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# Pretreatment with ranitidine does not reduce the bioavailability of orally administered topotecan

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**Abstract** *Purpose*: The purpose of this randomized, two-period crossover study was to determine the pharmacokinetics of orally administered topotecan in the presence and absence of oral ranitidine. *Methods*: Patients with solid malignant tumors refractory to standard treatment were given topotecan orally on a daily times five schedule repeated every 21 days. Topotecan was given initially at 2.3 mg/m$^2$ per day; dose adjustments were permitted after the first dose of course 2 if necessary. Blood samples for pharmacokinetic assessments were drawn at protocol-specified times for up to 10 h following oral administration of topotecan on day 1 of courses 1 and 2. Patients were randomly assigned to receive a total of nine doses of ranitidine: 150 mg twice daily for 4 days before day 1 of one of the first two courses and 150 mg given 2 h before the first topotecan dose. Plasma samples were assayed for concentrations of active topotecan lactone (TPT-L) and total topotecan (TPT-T, lactone plus open-ring carboxylate form) using high-performance liquid chromatography with fluorescence detection. After completion of courses 1 and 2, patients could continue on therapy for days 1–5 of every 21 days if not withdrawn due to unacceptable toxicity, disease progression, protocol violation, or by request. Patients continued on treatment for a maximum of six courses. *Results*: No pharmacokinetic parameter for either TPT-L or TPT-T differed significantly during administration of topotecan with ranitidine compared with topotecan alone ($n = 13$). Geometric mean ratios (95% confidence intervals, CIs) of areas under the curve in the presence and absence of ranitidine were 0.94 (0.80, 1.10) for TPT-L and 0.97 (0.80, 1.16) for TPT-T. Corresponding ratios (CIs) of peak plasma concentrations in the presence and absence of ranitidine were 1.06 (0.78, 1.44) for TPT-L and 1.07 (0.84, 1.38) for TPT-T. The median difference in time to peak plasma concentration was 0.0 h for TPT-L and −0.5 h for TPT-T (i.e. slightly faster in the presence of ranitidine). *Conclusions*: Administration of ranitidine prior to oral topotecan resulted in a similar extent of absorption. A slightly faster rate of absorption of topotecan was also observed, which is unlikely to be of clinical significance. Dosage adjustments of orally administered topotecan should not be necessary in patients who are pretreated with ranitidine, an H2 antagonist, or another agent that comparably raises gastric pH.

**Key words** Topotecan · Camptothecin · Drug interactions · Pharmacokinetics · DNA topoisomerase I

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## Introduction

Topotecan, a semisynthetic analog of the alkaloid camptothecin, is an inhibitor of topoisomerase-1, an enzyme involved in DNA replication and repair [1, 5, 9, 10, 12]. The structure of topotecan incorporates a stable

basic side-chain at the 9-position of the A-ring that affords water solubility to the compound but retains the closed E-ring lactone structure that is required for biological activity [5, 9, 10]. In aqueous media, the active lactone form of topotecan interconverts with the open-ring carboxylate form in a pH-dependent manner [5, 10]. Under acidic conditions (pH ≤ 4), the lactone structure is present extensively, while the open-ring carboxylate form predominates at physiological pH [5, 10].

Topotecan is effective in a number of solid tumor models that are refractory to established anticancer drugs, including chemosensitive tumors with acquired multidrug resistance [12]. The intravenous formulation of topotecan (Hycamtin) has received marketing approval for the treatment of metastatic carcinoma of the ovary after failure of initial or subsequent chemotherapy and small-cell lung cancer sensitive disease after failure of first-line chemotherapy [1, 9, 10, 12, 22].

An oral formulation of topotecan is currently in development [6]. In a prior phase I study, topotecan was administered orally in doses ranging from 1.2 to 2.7 mg/m$^2$ per day in a daily times five dosing schedule repeated every 21 days [7]. The maximum tolerated dose (MTD) of topotecan when administered orally as a single agent is 2.3 mg/m$^2$ per day, the dose-limiting toxicity is grade 4 neutropenia, and non-hematological toxicities are generally mild [7].

