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ORIGINAL ARTICLE

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Urinary and fecal excretion of topotecan in patients with malignant solid tumours

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Abstract *Purpose*: The objectives of the study were to determine the pharmacokinetics and routes of excretion of topotecan following intravenous or oral administration to patients with refractory solid tumours. *Methods*: Patients were randomized to receive either oral (2.3 mg/m^2) or intravenous (1.5 mg/m^2) topotecan once daily for 5 days in course 1. Patients who received in course 1 oral topotecan received in course 2 intravenous topotecan on day 1 followed by oral topotecan on days 2 to 5. Patients who received in course 1 intravenous topotecan received in course 2 oral topotecan once daily for 5 days. Plasma pharmacokinetics were performed on day 1 of course 1 (all patients) and course 2 (only patients receiving intravenous topotecan on that day). In course 1, urine and feces were collected for up to 9 days after the first dosage. The amounts of topotecan and *N*-desmethyl topotecan in plasma, urine and feces were determined by validated high-performance liquid chromatographic assays. *Results*: A total of 11 patients were enrolled in the study. Nine patients were evaluable for pharmacokinetics. Plasma pharmacokinetics were similar to those previously reported. The principal route of excretion was the urine, with approximately 49% of the intravenously administered topotecan dose and 20% of the oral dose collected in the urine as parent drug. Approximately 18% and 33% of the intravenous and oral dose, respectively, were recovered unchanged in the feces. Only small amounts of *N*-desmethyl topotecan were found in the excreta. *Conclusions*: Fecal and urinary excretion of unchanged topotecan were the major routes of topotecan elimination. Approximately 28% of the intravenous dose and 43% of the oral dose of topotecan were unaccounted for and eliminated through other routes.

Keywords Topotecan · *N*-Desmethyl topotecan · Oral · Intravenous · Feces · Urine

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Introduction

Topotecan (Hycamtin) is a lead compound of an important class of cytotoxic drugs that acts through inhibition of the nuclear enzyme topoisomerase I [12, 13]. Antitumour activity of topotecan has been demonstrated in several tumour types including ovarian cancer, small-cell and non-small-cell lung cancer, lymphoma, leukaemia and paediatric tumours [2, 3, 15]. Topotecan is currently registered in many European countries and in the USA for the second-line treatment of ovarian cancer [6, 22]. Topotecan is also registered in the USA for the treatment of refractory non-small-cell lung cancer [25]. An oral formulation of topotecan has recently been developed and it has shown in the clinic comparable activity to intravenously administered topotecan [3, 5].

The E-ring lactone in the basic structure of topotecan, which exists under physiological conditions in a dynamic, pH-dependent equilibrium with an inactive

carboxylate form (Fig. 1) [23], is considered to be essential for interaction with topoisomerase I [11, 17]. Previous studies in rats have indicated that topotecan is equally excreted in the urine and feces after intravenous administration of radiolabelled drug [1]. In humans, the urinary recovery of topotecan is approximately 40% [8]. Thus, approximately 60% of topotecan undergoes elimination via other routes. These may include biliary secretion and hepatic metabolism. Biliary sampling in one patient has demonstrated considerable concentrations of topotecan in the bile [21].

Previously, we have isolated a *N*-desmethyl metabolite of topotecan in plasma and urine samples of patients treated with topotecan (Fig. 1) [18]. *N*-Desmethyl topotecan has antitumour activity comparable to that of the parent compound. However, plasma concentrations are relatively low and the urinary recovery of this metabolite accounts for only 1 to 3% of the administered topotecan dose [9]. Other metabolites of topotecan found in the urine include small amounts of glucuronide metabolites [19]. The objectives of this study were to examine the urinary and fecal excretion and disposition of topotecan and its *N*-desmethyl metabolite following administration of unlabelled parent drug as the intravenous and oral formulations in patients with malignant solid tumours.

Methods

Patients

Patients were eligible for the study if they had a histologically confirmed malignant solid tumour, refractory to conventional therapy, or for which no standard effective therapy existed. Other eligibility criteria included an initial Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2, anticipated life expectancy of ≥12 weeks and age ≥18 years. Previous anticancer chemotherapy had to have been discontinued for at least 3 weeks before entry into the study, or 6 weeks in cases of pretreatment with a nitrosourea or mitomycin C. All patients had to have acceptable functional reserve as defined by white blood cell count (WBC) ≥3000/μl, absolute neutrophil count (ANC) ≥1500/μl, platelets ≥100,000/μl and haemoglobin ≥9.0 g/dl (5.6 mmol/l); serum bilirubin ≤ 2.0 mg/dl (34 μmol/l) and other liver function tests not more than twice the normal upper limit; serum creatinine ≤ 1.5 mg/dl (133 μmol/l) or creatinine clearance ≥60 ml/min.

