individuals

Plasma concentration–time profiles of curcumin in cancer patients at infusion rates of 37.5 and 50 mg/m^2/h and excluding patient #24 are shown in Fig. 3 panels a, b, respectively. Plasma concentration–time profiles of curcumin in healthy individuals at infusion rates of 120 and 160 mg/m^2/h are shown in Fig. 4 panels a, b, respectively. Despite the ~threefold lower infusion rates for curcumin in cancer patients, the plasma concentrations of curcumin during infusion were in a similar range as those in healthy individuals. In cancer patients, plasma levels of curcumin rapidly dropped to levels below the limit of detection immediately following infusion. In healthy individuals, a rapid drop after infusion was also observed, however, curcumin concentrations remained above the limit of detection for a longer period following the initial drop. In cancer patients, 2-h infusion plasma levels of curcumin exhibited two linear phases, one up to 25 mg/m^2/h where the linear relationship was similar to that for healthy individuals (Table 2; Fig. 5, panel a) and another between 25 and 50 mg/m^2/h where plasma levels increased to a greater extent than observed for healthy individuals. Over a greater range of infusion rates (5–160 mg/m^2/h) in healthy individuals, there was a linear relationship between infusion rate and plasma levels of curcumin (Fig. 5, panel b, Table 2). THC levels in plasma increased with increasing plasma levels of curcumin (Table 2).

The pharmacokinetics of curcumin are presented in Table 4. The pharmacokinetics were analyzed by the non-compartmental method. Infusion rates that produced similar and an adequate range of plasma concentrations of curcumin for characterization of the terminal phase in both cancer patients and healthy individuals were used. There were notable differences in the terminal phase pharmacokinetics of curcumin between cancer patients and

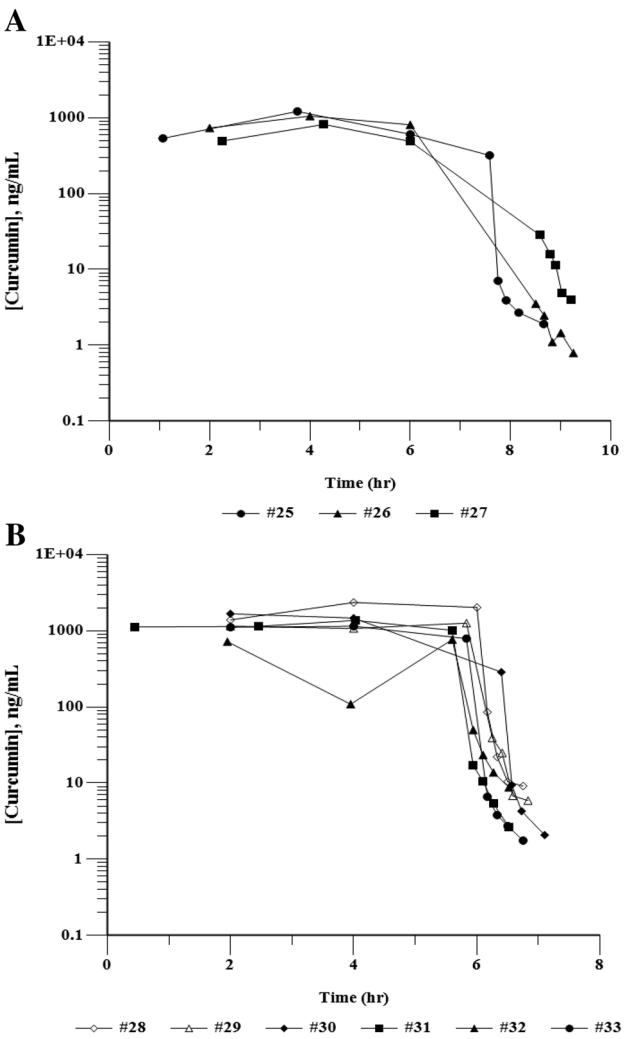

Fig. 3 Plasma time concentrations profiles of curcumin following infusion of Lipocurc™ at a dose of 300 mg/m^2 to cancer patients. Plasma concentration time profiles for curcumin are shown for cancer patients following infusion of Lipocurc™ over a period of 8 h; infusion rate 37.5 mg/m^2/h (**a**) and 6 h; infusion rate 50 mg/m^2/h (**b**)