Cancer patients frequently receive H2 antagonists such as ranitidine concomitantly with chemotherapeutic agents for a variety of comorbid conditions. Ranitidine is an H2 antagonist that blocks gastric acid secretion and increases gastric pH [13]. Because of the chemical properties of topotecan, there was the possibility that an increase in gastric pH might reduce the oral absorption and bioavailability of the drug. The primary purpose of the present study was to determine whether prior administration of ranitidine affects the bioavailability of oral topotecan in patients with malignant solid tumors. The secondary purpose was to evaluate the qualitative and quantitative toxicities associated with oral topotecan treatment.

## Materials and methods

### Protocol

This study was designed as a randomized, two-period crossover investigation of the pharmacokinetics of orally administered topotecan alone and following pretreatment with oral ranitidine. Adult patients who had malignant solid tumors were studied at the Regional Oncology Center of State University of New York, University Hospital, Health Science Center at Syracuse, Syracuse, New York. The study was performed in accordance with the precepts of the Declaration of Helsinki and its revisions, and of Good Clinical Practice. The protocol was reviewed and approved by an Institutional Review Board prior to initiation of the study. All patients provided written informed consent prior to undergoing any protocol-specific procedures.

For inclusion, patients had to be at least 18 years of age, have a histologically confirmed malignant solid tumor refractory to standard treatment, have a performance status of 0 or 1 on the Eastern Cooperative Oncology Group (ECOG) scale and a life expectancy 2 months or more. Any surgery was to have been performed at least 2 weeks prior to study entry. Radiotherapy, chemotherapy, hormonal therapy and/or immunotherapy were discontinued at least 3 weeks before study entry. The patients were to have recovered from all toxicities associated with prior therapy, and their laboratory values were required to be within the following limits: hemoglobin ≥9.0 g/dl; white blood cells ≥3000/mm$^3$; neutrophils ≥1500/mm$^3$; platelets ≥150,000/mm$^3$; creatinine ≤1.5 mg/dl (133 μmol/l) or creatinine clearance ≥60 ml/min; serum bilirubin ≤3.0 mg/dl; and SGOT/AST, SGPT/ALT and alkaline phosphatase less than five times the upper limit of normal.

Patients could not participate if they had uncontrolled emesis, acute porphyria, active peptic ulcer, diabetes mellitus, chronic gastritis, significant ascites, or clinical evidence of other gastrointestinal conditions that would alter absorption or motility. A history of prior abdominal irradiation, symptomatic bowel involvement related to a disease process, or known hypersensitivity to ranitidine also led to exclusion. Additionally, the presence of an uncontrolled infectious process or of a severe medical problem unrelated to the malignancy disqualified a patient from participation. Patients could not be enrolled if they were of childbearing potential and not practising an adequate form of contraception, or if they were female and pregnant or lactating.

The following therapies were not permitted: treatment with drugs which would alter absorption or GI motility (including cisapride, tricyclics, and glucocorticoids); treatment with another investigational drug within 30 days or five half-lives, whichever was longer, before study entry; and intermittent or chronic use of concomitant treatment for gastric or duodenal ulcers (including H2 antagonists, proton pump inhibitors, or antacids). The protocol did permit filgrastim (granulocyte colony stimulating factor, G-CSF) support following the first course of topotecan.

Upon entry into the study, patients were randomly assigned to receive either oral topotecan alone (treatment A) or oral topotecan following pretreatment with oral ranitidine (treatment B) during the first topotecan course. For treatment B, pretreatment consisted of a total of nine doses of ranitidine: 150 mg twice daily for 4 days before day 1 and one 150-mg dose on day 2, 2 h before oral topotecan administration. The alternative regimen was given during the second course. Ranitidine was obtained commercially as tablets containing 150 mg of the hydrochloride salt (Zantac 150, Glaxo Wellcome, Research Triangle Park, N.C.).