Patients were excluded if they had a haematological malignancy, gross ascites, uncontrolled infection, previously documented symptomatic brain or leptomeningeal metastases, evidence of any condition of the gastrointestinal (GI) tract or other condition that might affect GI absorption and motility, or if they were taking metoclopramide or cisapride. Pretreatment evaluation included a complete medical history and complete physical examination. Before each course, interim history (concomitant medications taken, toxicities and adverse experiences), physical examination, performance status, and urinalysis were performed. Haematology was checked weekly and blood chemistries and urine every 2 weeks. The study protocol was approved by the Medical Ethics Committee of the hospital and all patients gave written informed consent.

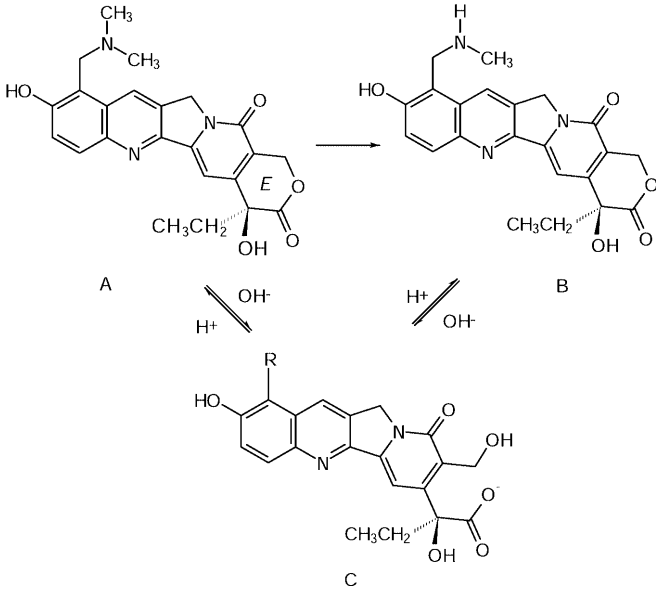

Fig. 1. Chemical structures of topotecan (*A*) and *N*-desmethyl topotecan (*B*). Topotecan undergoes oxidative metabolism to form the *N*-desmethyl metabolite. Both compounds exist under physiological conditions in a dynamic pH-dependent equilibrium with their respective ring-opened hydroxy carboxylate forms (*C*)

Dosage and administration

A schematic representation of the design of the study is shown in Fig. 2. Patients were randomized to receive either oral or intravenous topotecan once daily for 5 days in course 1. Patients who received in course 1 oral topotecan received in course 2 intravenous topotecan on day 1 followed by oral topotecan on days 2 to 5. Patients who received in course 1 intravenous topotecan received in course 2 oral topotecan once daily for 5 days. Oral topotecan was given during subsequent courses. All patients were fasted from midnight the evening prior to dosing and were given a light breakfast 30 min after dosing.

Oral topotecan was supplied by GlaxoSmithKline Pharmaceuticals (Collegeville, Pa.) as gelatin capsules containing 0.25 or 1.00 mg of the anhydrous free base. The oral dose was 2.3 mg/m^2 per day for five consecutive days. The calculated daily dose was rounded of to the nearest 0.25 mg. Intravenous topotecan was supplied as a lyophilized light yellow powder in vials containing 4 mg topotecan as the free base and as excipients 48 mg mannitol, 20 mg tartaric acid and hydrochloric acid/sodium hydroxide for pH adjustment to 3.0. The content of each vial was reconstituted with 4 ml sterile water for injection prior to dilution in 50 ml 0.9% sodium chloride and was administered intravenously over 30 min via a syringe pump. The intravenous dose was 1.5 mg/m^2 per day.