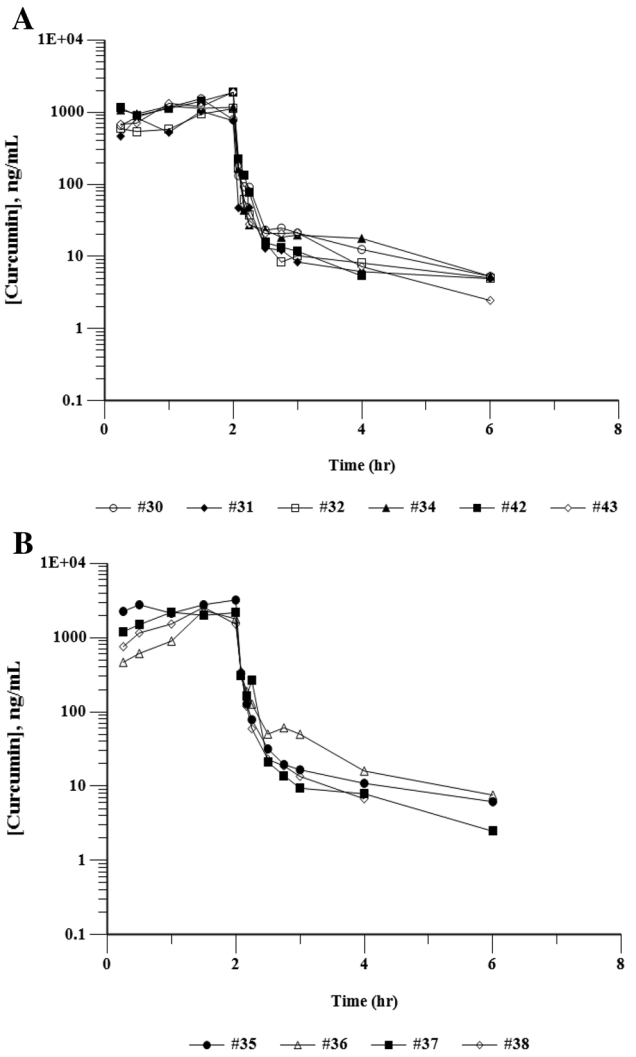

Fig. 4 Plasma time concentrations profiles of curcumin following infusion of Lipocurc™ to healthy individuals. Plasma concentration time profiles for curcumin are shown for healthy individuals following infusion of Lipocurc™ over a period of 2 h at a dose of 240 mg/m^2 infusion rate 120 mg/m^2/h (**a**) and a dose of 320 mg/m^2; infusion rate 160 mg/m^2/h (**b**)