For treatments A and B, topotecan was supplied in capsules containing topotecan hydrochloride equivalent to either 0.25 mg or 1.0 mg of topotecan as the anhydrous base (SmithKline Beecham Pharmaceuticals). The numbers of each capsule strength required to attain the target dose was calculated from the patient's weight at the beginning of each 21-day cycle. Topotecan capsules were administered once daily during the first 5 days of each cycle. Dosing was started at 2.3 mg/m$^2$ per day, the MTD [7]. The dose was held at the MTD through dose 1 of course 2 but subsequently could be adjusted according to the toxicity profile during the previous cycle. The investigator assessed the tumor response at the end of each cycle. Patients who had responded or whose disease was stable could continue topotecan treatment at the investigator's discretion until their disease progressed or unacceptable toxicity occurred.

The patients fasted from midnight on the night before day 1 of the first two courses. Topotecan was administered with 100 ml water in the morning under the supervision of the study center staff. Standardized light meals were served at 30 min and at 4 h after topotecan dosing. Blood samples (2 ml) for determination of plasma topotecan concentrations were drawn into evacuated tubes containing heparin at 0 (predose), 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, and 10 h following the topotecan dose. The patients were then discharged from the study center and self-administered the remaining topotecan doses for the course at home.

Each blood sample was immersed in ice-water within 30 s of collection. The tube was then centrifuged at 3000 rpm for 10 min at 4 °C. A 0.5-ml aliquot of the separated plasma was added to a plastic tube containing 1.0 ml of methanol at −30 °C to precipitate

plasma proteins and stop interconversion of the lactone and open-ring forms. After vortex mixing of the contents, the tube was centrifuged at 4000 rpm for 3 min, and the methanolic supernatant was immediately stored at −70 °C. The remainder of the plasma was transferred without treatment to a second tube and stored frozen at −70 °C until all samples were shipped to the analytical laboratory.

### Topotecan assays

Concentrations of topotecan lactone and total topotecan (lactone plus open-ring carboxylate forms) were assayed using high-performance liquid chromatography (HPLC) with fluorimetric detection of the lactone form [17]. The lactone form of topotecan was determined in the plasma samples (methanolic extracts) that had been deproteinized with cold methanol at the patient's bedside. These samples were diluted 1:2 (v/v) with distilled water just prior to injection onto the HPLC column. For determination of total topotecan, equal volumes of cold methanol and 7% (v/v) perchloric acid were added to aliquots of previously untreated plasma samples to precipitate the proteins and quantitatively convert the open-ring form to topotecan lactone. These samples were injected onto the column without dilution. The standard curve was linear over the range from 0.1 to 10 ng/ml of topotecan lactone. The limit of quantitation was 0.1 ng/ml, using 100 µl plasma or 100 µl plasma/200 µl methanolic extract as appropriate. Concurrent quality control samples showed interday coefficients of variation of 10.5% and mean deviations from nominal concentration ranging from −1.4% to +5.8%.

### Safety assessments

Safety was assessed by reports of adverse events and results of clinical laboratory evaluations, vital signs, physical examinations, and 12-lead electrocardiograms. Toxicities were graded according to the Common Toxicity Criteria (CTC). Blood samples for complete blood counts (CBC) were obtained at screening and on days 8 and 15 after the beginning of each topotecan course. Blood biochemistry and dipstick urinalysis was performed at screening and on day 15. Repeat determinations of CBC and/or blood biochemistry were also performed within 3 days prior to the beginning of a course if the day-15 values from the previous course showed deterioration from baseline or if any values at the screening visit failed to meet the inclusion criteria (course 1 only).

Physical examinations, vital signs, and performance status were assessed at the screening visit, on day 1 of course 1 (vital signs only), and within 3 days prior to initiation of subsequent courses. A 12-lead electrocardiogram was recorded at the screening visit and following the last topotecan course.

### Data analyses

Pharmacokinetic parameters for plasma topotecan lactone and total topotecan were determined according to noncompartmental methods using an in-house pharmacokinetic analysis program, which was validated so as to be consistent with all applicable GLP regulations. Values for the maximum observed plasma concentration (Cmax) and the time at which Cmax occurred (Tmax) were obtained by direct assessment of the data. The terminal elimination rate constant ($\lambda z$) was determined from the log-linear disposition phase of the concentration time curve using least squares regression. Visual inspection was used to determine the number of points that were in the terminal linear phase. The terminal elimination half-life (T1/2) was calculated as $\ln(2)/\lambda z$. Area under the plasma concentration-time curve from time zero to the last quantifiable plasma concentration [AUC(0-t)] was determined using the linear trapezoidal rule for each incremental trapezoid and the log trapezoidal rule for each decremental trapezoid [2]. The area under the plasma concentration-time curve extrapolated to infinity [AUC(0–inf)] was calculated as the sum of AUC(0-t) and $C(t)/\lambda_2$, where C(t) was the predicted concentration from the log-linear regression analysis at the time-point of the last quantifiable concentration. Because the tail area extrapolated from the last quantifiable concentration frequently exceeded 20% of the AUC(0-inf), values of AUC(0-t) rather than AUC(0-inf) were used to assess the extent of oral availability.