Pharmacokinetics

Blood samples for pharmacokinetic analysis were collected from all patients on day 1 of course 1, and also on day 1 of course 2 in patients receiving intravenous topotecan on that day. Blood samples (5 ml each) were taken from an indwelling intravenous cannula, which in the case of intravenous drug administration, was placed in the arm contralateral to the arm receiving topotecan. During intravenous administration samples were obtained preinfusion, at 15, 30, 45, 60 and 90 min and 2, 4, 6, 8 and 12 h after the start of the infusion; for oral administration time-points were predosing, 30 and 60 min and 2, 3, 4, 6, 8, 10, 12 and 14 h after ingestion. Samples were collected into heparinized tubes and immediately immersed in ice-water. Plasma was obtained by immediate refrigerated centrifugation of the samples (5 min, 2500 *g*, 4°C). Plasma protein was precipitated by adding 1.0 ml of the separated plasma to 2.0 ml of cold methanol (–20°C) followed by vortex-mixing for 10 s. The samples were centrifuged at 3000 *g* for 5 min and the clear supernatant was transferred to a polypropylene

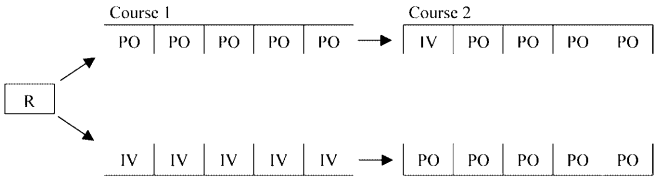

Fig. 2. Schematic representation of the design of the study. Course 2 commenced 21 days after day 1 of course 1 (*R* randomization, *PO* oral administration, *IV* intravenous administration)

tube and immediately stored at –70°C until analysis. The remaining plasma was stored at –20°C until analysis. In course 1 only, urine and feces were collected on the 5 days of topotecan administration and up to 4 days after the last dosage. Urine was collected over 24-h periods after dosing and aliquots were stored at –20°C until analysis. Complete fecal samples were refrigerated at 4°C until analysis. The amounts of topotecan and *N*-desmethyl topotecan in plasma, urine and feces were determined by validated HPLC assays [20].

Pharmacokinetic analysis

Pharmacokinetic parameters were obtained using a model-independent approach. For each individual, the maximum drug concentration (C_{max}) and time to maximum drug concentration (t_{max}) were generated directly from the experimental data. The area under the plasma concentration-time curve (AUC) and the area under the first-moment curve (AUMC) were estimated by the linear-logarithmic trapezoid rule up to the last measured time-point (AUC_t) with extrapolation to infinity using the terminal rate constant k. Total clearance of topotecan from plasma (CL) was calculated as the dose divided by the AUC. The terminal half-life ($t_{1/2}$) was calculated as 0.693/k. The volume of distribution at steady state (V_{dss}) was determined using the following equation: $Vdss = [(dose \times AUMC)/AUC^2] - [(dose \times infusion\ duration)/(2 \times AUC)]$. The absolute bioavailability (F) was calculated as the ratio of the topotecan AUC after oral and intravenous administration corrected for differences in actual administered dose. The percentage of the administered dose recovered in the urine and feces over 9 days was calculated as the amount excreted in the urine and feces, respectively, divided by the total administered dose ×100%. Renal clearance (CL_R) of topotecan was calculated as the amount excreted in the urine unchanged divided by the AUC. Data are presented as means ± SD.

Results

Patients and treatment

A total of 11 patients (4 males and 7 females) were enrolled in the study. The median age was 58 years (range 39 to 66 years). The median performance score at study entry was 1 (range 0 to 2). Primary tumour types included ovarian (five), colorectal (three), small-cell lung cancer (two) and cancer of unknown primary (one).

All patients had received previous chemotherapeutic treatment (median one regimen, range one to two). All patients used concomitant medication, consisting of one or a combination of the following drugs: paracetamol, codeine, temazepam, oxazepam, lorazepam, diazepam, lactulose, magnesium oxide, morphine sulphate (MS-contin), naproxen, valproic acid, levodopa, clonidine, zolpidem, omeprazol, granisetron, ibuprofen. One patient (patient 5) treated with intravenous topotecan in course 1 took domperidone, a GI-influencing drug (Motilium) on days 4 and 5 of treatment, which was against the protocol. However, influence on plasma pharmacokinetics was unlikely as the patients were assessed on day 1 of treatment and no significant inconsistency in urine and fecal excretion was found; therefore this patient was considered evaluable for pharmacokinetics.

A total of 67 full courses were administered, with a median number of 5 (range 1 to 16) per patient. One patient, randomized for oral administration, developed a bowel obstruction during the first treatment course. He was hospitalized on day 18 and received a colostoma on the colon transversum. The patient was withdrawn from the study and did not receive a second course, for which reason he was not evaluable for pharmacokinetics. Another patient, randomized for oral administration, was not evaluable because no pharmacokinetic sampling was performed.

