The Oncologist®
Clinical Pharmacology

Medicinal Cannabis Does Not Influence the Clinical Pharmacokinetics of Irinotecan and Docetaxel

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Key Words. Medicinal cannabis • Irinotecan • Docetaxel • Pharmacokinetics • CYP3A • Drug interaction

ABSTRACT

Objective. **To date, data regarding the potential of cannabinoids to modulate cytochrome P450 isozyme 3A (CYP3A) activity are contradictory. Recently, a standardized medicinal cannabis product was introduced in The Netherlands. We anticipated an increased use of medicinal cannabis concurrent with anticancer drugs, and undertook a drug-interaction study to evaluate the effect of concomitant medicinal cannabis on the pharmacokinetics of irinotecan and docetaxel, both subject to CYP3A-mediated biotransformation.**

Patients and Methods. **Twenty-four cancer patients were treated with i.v. irinotecan (600 mg, $n = 12$) or docetaxel (180 mg, $n = 12$), followed 3 weeks later by the same drugs concomitant with medicinal cannabis (200 ml herbal tea, 1 g/l) for 15 consecutive days, starting 12 days before the second treatment. Blood samples were obtained up to 55 hours after dosing and analyzed for irinotecan and its metabolites (SN-38, SN-38G), respectively, or docetaxel. Pharmacokinetic analyses were performed during both treatments. Results are reported as the mean ratio (95% confidence interval [CI]) of the observed pharmacokinetic parameters with and without concomitant medicinal cannabis.**

Results. **Medicinal cannabis administration did not significantly influence exposure to and clearance of irinotecan (1.04; CI, 0.96–1.11 and 0.97; CI, 0.90–1.05, respectively) or docetaxel (1.11; CI, 0.94–1.28 and 0.95; CI, 0.82–1.08, respectively).**

Conclusion. **Coadministration of medicinal cannabis, as herbal tea, in cancer patients treated with irinotecan or docetaxel does not significantly influence the plasma pharmacokinetics of these drugs. The evaluated variety of medicinal cannabis can be administered concomitantly with both anticancer agents without dose adjustments.** ***The Oncologist*** 2007;12:291–300

Disclosure of potential conflicts of interest is found at the end of this article.

INTRODUCTION

For the past 4,000 years [1], patients and doctors of each era have resorted to cannabis when conventional treatments were ineffective or lacking [2, 3]. Indeed, in oncology beneficial effects have been reported for cancer-associated anorexia, (delayed) chemotherapy-induced nausea and

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vomiting, and palliation [4–8]. However, largely as a result of the lack of well-designed clinical trials and registered, and thus standardized, products, much controversy remains regarding the claimed benefits [9].

The only U.S. Food and Drug Administration (FDA)-approved medicinal cannabis products are an oral formulation containing dronabinol (Marinol®; Solvay Pharmaceuticals Inc, Marietta, GA), the synthetic version of delta9-tetrahydrocannabinol (THC), the main pharmacologically active cannabinoid [10], and capsules containing nabilone, an analog of dronabinol (Cesamet®; Valeant Pharmaceuticals Int., Costa Mesa, CA). In Canada, where seriously ill patients can apply for medicinal cannabis under the Canadian Marihuana Medical Access Regulations, the government licensed the prescription sale of an oromucosal spray called Sativex® (GW Pharm Ltd, Salisbury, United Kingdom) containing both THC and cannabidiol (CBD) in April 2005. This buccal spray was designed to circumvent the substantial first-pass effect that occurs after oral administration, resulting in low and variable bioavailability of THC. However, after inhalation of THC (following pulmonary administration through vaporization or smoking of *Cannabis sativa* L. extract), absorption of THC is increased even more, to up to 50% of the administered dose, leading to higher systemic exposure and more effects. Indeed, many patients claim (subjectively) that a whole or partially purified extract of *Cannabis sativa* L. offers advantages over a single isolated ingredient [10–12]. In The Netherlands, the unavailability of a legal product forced patients to frequent "coffee shops," which, although not prosecuted according to the Dutch soft-drugs policy, remain illegal. In September 2003, in order to stimulate the conduct of representative clinical trials evaluating the safety and efficacy of medicinal cannabis, whilst simultaneously offering patients access to a prescription product meeting pharmaceutical quality standards (standardized content, free of microbiological impurities) [13], a legal medicinal cannabis product was introduced in The Netherlands [14]. However, as it is not an officially registered drug, pharmacokinetic drug interactions have not been evaluated as recommended for new drug applications [15]. Yet, it has previously been shown that pharmacokinetic drug interactions with herbal products (increasingly used by cancer patients) [16, 17] can result in under- or overdosing [18–20].