Statistical analyses were performed using Statistical Analysis System statistical software [20]. An effect was considered to be statistically significant if the two-sided *P*-value was $< 0.05$. Cmax and AUC(0-t) values were natural log-transformed prior to analysis. Log-transformed values for AUC(0-t) and Cmax and untransformed values for T1/2 were compared using an analysis of variance (ANOVA) model appropriate to a two-period, two-regimen balanced incomplete block crossover study. The model included effects for sequence, subject nested within sequence, period and regimen (presence versus absence of ranitidine). The residual variance from the ANOVA was used to provide point estimates and 95% confidence intervals (CIs) for the difference between the two regimens with respect to the log-transformed Cmax and AUC(0-t) values and untransformed T1/2 values of topotecan lactone and total topotecan. For log-transformed AUC(0-t) and Cmax values, point estimates and CIs of the difference between the two regimens were exponentially back-transformed to estimate the ratios of values in the presence of ranitidine compared to those in the absence of ranitidine. Additionally, between-patient coefficients of variation (CVB%) were calculated for AUC(0-t) and Cmax using the formula $CVB\% = [\exp(SD^2) - 1]1/2 \times 100$, where SD is the standard deviation of the natural log-transformed values.

Between-regimen differences in Tmax values were analyzed using a nonparametric approach that took into account period effects. Point estimates and associated 95% CIs were constructed for the median difference in Tmax values between topotecan with ranitidine and topotecan alone [8].

## Results

### Patient disposition and demography

A total of 18 patients with malignant solid tumors refractory to standard therapy began treatment with topotecan. All patients finished course 1, 16 patients finished course 2, and 9 patients went on to complete three or more courses. Due to the two dropouts after the first course and sample losses during shipment, pharmacokinetic data were missing for four patients for the topotecan with ranitidine regimen and one patient for the topotecan alone regimen. Therefore, analyses of pharmacokinetic data were based on the 13 patients with complete data for both regimens, while assessment of safety parameters was based on all 18 patients.

Demographic and baseline characteristics of the patients are summarized in Table 1. The predominant primary tumor types in these 18 patients were non-small-cell (6, 33%), small-cell (4, 22%). and colorectal (2, 11%). For the other 6 patients, breast, ovarian, and renal were the primary tumor type for 1 patient (6%) each, while 4 patients (22%) were classified as 'other'. All patients had had at least one prior chemotherapy, and 13 (72%) had had prior radiotherapy. Performance status (ECOG scale) at study entry was 0 for 7 patients (39%) and 1 for 11 patients (61%).

**Table 1** Demographic and baseline characteristics of all patients ($n = 18$)

| | |
|---|---|
| Sex | |
| Male | 10 (56%) |
| Female | 8 (44%) |
| Race | |
| White | 17 (94%) |
| Black | 1 (6%) |
| Age (years) | |
| Mean | 60.1 |
| Range | 38 to 84 |
| Weight (kg) | |
| Mean | 68.1 |
| Range | 49 to 90 |
| Body surface area ($m^2$) | |
| Mean | 1.77 |
| Range | 1.48 to 2.14 |
| Primary tumor type | |
| Non-small-cell | 6 (33%) |
| Small-cell | 4 (22%) |
| Colorectal | 2 (11%) |
| Breast | 1 (6%) |
| Ovarian | 1 (6%) |
| Renal | 1 (6%) |
| Other | 3 (17%) |
| Prior anticancer therapy | 18 (100%) |
| Chemotherapy | 18 (100%) |
| Radiotherapy | 13 (72%) |
| Hormone therapy | 1 (6%) |
| Surgery | 0 |
| Performance status at entry | |
| 0 | 7 (39%) |
| 1 | 11 (61%) |