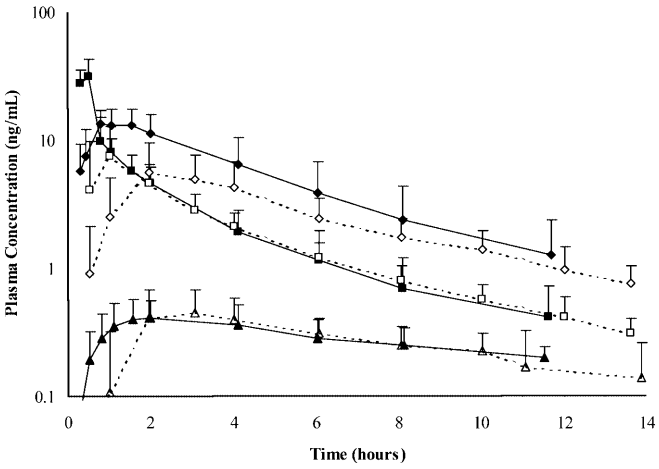

Fig. 3. Mean (±SD) concentration-time curves of topotecan lactone (*squares*) and carboxylate forms (*diamonds*) and total *N*-desmethyl topotecan (*triangles*) after a 30-min intravenous infusion ($n = 9$, *solid symbols*) or oral ingestion ($n = 4$, *open symbols*) of topotecan. The intravenous and oral doses were 1.5 and 2.3 mg/m^2 per day, respectively

Pharmacokinetics

Mean plasma concentration-time curves of topotecan and *N*-desmethyl topotecan as their lactone and carboxylate forms after oral and intravenous administration are shown in Fig. 3. Individual pharmacokinetic parameters are given in Tables 1 and 2. For *N*-desmethyl topotecan the percentage of the AUC extrapolated was >20% in all patients. Therefore AUC_t values are reported. Plasma pharmacokinetics were similar to those previously reported [8, 10].

The bulk of the dose excreted in the urine was recovered within 24 h of the last topotecan administration on day 5. Negligible amounts of the parent compound

were excreted in the urine on day 6, whereas on days 7 to 9 topotecan concentrations in 24-h urine samples were below the detection limit of the analytical assay. In four of the six patients topotecan was excreted in feces within 7 days of the start of the treatment course. In two patients topotecan was still detectable in the feces on day 9, but the relative amount excreted in these samples only represented 1.7% and 8.9%, respectively, of the total amount excreted over the total collection period. In most patients low but detectable levels of *N*-desmethyl topotecan were also seen in urine and fecal samples collected 4 days after the fifth topotecan dose.

The total excretion of topotecan and *N*-desmethyl topotecan within 9 days amounted to $71.8 \pm 4.0\%$ and $56.9 \pm 10.0\%$ of the administered intravenous and oral dose, respectively (Table 3). Urinary excretion was predominant ($52.1 \pm 5.1\%$ of the intravenous dose). Topotecan was largely excreted unchanged ($67.6 \pm 2.8\%$ and $53.4 \pm 9.1\%$ of the intravenous and oral dose, respectively). *N*-Desmethyl topotecan accounted for only $4.2 \pm 1.7\%$ and $3.5 \pm 1.2\%$ of the intravenous and oral dose, respectively, in the excreta. Following oral administration of 2.3 mg/m^2 per day, topotecan was incompletely bioavailable ($44 \pm 11\%$). When combined with the data derived after intravenous dosing, the fraction of the administered oral dose appearing in the feces as parent drug (33%) most likely consisted of approximately 8% of systemically available topotecan and 25% of unabsorbed drug.

Discussion

This is the first report of the fecal excretion of topotecan and *N*-desmethyl topotecan in humans. After intravenous administration, topotecan was excreted primarily as unchanged drug (68% of the cumulative dose). The major route of excretion was via the kidneys (49%). Previous studies have reported the urinary recovery of topotecan to range from 20% to 80% of the dose [7, 21, 24, 26]. However, in our study the interpatient variability was remarkably low (coefficient of variation of 8% and 37% after intravenous and oral dosing, respectively), which may be related to the strict urine collection method and the eligibility criteria used.