Cannabinoids appear able to modulate the catalytic activity of several hepatic cytochrome P450 (CYP) isozymes, including isozyme 3A (CYP3A), responsible, in part, for the metabolism of 37% of all currently FDA-approved anticancer drugs [21]. The majority of in vitro and animal data suggest an inhibitory effect on CYP3A-mediated metabolism [22–25], yet induction of CYP3A has been observed after repeated administration [26, 27]. In vivo data are also contradictory; both CYP3A inhibition [28] and induction [29] have been reported. Moreover, clinical drug-interaction studies adequately assessing the effect of medicinal cannabis on the pharmacokinetics of concomitantly administered (anticancer) drugs are absent [30, 31].

We anticipated that the introduction of a legal cannabis product in The Netherlands would result in an increased use of medicinal cannabis concomitant with cytotoxic drugs, many of which are highly toxic and characterized by narrow therapeutic windows. The postulated, albeit contradictory, effects of cannabinoids on CYP3A function and the absence of clinical drug-interaction studies led us to initiate a drug-interaction study to assess the influence of medicinal cannabis on the pharmacokinetics of the anticancer drugs irinotecan and docetaxel, both CYP3A substrates [32, 33]. We here report on the plasma pharmacokinetics of irinotecan and docetaxel after i.v. infusion to cancer patients, with and without concomitant oral medicinal cannabis administration.

Patients and Methods

Patients and Treatment

Patients were eligible if they had a histologically or cytologically confirmed diagnosis of (metastatic) cancer for which irinotecan or docetaxel was considered an adequate option, which was refractory to conventional treatment or for which there was no standard regimen. Eligibility criteria were identical to those documented elsewhere [20, 34]. In addition, patients with a history of, or current, cannabis use (assessed through patient interview and evaluation of patient records) were not eligible. The protocol was approved by the institutional review board of the Erasmus MC and written informed consent was obtained from all patients prior to study entry.

The primary study endpoint was a measurable effect of medicinal cannabis on the plasma pharmacokinetics of irinotecan and its metabolites SN-38 and SN-38-glucuronide (SN-38G) or on docetaxel plasma pharmacokinetics. Based on the assumption that the within-patient standard deviation of the response variable (i.e., irinotecan or docetaxel pharmacokinetic parameters) for two measurements is 0.2 (interoccasion variability, 20%), a power $(1 - \beta)$ of 0.9 (90%), a clinically relevant difference of 30% [35, 36], and a two-sided significance level of 0.05 (5%), a sample size of (at least) 12 patients per treatment arm (i.e., irinotecan or docetaxel) was required in a paired two-sided analysis [37]. It was assumed that the interval between the two treatments was an adequate washout period, with no carryover effects.

Patients meeting eligibility criteria received their first treatment of either irinotecan, as a 90-minute i.v. infusion, or docetaxel, as a 1-hour i.v. infusion, at a fixed dose of 600 mg or 180 mg, respectively, followed 3 weeks later by a second treatment of the same drug in combination with medicinal cannabis. The decision to administer a fixed dose, instead of a body surface area (BSA)-based dose, was based on analyses demonstrating that BSA-based dosing does not substantially decrease interindividual variability in drug clearance for these two drugs [38–41]. For the second treatment, the first three patients were dosed irinotecan and docetaxel at 75% (450 mg and 135 mg, respectively), after which a protocol-scheduled interim safety analysis, including a pharmacokinetic analysis, was performed to determine whether subsequent dose adjustments were necessary. If no clinically relevant [35, 36, 42] pharmacokinetic interaction or increased hematological toxicity was observed, the following nine patients were to be administered the same dose as in the first treatment. Dose reductions for the second treatment were allowed and based on the worst toxicity observed during the previous treatment (i.e., either febrile neutropenia, grade 4 neutropenia lasting more than 1 week, severe cutaneous reactions, or severe peripheral neuropathy for docetaxel patients and diarrhea, grade 3 or 4, and neutropenia, grade 4, for irinotecan patients).