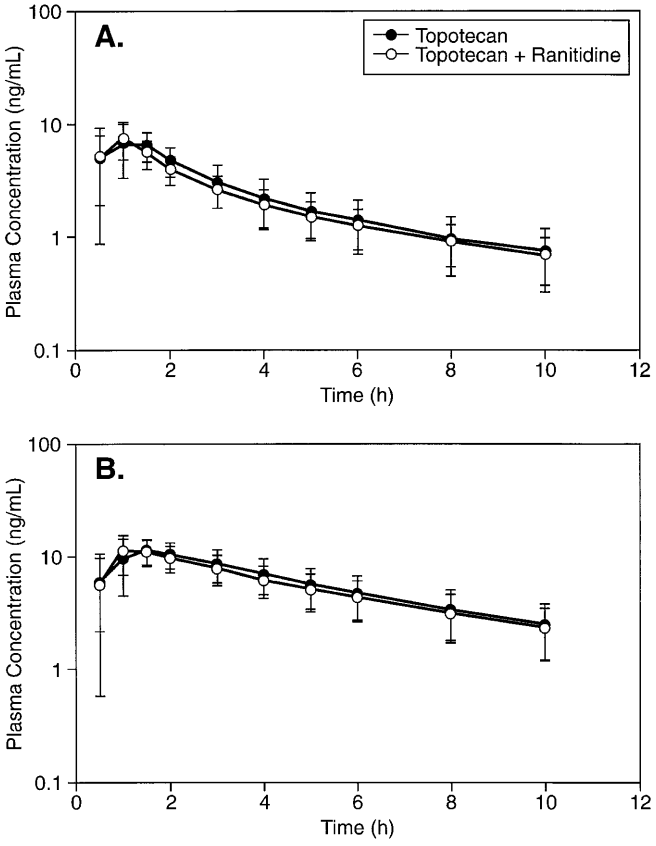


**Fig. 1A,B** Mean (±SD) plasma concentration-time profiles of topotecan lactone (**A**) and total (lactone plus open-ring) topotecan (**B**) following oral administration of a 2.3 mg/$m^2$ dose of topotecan alone or following prior administration of ranitidine in 13 patients

## Pharmacokinetics

Mean concentration-time plots for topotecan lactone and total topotecan in plasma are shown in Fig. 1. Following administration of topotecan alone, the mean peak concentration of active topotecan lactone was approximately two-thirds that of total topotecan (lactone plus open ring carboxylate form) and was observed at a slightly earlier time-point than total topotecan (Table 2). Both the active lactone and total topotecan disappeared from plasma in an approximately monoexponential fashion and exhibited similar half-lives during the terminal phase (Fig. 1, Table 2). The geometric mean ratio of AUC values for active lactone and total topotecan was 0.40 for the ranitidine plus topotecan regimen and 0.41 for topotecan alone (data not shown).

When an oral dose of topotecan was administered following ranitidine treatment, the mean concentration-time profiles were essentially identical to those observed when topotecan was administered alone (Fig. 1, Table 2). There were no significant differences by ANOVA between the two regimens in any of the plasma pharmacokinetic parameters for either the active lactone or total topotecan (Table 2). These analyses did not find any significant effects of sequence or period, indicating that the unbalanced loss of data for five patients did not hinder an accurate assessment of the difference between regimens.

Point estimates comparing pharmacokinetic parameters in the presence of ranitidine to those in the absence of ranitidine are shown in Table 3. The point estimate of the AUC ratios was close to unity for both topotecan lactone and total topotecan, and the 95% CIs were within the interval 0.80 to 1.16. The AUC results indicate that systemic exposure to both topotecan lactone and total topotecan was equivalent in the presence and absence of ranitidine. With the paired bioavailability data from 13 patients and $\alpha = 0.05$, the data provided an 84% power to detect a 20% difference in the exposure to topotecan lactone.