For most drugs, the kidneys are the primary site of excretion of unchanged drug. The liver is the usual organ for drug metabolism, but it may also secrete unchanged drug into the bile. Saltz et al. have demonstrated considerable concentrations of topotecan in bile [21]. Once excreted in the bile topotecan may be reabsorbed from the intestinal tract. In renally impaired patients with reduced renal clearance of topotecan, a second peak in plasma concentrations has been observed after the end of a 30-min infusion, which is suggestive of enterohepatic recycling [16]. However, a similar peak was not observed in a study with patients with normal organ function [8], and this may therefore point to an increase in hepatic excretion of topotecan in patients with renal impairment [16]. It appears that enterohepatic recirculation does not significantly contribute to the disposition of topotecan. Only the lactone form of topotecan is assumed to be sufficiently lipophilic to traverse the GI walls, but the relatively high pH in the intestines favours conversion to the carboxylate form, which is poorly absorbed [4]. Furthermore, bioavailability might be influenced by active excretion of topotecan by protein-mediated drug transport. Recently, it has been found that the murine homologue of the human breast cancer resistance protein (BCRP) mediates apically directed drug transport of topotecan and appears to reduce bioavailability [14]. Other factors possibly mediating bioavailability of topotecan include binding of topotecan to food, proteins, and/or intestinal

Table 1. Pharmacokinetic parameters of topotecan after intravenous (1.5 mg/m^2) and oral administration (2.3 mg/m^2). For abbreviations see Methods. The suffixes *lac* and *tot* refer to lactone and total drug (lactone plus carboxylate) forms, respectively

Patient no.[a]	Intravenous								Oral					
	$C_{max,tot}$ (ng/ml)	AUC_{tot} (h·μg/l)	$t_{1/2,tot}$ (h)	CL_{tot} (l/h)	CL_{lac} (l/h)	$V_{dss,tot}$ (l)	$V_{dss,lac}$ (l)	Lactone-to-total ratio	$T_{max,tot}$ (h)	$C_{max,tot}$ (ng/ml)	AUC_{tot} (h·μg/l)	$t_{1/2,tot}$ (h)	F (%)	Lactone-to-total ratio
1	27.5	76.5	2.49	43.1	130.6	145.5	291	0.33						
2	43.7	124.8	2.47	24.8	73.6	85.8	156	0.34						
3	59.4	225.6	4.01	12.6	41.1	69.4	163	0.31						
4	32.0	93.4	2.18	25.7	68.8	75.2	133	0.37						
5	41.9	81.6	3.93	30.6	81.3	106.7	346	0.38						
6	45.3	95.0	2.64	24.3	54.4	79.4	109	0.47	1.93	11.5	72.1	4.41	0.49	0.43
7	48.7	134.6	2.71	19.3	50.0	69.0	118	0.39	0.98	19.5	109.3	5.25	0.53	0.38
8	33.3	63.1	2.92	47.5	125.3	141.3	267	0.38	3.90	3.6	27.3	4.39	0.29	0.40
9[b]	25.8	47.9	3.01	31.3	77.9	85.2	217	0.40	2.02	9.17	41.4	4.48	0.43	0.45
Mean	41.5	111.8	2.93	28.8	78.1	95.3	200	0.37	2.21	10.94	62.5	4.63	0.44	0.42
SD	10.3	51.8	0.64	11.0	31.3	29.5	85	0.05	1.22	6.60	36.4	0.41	0.11	0.03

[a]Patients 1–5 received intravenous topotecan during course 1, patients 6–9 were treated with oral topotecan during course 1 and intravenous topotecan on day 1 of course 2. The allocated patient number does not refer to the order of study entry

[b]Patient 9 had a dose reduction and received 1.1 mg/m^2 intravenous topotecan during course 2 Data obtained during course 2 were not used to calculate the mean

Table 2. Pharmacokinetic parameters of *N*-desmethyl topotecan after intravenous (1.5 mg/m^2) and oral administration (2.3 mg/m^2) of topotecan (*NR* no result: *N*-desmethyl topotecan lactone levels were all under the LLOQ – no pharmacokinetic parameters could be calculated; for other abbreviations see Methods). The suffixes *lac* and *tot* refer to lactone and total drug (lactone plus carboxylate) forms, respectively