Irinotecan (Campto®; Pfizer, Capelle aan den IJssel, The Netherlands) and docetaxel (Taxotere®; Sanofi-Aventis, Gouda, The Netherlands) were diluted in 250 ml 0.9% (weight/volume) sodium chloride prior to drug administration. Patients received oral and written instructions to prepare the medicinal cannabis (*Cannabis sativa* L. Flos, variety Bedrocan®, Office for Medicinal Cannabis, The Hague, The Netherlands) containing 18% THC and 0.8% CBD, as 200 ml of herbal tea (1 g/l), and to administer it once daily in the evening [26] at home, for a total of 15 consecutive days as recommended [15], starting on day 10 of the first treatment. In addition, patients were requested to fill out a diary to record their adherence to the instructed medicinal cannabis regimen and to record any additional medication administered between the two chemotherapy treatments. During both treatments, patients administered irinotecan received granisetron (1 mg i.v.) and dexamethasone (10 mg i.v.) 30 minutes prior to chemotherapy. Atropine (0.25 mg) was administered s.c. as treatment or prophylaxis for irinotecan-induced acute cholinergic syndrome. To prevent allergic reactions and edema for patients treated with docetaxel, premedication consisted of dexamethasone (8 mg, orally) given twice daily for three consecutive days, starting on the evening before docetaxel infusion.

During both treatments, physical examination, toxicity assessment [43], and a CBC with differential and serum chemistry tests, including creatinine, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, total bilirubin, and albumin, were performed weekly.

Pharmacokinetic Analyses

Irinotecan, its metabolites (SN-38, SN-38G), and docetaxel pharmacokinetic analyses were performed during both treatments. Blood samples (approximately 7 ml in lithium-heparinized tubes) were collected immediately prior to irinotecan infusion and 30 minutes after the start of infusion, just before the end of infusion (EOI), at 10, 20, and 30 minutes, and at 1, 1.5, 2, 3, 4, 5, 6, 22.5, 30, 46.5, and 54 hours after the EOI for irinotecan pharmacokinetics [18] (total number of samples, 17). For docetaxel pharmacokinetics, blood samples (as described above) were collected immediately prior to docetaxel infusion and 30 minutes after the start of infusion, just before the EOI, at 10, 20, and 30 minutes, and at 1, 1.5, 2, 4, 5, 6, 7.5, 23, 31.5, and 47 hours after the EOI [44] (total number of samples, 16). All samples were processed to plasma by centrifugation for 10 minutes at 3,000 × g (4°C) and stored at -80°C until analysis. Irinotecan and its metabolite concentrations were determined by validated assays based on reversed-phase high-performance liquid chromatography (HPLC) with fluorescence detection [45, 46]. Docetaxel plasma concentrations were determined using HPLC with tandem mass-spectrometric detection [44].

Based on a previously developed population model [47, 48] and the observed individual plasma concentrations, individual pharmacokinetic parameter estimates for irinotecan and its metabolites were derived as Bayesian (post hoc) estimates without re-estimation in the NONMEM (nonlinear mixed-effects model) software program (double precision, version V, level 1.1; GloboMax; Hanover, MD) [49]. The area under the plasma concentration–time curve (AUC) was predicted for irinotecan and its metabolites from time 0 to 100 hours after the start of the infusion for both treatments. Total individual AUCs were computed as dose divided by individual predicted clearance (CL) (or apparent clearance [CL/fm] for the metabolites). Metabolic ratios, that is, the relative extent of conversion (REC) (AUC_{0-100} ratio of SN-38 to irinotecan × 100%) and the relative extent of glucuronidation (REG) (AUC_{0-100} ratio of SN-38G to SN-38), were calculated based on individual Bayesian predicted AUC values.

For docetaxel, individual pharmacokinetic parameters were estimated using model-dependent methods implemented in WinNonLin 4.0 (Pharsight, Mountain View, CA). Concentration–time data were fit with a three-com-

partment model with reciprocal squared prediction weighting. Model adequacy was guided by inspection of the coefficient of variation of the fitted pharmacokinetic parameters, and by the Akaike information criterion [50]. Maximum plasma concentrations were obtained from the model-estimated plasma concentration at the end of infusion. Calculated secondary parameters included systemic exposure (AUC), total systemic clearance, half-life during the terminal phase of the disposition curve, and (apparent) volume of distribution.