Estimates of the median difference in Tmax values showed that in the presence of ranitidine, total topotecan peaked somewhat sooner (median decrease in Tmax of 0.5 h), while the Tmax for topotecan lactone was not consistently changed (Table 3). Point estimates for the Cmax ratios were 1.06 and 1.07 for the lactone form and total topotecan, respectively, with wide confidence intervals. Taken together, these results suggest a slightly faster rate of absorption when topotecan is administered orally with ranitidine, which is an unexpected finding.

The mean terminal elimination half-lives of topotecan lactone and total topotecan were similar between the

**Table 2** Plasma pharmacokinetic parameters of topotecan lactone and total topotecan after oral administration of topotecan (2.3 mg/m$^2$ per day) alone or following ranitidine in 13 patients Values are median (range) for Tmax, mean ± standard deviation for the others. Values in brackets for Cmax and AUC(0-t) are between-patient coefficients of variation (*Cmax* peak concentration, *Tmax* time of peak concentration, *AUC(0-t)* area under the curve from zero to the last quantifiable concentration, *T1/2* terminal disposition half-life)

| | Parameter | Topotecan alone | Topotecan + ranitidine |
|---|---|---|---|
| Topotecan lactone | Cmax (ng/ml) | 8.41 ± 2.03 [27.0%] | 8.70 ± 2.69 [37.9%] |
| | Tmax (h) | 1.00 (0.5 to 1.5) | 1.00 (0.5 to 1.5) |
| | AUC(0-t) (ng · h/ml) | 24.2 ± 6.9 [26.8%] | 22.0 ± 5.3 [26.6%] |
| | T1/2 (h) | 4.10 ± 1.09 | 4.55 ± 1.55 |
| Total topotecan | Cmax (ng/ml) | 12.2 ± 2.9 [24.4%] | 12.9 ± 3.7 [32.8%] |
| | Tmax (h) | 1.50 (1.0 to 3.0) | 1.50 (0.5 to 1.5) |
| | AUC(0-t) (ng · h/ml) | 59.3 ± 17.7 [30.9%] | 56.0 ± 16.4 [30.3%] |
| | T1/2 (h) | 4.29 ± 1.21 | 4.64 ± 1.98 |

**Table 3** Comparison of pharmacokinetic parameters after oral administration of topotecan following ranitidine (*test*) to those after administration of topotecan alone (*reference*) (*Cmax* peak concentration, *Tmax* time of peak concentration, *AUC(0-t)* area under the curve from zero to the last quantifiable concentration, *T1/2* terminal disposition half-life)

| | Parameter | Test:reference comparison | Point estimate | 95% confidence interval |
|---|---|---|---|---|
| Topotecan lactone | Cmax | Ratio | 1.06 | (0.78, 1.44) |
| | Tmax | Median difference | 0.00 h | (−0.25, 0.00) h |
| | AUC(0-t) | Ratio | 0.94 | (0.80, 1.10) |
| | T1/2 | Mean difference | 0.52 h | (−0.33, 1.38) h |
| Total topotecan | Cmax | Ratio | 1.07 | (0.84, 1.38) |
| | Tmax | Median difference | −0.50 h | (−0.75, 0.00) h |
| | AUC(0-t) | Ratio | 0.97 | (0.80, 1.16) |
| | T1/2 | Mean difference | 0.35 h | (−0.64, 1.35) h |

two regimens (Table 2). The 95% CI around the mean difference in T1/2 values included zero for both the lactone form and total topotecan (Table 3).

## Clinical results

During this study, 18 patients received between 1 and 6 (median 2.5) courses of oral topotecan, for a total of 54 courses (Table 4). Dose reductions or escalations were permitted after day 1 of course 2. All 18 patients completed course 1, and 16 patients completed course 2, with 32 of their 34 courses administered at the target dose of 2.3 mg/m$^2$ per day, the previously determined MTD for oral topotecan. Nine patients entered the third course and received a lower topotecan dose of 1.9 mg/m$^2$ per day. This dose was administered over a total of 21 courses during courses 3 through 6. One patient had an upward dose adjustment to 2.7 mg/m$^2$ per day for days 2 to 5 of course 2.