Patient no.[a]	Intravenous					Oral				
	$T_{max,tot}$ (h)	$C_{max,tot}$ (ng/ml)	AUC_{tot} (h·μg/l)	$t_{1/2,tot}$ (h)	Lactone-to-total ratio	$T_{max,tot}$ (h)	$C_{max,tot}$ (ng/ml)	AUC_{tot} (h·μg/l)	$t_{1/2,tot}$ (h)	Lactone-to-total ratio
1	2.02	0.225	1.00	5.19	0.44					
2	2.00	0.482	3.11	5.74	0.18					
3	1.55	0.559	4.5	7.38	0.11					
4	2.00	0.389	3.17	4.57	0.3					
5	1.52	0.653	3.22	3.66	0.71					
6	1.97	0.345	1.76	8.94	0.48	4.05	0.320	3.34	5.32	0.50
7	1.98	0.459	4.19	20.77	0.22	1.97	0.765	11.99	16.54	0.36
8	1.98	0.644	5.11	4.74	0.24	8.05	0.317	3.02	6.74	0.50
9[b]	1.57	0.214	0.77	5.88	NR[e]	3.08	0.586	2.54	6.98	0.46
Mean	1.88	0.470	2.98	7.43	0.34	4.29	0.500	5.22	8.90	0.46
SD	0.21	0.148	1.53	5.25	0.20	2.65	0.219	4.52	5.15	0.07

[a]Patients 1–5 received intravenous topotecan during course 1, patients 6–9 were treated with oral topotecan during the course 1 and intravenous topotecan on day 1 of course 2. The allocated patient number does not refer to the order of study entry

[b]Patient 9 had a dose reduction and received 1.1 mg/m^2 intravenous topotecan during course 2; data obtained during course 2 were not used to calculate the mean

fluids or decomposition in the GI fluid. No data concerning decomposition in the GI fluid of the lactone or carboxylate form of topotecan are available, but as both forms of topotecan are relatively stable this is expected to be minimal.

Metabolism to *N*-desmethyl topotecan was a minor mechanism for elimination of topotecan in our study. Plasma levels of *N*-desmethyl topotecan were low and the metabolite accounted for only 4.2% and 3.5% of the intravenous and oral dose, respectively, in the excreta. Recently, *O*-glucuronidation has been identified as a detoxification pathway for topotecan and *N*-desmethyl topotecan, but concentrations in human urine are relatively low [19]. After a 30-min intravenous infusion of topotecan, the recoveries of topotecan-*O*-glucuronide and *N*-desmethyl topotecan-*O*-glucuronide in a 24-h urine sample of one patient represented only 1.9% and 0.7%, respectively, of the administered topotecan dose (unpublished data, J.H.B. and J.H.M.S.). In our study one patient (no. 2 in Tables 1, 2 and 3) used concomitantly valproic acid, which is an inhibitor of glucuronidation. No alterations in topotecan or *N*-desmethyl topotecan pharmacokinetics and excretion were observed in this patient compared to data obtained from the other patients in this study and previously published data [8]. Therefore, the clinical relevance of the glucuronide conjugates in the pharmacology and toxicology of topotecan seems limited, but needs further investigation.

In summary, the total urinary and fecal excretion of topotecan and *N*-desmethyl topotecan amounted to 72% and 57% of the administered intravenous and oral dose, respectively. Thus, approximately 28% of an intravenous dose and 43% of an oral dose of topotecan could be lost by decomposition in the GI lumen, irreversible binding to food or other contents of the intestines or metabolism to yet-unidentified metabolites.

Table 3. Urinary and fecal excretion of topotecan and *N*-desmethyl topotecan after intravenous (1.5 mg/m^2) and oral administration (2.3 mg/m^2) of topotecan

Patient no.	Route	Topotecan			*N*-Desmethyl topotecan	
		Urinary excretion (%)	Renal clearance (l/h)	Fecal excretion (%)	Urinary excretion (%)	Fecal excretion (%)
1	Intravenous	47.4	20.4	20.4	1.75	1.42
2	Intravenous	54.2	13.4	14.0	2.97	1.13
3	Intravenous	43.7	5.5	19.9	1.2	1.03
4	Intravenous	49.9	12.8	21.4	3.47	1.6
5[a]	Intravenous	51.7	15.8	15.6	4.09	2.53
6	Oral	18.5[b]	6.8	30.7[b]	2.08	2.03
7	Oral	26.2[b]	13.6	25.3[b]	1.51	0.65
8	Oral	10.5[b]	17.4	35.9[b]	1.44	1.28
9	Oral	26.2[b]	19.2	40.3[b]	3.01	1.83
Mean (SD)	Intravenous	49.4 (4.0)	13.6 (5.4)	18.3 (3.3)	2.70 (1.20)	1.54 (0.60)
Mean (SD)	Oral	20.4 (7.6)[b]	14.2 (5.5)	33.0 (6.5)[b]	2.01 (0.73)	1.45 (0.62)

[a]This patient took domperidone on days 4 and 5 of the first course

[b]The percentage of topotecan administered orally that was recovered unchanged in excreta was not corrected for the bioavailability of the drug

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