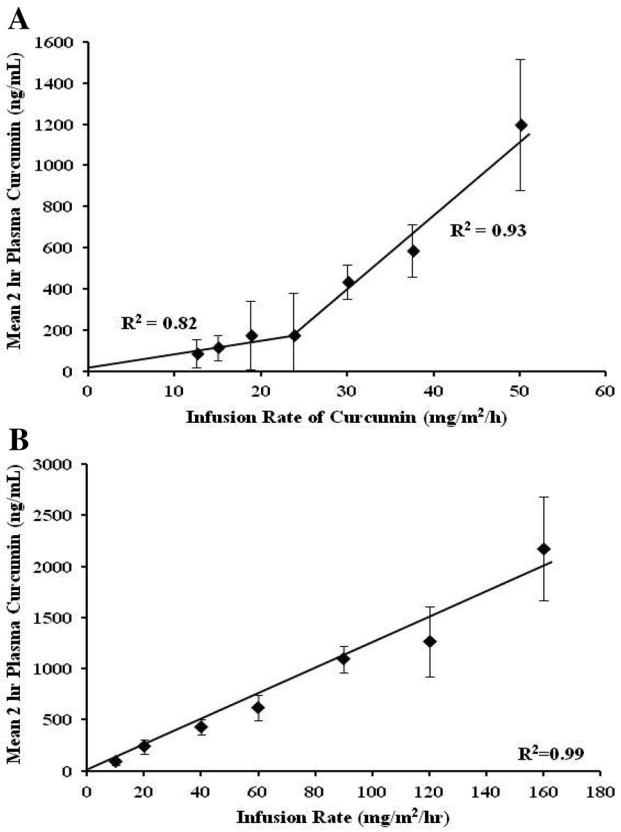

Fig. 5 Comparison of the relationship between infusion rates for curcumin and plasma concentrations of curcumin at 2 h during infusion in cancer patients and healthy individuals. The relationship between infusion rate and plasma levels of curcumin measured at 2 h during infusion is shown for cancer patients up to an infusion rate of 50 mg/m^2/h (**a**) and in healthy individuals up to an infusion rate of 160 mg/m^2/h (**b**). R^2 represents the correlation coefficient of linear regression of the line or line segment

healthy individuals. In cancer patients, the mean terminal $t_{1/2}$ was considerably shorter, the mean Vz and Vss of curcumin were smaller, and the mean terminal Cl values were lower compared to healthy individuals. MRT_{ob} values were similar for cancer patients and healthy individuals. Terminal Cl values were in good agreement with the values for clearance during infusion both in cancer patients and healthy individuals and were at or above human liver blood flow, which is ~ 1.2 L/h/kg [25].

The relationship between the plasma levels of THC and curcumin in cancer patients and healthy individuals was investigated by normalizing the plasma levels of THC to the plasma levels of curcumin (based on $AUC_{0-Tlast}$). The data are presented in Table 5. Curcumin normalized THC levels were quite similar in cancer patients compared to healthy individuals, albeit slightly less.

Discussion

The effect of co-medication on plasma levels of curcumin and THC in cancer patients was evaluated focusing on co-medications with the potential to interact with hepatic uptake transporters (i.e., pantoprazole, metformin, and statins [26, 27]; Table 1) as liver metabolism is a major route for the elimination of curcumin from the plasma [13, 14]. Furthermore, curcumin has been reported to be a substrate for the hepatic uptake transporters OATP1B1, OATP1B3 and OATP2B1 [28]. For the majority of co-medications, there was no relationship between the number of medications used and infusion normalized plasma levels of curcumin or THC with the exception of patients #3 and #19 taking the ACEI Lisinopril and Ramipril, and patient #24 taking the

Table 4 Pharmacokinetics of curcumin in healthy individuals and cancer patients infused with Lipocurc™

Subject or patient #	Curcumin infusion rate (mg/m^2/h)	$AUC_{0-\infty}$ (ng*h/mL)	C_{max} (ng/mL)	$t_{1/2}$ (h)	Vz (L/kg)	Vss (L/kg)	Cl (L/h/kg)	CDI (L/h/kg)	MRT_{ob} (h)
Healthy individuals									
30	120	2162	1536	1.47	6.4	0.80	3.0	4.1	0.27
31		1491	1033	2.89	18.1	1.51	4.4	4.3	0.35
32		1512	1120	2.92	18.1	1.87	4.3	2.9	0.44
34		2224	1212	1.71	7.2	0.68	2.9	2.8	0.23
42		2512	1876	0.96	3.6	0.65	2.6	1.7	0.25
43		2316	1897	1.05	4.2	0.89	2.8	1.7	0.32
Mean		2036	1446	1.83	9.6	1.07	3.3	2.9	0.31
±SD		431	382	0.87	6.7	0.50	0.8	1.1	0.08
35	160	5110	3214	2.00	4.9	0.34	1.7	1.4	0.20
36		2647	2323	1.08	5.1	1.57	3.3	2.4	0.15
37		3710	2196	1.26	4.3	0.52	2.3	2.0	0.22
38		3192	2565	0.85	3.3	0.73	2.7	2.9	0.27
Mean		3665	2574	1.30	4.4	0.79	2.5	2.2	0.21
±SD		1057	453	0.50	0.8	0.54	0.7	0.6	0.05
Cancer patients									
6-h infusion									
28	50	9708	2351	0.35	0.42	0.74	0.8	1.0	0.88
29		5785	1262	0.20	0.40	0.93	1.4	1.2	0.66
30		6943	1673	0.26	0.44	0.19	1.2	0.8	0.16
31		6554	1368	0.21	0.38	0.02	1.2	1.2	0.02
32		2405	767	0.24	1.15	1.06	3.4	1.9	0.31
33		5285	1148	0.31	0.69	0.70	1.5	1.2	0.46
Mean		6113	1428	0.26	0.58	0.61	1.6	1.2	0.42
±SD		2381	540	0.06	0.30	0.41	0.9	0.4	0.32
8-h infusion									
25	37.5	5433	1212	0.53	1.13	0.22	1.5	1.9	0.14
26		5389	1051	0.36	0.79	0.20	1.5	1.4	0.14
27		3677	816	0.20	0.65	0.53	2.2	2.1	0.24
Mean		4833	1027	0.36	0.86	0.32	1.7	1.8	0.17
±SD		1001	199	0.17	0.25	0.19	0.4	0.4	0.06