None of these patients with refractory advanced disease had an objective tumor response by World Health Organization criteria. Ten patients (56%) had stable disease by the 8-week minimum criterion. Their median time to disease progression was 13.3 weeks (range 9.3–42.0 weeks). The remaining eight patients (44%) had progressive disease.

No patient was withdrawn from the study due to adverse or serious adverse experiences. The incidence of grade 3 or 4 hematological toxicity was highest following the first course of topotecan at the MTD (Table 4), in part due to the effects of G-CSF support and dose adjustment on subsequent courses. G-CSF support was used in 3 of 18 patients (17%) in 9 of 54 courses (17%).

**Table 4** Number (%) of patients with CTC (National Cancer Institute Common Toxicity Criteria) grade 3 or 4 hematological toxicity by topotecan course number (*note:* the numbers of patients summed over all courses may sum to a number larger than that for "any" course, since a patient may have had grade 3/4 toxicity during more than one course)

| Course | Patients[a] | Neutropenia | Thrombocytopenia | Anemia | Leukopenia |
|---|---|---|---|---|---|
| No. 1 | 18 | 7 (39%) | 7 (39%) | 4 (22%) | 4 (22%) |
| No. 2 | 16 | 3 (17%) | 2 (11%) | 1 (6%) | 3 (19%) |
| No. 3 | 9 | 1 (11%) | 0 | 1 (11%) | 1 (11%) |
| No. 4 | 7 | 0 | 0 | 1 (14%) | 0 |
| No. 5 | 3 | 0 | 0 | 0 | 0 |
| No. 6 | 1 | 0 | 0 | 0 | 0 |
| Any | 18 | 8 (44%) | 9 (50%) | 6 (33%) | 7 (39%) |

[a] Number of patients who completed the course and had hematology results

**Table 5** Number (%) of courses in which a non-hematological toxicity was reported in more than 10% of the courses (*n.a.* not applicable)

| Toxicity (preferred term) | Common Toxicity Criteria grade | | | | Total (%)[a] |
|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | |
| Nausea | 19 (35%) | 3 (6%) | 3 (6%) | 0 | 25 (46%) |
| Fatigue | 13 (24%) | 4 (8%) | 2 (4%) | 0 | 19 (35%) |
| Anorexia | 11 (20%) | 6 (11%) | 0 | 0 | 17 (32%) |
| Vomiting | 9 (17%) | 5 (9%) | 2 (4%) | n.a. | 16 (30%) |
| Alopecia | 8 (15%) | 3 (6%) | n.a. | n.a. | 11 (20%) |
| Diarrhea | 8 (15%) | 1 (2%) | 0 | 0 | 9 (17%) |
| Coughing | 4 (7%) | 4 (7%) | 0 | 0 | 8 (15%) |
| Skeletal pain | 4 (7%) | 3 (6%) | 0 | 0 | 7 (13%) |
| Abdominal pain | 4 (7%) | 1 (2%) | 1 (2%) | 0 | 6 (11%) |
| Dyspnea | 5 (9%) | 1 (2%) | 0 | 0 | 6 (11%) |
| Depression | 4 (7%) | 0 | 2 (4%) | 0 | 6 (11%) |

[a] As a percentage of the 54 topotecan courses administered

Delays in therapy of greater than 7 days occurred in 3 of the 36 courses beyond course 1 (8%).

Most nonhematological toxicities were rated as CTC grade 1 or 2. Nausea, fatigue, anorexia and vomiting were the most frequent complaints (Table 5). No grade 3 or 4 diarrhea was reported. There were additional grade 3 or 4 nonhematological toxicities observed in $< 10\%$ of courses. One patient experienced grade 3 fever, one patient experienced grade 4 fever, and two patients experienced grade 3 dehydration reported as related or possibly related to treatment.