Cannabis Screening

A urine sample was collected just before the start of the second treatment and stored at −80°C until analysis. Samples were screened semiquantitatively (i.e., results are reported as "positive," i.e., above, or "negative," i.e., below, the threshold level of 50 μg/l) for presence of the primary urinary metabolite of orally ingested THC (11-nor-THC-9-carboxylic acid) using a validated cannabinoids assay (TDx/FLx® cannabinoids assay; Abbott Laboratories, Abbott Park, IL). The presence of cannabinoids and/or metabolite(s) in urine indicates previous cannabis exposure [51].

Statistics

All parameter estimates are reported as mean values with 95% confidence intervals (CIs) in parentheses unless stated otherwise. The difference in irinotecan and docetaxel pharmacokinetic parameters between the first and second treatment was evaluated by calculating 95% CIs for the geometric mean ratios of the observed pharmacokinetic parameters in the presence and absence of medicinal cannabis (e.g., 95% CI for ratio $CL_{treatment2}$:$CL_{treatment1}$) [52]. The CI for the geometric mean ratio provides an estimate of the distribution of the observed systemic exposure measure ratio of substrate and interacting drug versus substrate alone and conveys a probability of the magnitude of the interaction. The difference in hematological toxicity, expressed as percentage decrease in white blood cell count (WBC) and percentage decrease in absolute neutrophil count (ANC), at nadir compared with baseline (calculated as follows: [(pretreatment value − nadir value) / (pretreatment value)] × 100%), in those patients who received identical doses in both courses, was evaluated statistically using nonparametric, two-tailed, Wilcoxon signed rank tests for paired observations, and the significance level was set at $p < .05$. Statistical calculations were performed with SPSS, version 11.5 (Chicago, IL).

Results

Patient Accrual

To determine the influence of medicinal cannabis on irinotecan and docetaxel pharmacokinetics and hematological toxicity, 17 and 14 patients, respectively, were enrolled. Four patients did not continue irinotecan treatment after course 1 because of unacceptable treatment-related toxicity or progressive disease. One patient did not take medicinal cannabis tea as prescribed and was replaced. In the docetaxel group, one patient declined further treatment after course 1 and one patient died on day 10 of course 1 following multiple organ failure, which was unlikely to be related to docetaxel treatment, but most probably a result of rapid disease progression. For both the irinotecan and docetaxel treatment arms, 12 patients completed two treatments, did not use comedication and/or dietary supplements known to modulate CYP3A function, took their medicinal cannabis as prescribed (based on cannabis screening, patient oral declaration, and patient treatment diaries), and were evaluable for irinotecan and docetaxel pharmacokinetic analyses. Table 1 lists a summary of the baseline characteristics of the 12 patients in each treatment group.

Irinotecan Treatment and Pharmacokinetics

All patients were administered 600 mg irinotecan during the first treatment. Two patients enrolled after the interim analysis, which did not demonstrate a substantial change in irinotecan pharmacokinetics or increased hematological toxicity, also received a reduced second irinotecan dose because of toxicity, that is, grade 3 diarrhea (450 mg) and grade 3 liver function abnormalities (300 mg). All other patients ($n = 7$) were administered 600 mg during the second treatment.

Upon concurrent medicinal cannabis use, irinotecan clearance and dose-normalized AUC were not significantly affected, as reflected by the geometric mean ratios and the corresponding 95% CIs for the two parameters of 0.97 (0.90–1.05) and 1.04 (0.96–1.11), respectively. Similarly, metabolic clearance and dose-normalized AUC of SN-38 and SN-38G were not significantly changed. Table 2 summarizes the pharmacokinetic parameters for irinotecan with and without concomitant medicinal cannabis administration. The mean ($n = 12$) irinotecan, SN-38, and SN-38G dose-normalized plasma concentration–time curves for the two treatments further illustrate the similarity between the two treatments (Fig. 1).