Values are presented ± SD of the number of subjects or patients shown

$AUC_{0-\infty}$ area under the plasma concentration time curve to infinity, C_{max} maximum plasma concentration, $t_{1/2}$ terminal elimination half-life, *Vz* terminal volume of distribution, *Vss* terminal volume of distribution at steady-state, *Cl* total body clearance, *CDI* clearance during infusion, MRT_{ob} mean residence time

Table 5 Levels of THC compared to curcumin in healthy subjects and cancer patients infused with Lipocurc™

Curcumin infusion rate (mg/m^2/h)	Length of infusion (h)	$AUC_{0-Tlast}$ curcumin (ng*h/mL)	$AUC_{0-Tlast}$ THC (ng*h/mL)	Ratio of $AUC_{0-Tlast}$ THC/curcumin
Healthy subjects				
120	2	1981 ± 434	174 ± 56	0.0878
160	2	3607 ± 1056	261 ± 62	0.0723
Cancer patients				
50	6	6111 ± 2381	323 ± 115	0.0528
37.5	8	4832 ± 1156	344 ± 156	0.0712

Values are presented as the mean ± SD. Data for Healthy Subjects was taken from the literature [19]

$AUC_{0-Tlast}$ area under the plasma concentration time curve to the last measurable plasma concentration

angiotensin II receptor antagonist Valsartan, for which high plasma levels of curcumin and THC were observed. When factors such as clinical chemistry and hematology were also taken into consideration, the only common factor remaining was that these three patients were taking full prescription doses of drugs targeting the renin–angiotensin system. For patient #19, plasma concentrations of both curcumin and THC continued to increase during the infusion period. This suggests that the clearance of curcumin from the plasma during infusion in this patient was reduced. Patient #26 was also taking ramipril, but every 2 days, and did not have higher plasma levels of curcumin and THC compared to other patients suggesting that the possible interaction between ramipril and curcumin may be exposure-dependent.