## Discussion

Ranitidine is among the H2-antagonists with a low potential for interaction with other drugs [3, 13]. Very few interactions have been reported to involve inhibition of drug metabolism by ranitidine [3, 13]. The results of in vitro studies indicate that ranitidine does not appreciably inhibit the cytochrome P450 isoforms 1A2, 2D6, and 3A4/5 [15]. Renal excretion (as total topotecan) accounts for a substantial proportion (i.e. 20–60%) of the elimination of an intravenous dose of topotecan in humans [1, 5, 16]. Although *N*-desmethyl-topotecan, its *O*-glucuronide, and topotecan *O*-glucuronide have been identified as metabolites, they are present in only minor amounts [18, 19]. Ranitidine has been found to decrease the renal clearance of a few compounds (e.g. triamterene) via competition for renal cation transporters [3, 13]. One would not expect ranitidine and topotecan to interact at this level, since it has been shown in mice that the acid form of topotecan is cleared by anion transporters sensitive to probenecid [26], although it is not known whether the same is the case with the lactone form of topotecan. However, pH-dependent decreases in the oral availability of some drugs, including ketoconazole and cefpodoxime proxetil, have been observed during concomitant administration of ranitidine [3, 13].

H2 antagonists such as ranitidine are frequently prescribed to patients undergoing cancer chemotherapy for a variety of indications, including the prevention or treatment of gastrointestinal toxicity and for comorbid conditions. Like other camptothecin analogues, topotecan lactone is converted nonenzymatically to the open-ring carboxylate form in a pH-dependent manner. Because the open-ring form predominates above a pH of 4, it was of interest to ascertain whether a decrease in gastric acidity due to pretreatment with ranitidine would reduce the extent of absorption of orally administered topotecan.

The present study was designed to determine whether the pharmacokinetics of oral topotecan were affected by prior and coadministration of ranitidine (150 mg twice daily for 4 days before and 150 mg 2 h before topotecan). The results of this study showed that ranitidine did not reduce the extent of absorption [AUC(0-t)] of topotecan. The slightly shorter time to peak concentration for total topotecan, together with the small average increases in Cmax value for both lactone and total topotecan, suggested a slight, but not significant, increase in the rate of absorption of orally administered topotecan when patients were pretreated with ranitidine.

In a bioavailability and pharmacokinetic study, patients with solid tumors received this capsule formulation of topotecan (2.3 mg/m$^2$) on one occasion and 1.5 mg/m$^2$ by intravenous infusion on another occasion [11]. The mean value for absolute bioavailability of the capsules was approximately 40%. While there was no significant difference between oral and intravenous topotecan in the lactone-total AUC ratio, the terminal half-life was significantly longer after administration of the oral formulation ($4.0 \pm 1.0$ h) than after administration of the intravenous formulation ($2.8 \pm 0.4$ h) of topotecan. This apparent change in the terminal half-life is due to the fact that the rate of absorption is slower than the rate of elimination, resulting in an oral terminal half-life that reflects the absorption rate rather than the elimination rate of topotecan.

The relative bioavailability of topotecan given orally with or without food was also assessed in the same study. When topotecan was administered to patients after they had eaten a high-fat breakfast, a small increase (approximately 15% on average) in the extent of bioavailability was observed. Considering the lack of effect of ranitidine in the present study, it is unlikely that

a change in the pH of the gastric contents would account for the small increase in the oral bioavailability of topotecan when administered with food. Other factors such as improved solubilization and dispersion of topotecan, increased splanchnic blood flow, or prolonged exposure at an absorption window may contribute to the food-induced change in bioavailability [23, 24, 25].

In an earlier bioavailability study, the degree of interconversion between the lactone and acid forms could not be determined because the open-ring acid form of topotecan was not administered separately [21]. However, the bioavailability of topotecan has been assessed in a three-way crossover study in which dogs received the lactone and acid forms of topotecan by intravenous infusion and topotecan in capsules. Average oral bioavailability of topotecan capsules was estimated as approximately 50% in this species and showed little dependence on whether or not the calculations accounted for interconversion between the lactone and acid forms [4]. In the dog, conversion of the lactone to the acid form proceeded at an appreciably slower rate than either distribution to the peripheral compartment or elimination by the kidney and liver [4].

In this clinical study, prior administration of ranitidine resulted in a similar extent of absorption of orally administered topotecan. A slightly faster rate of absorption for oral topotecan after ranitidine pretreatment was observed, which is unlikely to be of clinical significance. These results suggest that dosage adjustments of orally administered topotecan should not be necessary in patients who are pretreated with an H2 antagonist, such as ranitidine, or other agents which comparably raise gastric pH.

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