Docetaxel Treatment and Pharmacokinetics

In the absence of medicinal cannabis, all patients were administered 180 mg docetaxel. In the presence of medicinal

Table 1. Baseline patient characteristics ($n = 12$ per treatment arm)

Characteristic	Irinotecan	Docetaxel
Age, years	58 (27–66)	55 (40–67)
Sex		
Male	7	7
Female	5	5
Body surface area, m^2	1.90 (1.56–2.20)	1.78 (1.50–2.16)
WHO performance status	1 (0–1)	1 (0–1)
Tumor type		
Pancreas	5	1
Breast	–	4
Melanoma	–	3
Head and neck	–	2
ACUP	2	–
Lung	1	1
Gastric	1	1
Sarcoma	1	–
Cholangiocarcinoma	1	–
PNET	1	–
Hematology		
WBC, $\times 10^9$/l	7.4 (4.4–13.5)	6.5 (4.3–15.6)
ANC, $\times 10^9$/l	4.9 (2.1–11.2)	4.2 (2.8–14.5)
Platelets, $\times 10^9$/l	233 (116–447)	293 (144–620)
Hemoglobin, mmol/l	8.2 (5.8–9.3)	8.2 (6.6–10.5)
Clinical chemistry		
ASAT, U/l	31 (16–104)	30 (14–64)
ALAT, U/l	35 (10–133)	21 (12–65)
Alkaline phosphatase U/l	109 (66–323)	96 (61–401)
Total bilirubin, μmol/l	8 (4–21)	7 (3–25)
Total protein, g/l	75 (66–88)	64 (48–80)
Serum albumin, g/l	42 (29–45)	39 (32–48)
Serum creatinine μmol/l	63 (51–88)	64 (48–80)
Serum AAG, g/l	1.41 (0.74–2.84)	0.71 (0.47–2.16)

Values are given as median with range in parentheses (except for sex and tumor type).
Abbreviations: AAG, alpha-1 acid-glycoprotein; ACUP, adenocarcinoma of unknown primary; ALAT, alanine aminotransferase; ANC, absolute neutrophil count; ASAT, aspartate aminotransferase; PNET, primitive neuroectodermal tumor; WHO, World Health Organization.

cannabis, three patients, enrolled after the interim analysis, which did not demonstrate a substantial change in docetaxel pharmacokinetics or increased hematological toxicity, also received a reduced dose (135 mg) because of treatment-related hematological toxicity (leukopenia and neutropenia grade 4). Table 3 summarizes the pharmacokinetic parameters for docetaxel with and without concomitant medicinal cannabis administration. Interindividual variability in clearance (l/hour) expressed as a coefficient of variation was 19.7%. BSA-based normalization of clearance (l/hour/m^2) reduced the interindividual variability in clearance to 17.3%, indicating a relative reduction in interindividual variability in clearance of 12%, which is not considered a statistically significant reduction in interindividual variability in clearance [40].

Upon concurrent medicinal cannabis use, docetaxel clearance and the dose-adjusted AUC were not significantly affected, as reflected by the geometric mean ratios and the corresponding 95% CIs for the two parameters of 0.95 (0.82–1.08) and 1.11 (0.94–1.28), respectively. Fur-

Table 2. Irinotecan pharmacokinetic parameters ($n = 12$) in the absence (−) and presence (+) of medicinal cannabis

Parameter[a]	Cannabis −	Cannabis +	Ratio[b]
Absolute dose, mg	600	525 (461–589)[c]	NA
Irinotecan			
CL, l/hour	29.3 (23.8–34.7)	28.4 (22.7–34.0)	0.97 (0.90–1.05)
AUC_{0-inf}, ng*hour/ml[d]	22,825 (17,141–28,509)	23,644 (17,703–29,932)	1.04 (0.96–1.11)
SN-38			
CL, l/hour	400 (330–469)	341 (290–392)	0.90 (0.74–1.05)
AUC_{0-100}, ng*hour/ml[d]	422 (325–519)	448 (364–532)	1.11 (0.98–1.23)
SN-38G			
CL, l/hour	53.7 (36.6–70.9)	45.8 (30.4–61.2)	0.93 (0.74–1.12)
AUC_{0-100}, ng*hour/ml[d]	3,837 (2,217–5,457)	4,101 (2,385–5,818)	1.10 (0.94–1.26)
Relative AUCs			
REC, %	1.95 (1.48–2.41)	2.04 (1.58–2.49)	1.07 (0.94–1.20
REG	7.39 (5.30–10.93)	6.90 (5.40–10.28)	0.98 (0.87–1.09)