As a follow-up to the effect of ramipril on plasma curcumin and THC levels, the effect of ramipril and its active metabolite Ramiprilat were investigated on the distribution of curcumin and THC in hepatocytes and red blood cells from dog and human. The distribution of curcumin into hepatocytes was not impacted by ACEI, suggesting that the liver might not be a target for the elevation of plasma curcumin levels by Ramipril. However, there were effects on curcumin distribution into red blood cells leading to an investigation of curcumin and THC levels in red blood cell medium following incubation. Several observations were made from this study. In human red blood cells, there was a reduction of the cell and medium levels of curcumin by ACEI with little impact on THC levels. In dog red blood cells, there was an increase in the cell and medium levels of curcumin following incubation with ACEI with little impact on the cell levels of THC and a substantial decrease in the medium concentrations of THC. These findings suggest that the red blood cell metabolism of curcumin may be a target for ACEI to increase plasma levels of curcumin since it is highly relevant to the pharmacokinetics of curcumin both in the dog and human [20]. Furthermore, exposure to drugs acting on the renin–angiotensin system may have an effect on the reported drug metabolizing capacity of red blood cells [29]. Drugs acting on the renin–angiotensin system have been reported to reduce erythropoietin levels [30–33] and to have direct effects on red blood cell sodium and potassium transport [33–36]. In addition to the metabolism of curcumin by red blood cells, curcumin in the form of Lipocurc™ has been shown to interact with and alter the configuration of the red blood cell membrane [37]. Thus, exposure to full clinical doses of ACEI and angiotensin II antagonist and alteration of the red blood cell disposition of curcumin may be linked to the elevated levels of curcumin upon infusion.

In healthy individuals, plasma levels at 2 h during infusion displayed a linear correlation over a wide range of infusion rates (10–160 mg/m^2/h) while in cancer patients, the relationship was best described by a segmented line fit, with plasma levels being similar to healthy individuals at lower infusion rates and then increasing to become greater than healthy individuals at higher infusion rates. In cancer patients, these observations are consistent with a limitation either on the tissue distribution or the clearance of curcumin from the plasma as curcumin infusion rates are increased. Thus, a pharmacokinetic analysis of curcumin plasma levels was performed at infusion rates that produced similar maximal plasma exposures and a defined terminal phase in cancer patients and healthy individuals. Following termination of infusion, plasma levels of curcumin dropped rapidly. The terminal phase in healthy individuals was well defined, while in cancer patients it was abbreviated and almost completely absent despite longer times of infusion. Derivation of the pharmacokinetic parameters reflected this difference. Mean terminal phase $t_{1/2}$ values were shorter in cancer patients compared to healthy individuals and similar to the MRT_{ob} values, with the mean MRT_{ob} values being similar in cancer patients and healthy individuals. In addition, the mean terminal Vz and Vss for curcumin were smaller in cancer patients compared to healthy individuals. Health status and possibly co-medication may be contributors to the reduced volume of distribution for curcumin in cancer patients. Mean total body clearance values were lower in cancer patients compared to healthy individuals and were not significantly different from those calculated during infusion. The lower volume of distribution for curcumin in cancer patients compared to healthy individuals possibly contributes to the increased infusion rate normalized plasma levels of curcumin observed in cancer patients at higher infusion rates. Furthermore, the lower volume of distribution in cancer patients may result in a more rapid decrease of plasma curcumin due to metabolism following termination of infusion.

Given the low plasma levels of THC measured over time, a defined terminal phase was not available, and therefore, the terminal phase pharmacokinetics for THC could not be determined. Therefore, the pharmacokinetic analysis was restricted to comparisons with the $AUC_{0-Tlast}$. The mean $AUC_{0-TLast}$ for THC plasma levels in cancer patients at infusion levels of 37.5 and 50 mg/m^2/h were higher than in healthy patients at infusion levels of 120 and 160 mg/m^2/h. However, when normalized to the $AUC_{0-Tlast}$ for curcumin, the levels of THC were only slightly lower in cancer patients compared to healthy individuals, suggesting that the level of metabolism of curcumin to THC is similar in cancer patients and healthy individuals.

In summary, this study has revealed the potential for interactions between medications targeting the renin–angiotensin system and curcumin leading to increased plasma levels of curcumin and THC during infusion of Lipocurc™. The potential target for this interaction may be the disposition of curcumin in red blood cells. Pharmacokinetic analysis revealed that in cancer patients curcumin was found to have a lower volume of distribution and a shorter terminal

half-life compared to healthy individuals possibly due to health status and the use of co-medications.

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Compliance with ethical standards

Conflict of interest PPS is vice president and chief scientific officer at SignPath Pharma Inc. No potential conflict of interest was disclosed by RG, BV, SGR, LW, CS, TM, BR, MM, GB, AL and AT. Cancer patients enrolled in this study provided written informed consent.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

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