[a]Values are reported as mean with 95% confidence interval in parentheses.
[b]Geometric mean ratio of the observed pharmacokinetic parameters with medicinal cannabis and without medicinal cannabis; a significant difference exists when the value 1.00 is not included within the 95% confidence interval.
[c]Four patients received a reduced dose of 450 mg (75%) and one patient received a reduced dose of 300 mg (50%).
[d]Dose-normalized to 600 mg.
Abbreviations: AUC, area under the plasma concentration–time curve; AUC_{0-inf}, AUC extrapolated to infinity; AUC_{0-100}, AUC extrapolated up to 100 hours; CL, clearance; NA, not applicable; REC, relative extent of conversion (AUC_{0-100} SN-38 over AUC_{0-100} irinotecan × 100%); REG, relative extent of glucuronidation (AUC_{0-100} SN-38G over AUC_{0-100} SN-38).

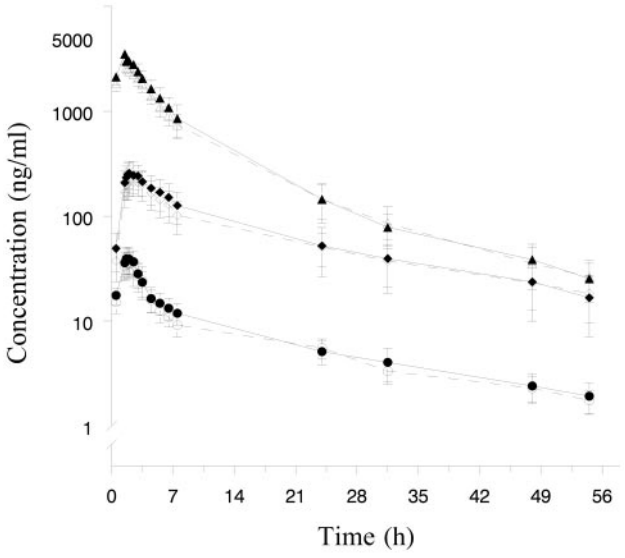

Figure 1. Mean (95% confidence interval, $n = 12$) plasma concentration of irinotecan (dose, 600 mg) in the absence (solid line, closed symbols and error bars) and presence (dose-normalized to 600 mg, dashed line, open symbols and error bars) of medicinal cannabis. Triangles, diamonds, and circles represent concentrations of irinotecan, SN-38G, and SN-38, respectively.

thermore, for the two parameters, interpatient variability, expressed as a coefficient of variation, was only marginally higher in the presence of medicinal cannabis (26% versus 20% and 30% versus 21%, respectively), yet within previously reported ranges [53, 54]. The mean ($n = 12$) docetaxel plasma concentration–time curves for the two treatments illustrate the similarity between the two treatments (Fig. 2).

Cannabis Screening

All urine samples tested positive for cannabinoids and/or metabolites. Although this is not definite confirmation of patient adherence, we have no reason to believe that patients did not take their medicinal cannabis as prescribed, which could explain the lack of a pharmacokinetic drug interaction.

Toxicity

For both drug treatments, hematological toxicity was the predominant side effect. Upon concurrent medicinal cannabis use, the relative hematological toxicity (expressed as percentage decrease in WBC at nadir compared with baseline and percentage decrease in ANC at nadir compared with baseline) in those patients who received full-dose docetaxel (180 mg) during both treatments ($n = 6$) was not significantly affected, with mean values (95% CI) for the first versus second treatment of 82.6% (75.2%–90.1%) versus 80.6% (73.2%–88.0%) and 91.3% (85.7%–96.8%) versus 92.0% (87.4%–96.5%), respectively ($p = .75$) (Table 4).

Table 3. Docetaxel pharmacokinetic parameters ($n = 12$) in the absence (−) and presence (+) of medicinal cannabis

Parameter[a]	Cannabis −	Cannabis +	Ratio[b]
Absolute dose, mg	180	158 (143–172)[c]	NA
CL, l/hour	40.4 (35.4–45.5)	37.9 (31.7–44.2)	0.95 (0.82–1.08)
AUC,[d] ng*hour*ml^{-1}*mg^{-1}	25.7 (22.2–29.2)	28.3 (22.9–33.7)	1.11 (0.94–1.28)
C_{max},[d] ng/ml*mg^{-1}	17.8 (15.7–20.0)	19.5 (15.8–23.2)	1.10 (0.94–1.27)
Vss, l	304 (250–358)	359 (264–454)	1.18 (0.94–1.43)
$T_{1/2,\ \gamma}$, hours	22.0 (17.9–26.1)	26.7 (21.3–32.2)	1.24 (1.00–1.48)

[a]Values are reported as mean with 95% confidence interval in parentheses.
[b]Geometric mean ratio of the observed pharmacokinetic parameters with medicinal cannabis and without medicinal cannabis; a significant difference exists when the value 1.00 is not included within the 95% confidence interval.
[c]Six patients were administered a reduced dose of 135 mg (75%).
[d]Dose-normalized, i.e., divided by dose.
Abbreviations: AUC, area under the plasma concentration–time curve; CL, clearance; C_{max}, peak plasma concentration; NA, not applicable; $T_{1/2,\ \gamma}$, terminal elimination half-life; V_{ss}, apparent volume of distribution.

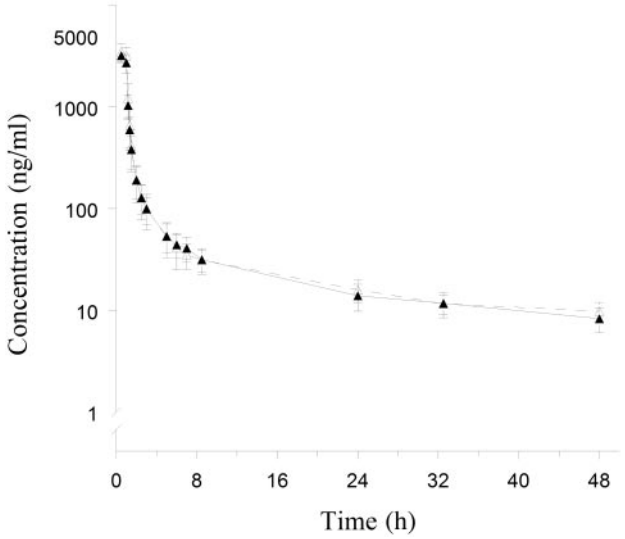

Figure 2. Mean (95% confidence interval, $n = 12$) plasma concentration of docetaxel (dose, 180 mg) in the absence (solid line, closed symbols and error bars) and presence (dose-normalized to 180 mg, dashed line, open symbols and error bars) of medicinal cannabis.

Patients treated with full-dose irinotecan (600 mg) during both treatments ($n = 7$) showed a smaller percentage decrease during the second treatment ($p < .04$) in WBC, 38.8% (20.2%–57.4%) versus 23.5% (11.1%–35.8%), and in ANC, 44.4% (22.0%–66.7%) versus 25.4% (10.9%–40.0%), for the first versus second treatments, respectively (Table 4). However, the nadir values for WBC and ANC were not significantly different for the two treatments, being 4.8×10^9/l ($3.1–6.4 \times 10^9$/l) versus 4.6×10^9/l ($3.6–6.0 \times 10^9$/l) and 3.0×10^9/l ($1.91–4.0 \times 10^9$/l) versus 2.9×10^9/l ($1.91–3.9 \times 10^9$/l), respectively ($p > .60$), for the first versus the second treatment.

For each treatment arm, the incidence and severity of nonhematological toxicities (irinotecan: fatigue, nausea, vomiting and diarrhea; docetaxel: fatigue, increased hepatic transaminases and bilirubin) appeared similar between the first and second treatments, although the small number of patients and low incidence precluded statistical evaluation. Patients tolerated the medicinal cannabis tea well; the majority (> 80%) of patients indicated that they slept better and only a minority (< 25%) complained of minor headaches, mood disturbances, or weird dreams.

Discussion

Currently, in vitro and in vivo reports on the (potential) inducing or inhibitory effects of medicinal cannabis with regard to CYP3A (responsible, at least in part, for the metabolism of up to 37% of approved drugs and thus involved in clinically relevant drug interactions) are contradictory and inconclusive [22–31]. Yet, in The Netherlands, since September 2003, a legal cannabis product for medicinal purposes has become available for patients. However, as it is not an officially registered drug, pharmacokinetic drug interactions have not been evaluated as part of an adequate safety and efficacy assessment, which is recommended for new drug applications. Indeed, the product information states that basically no research has been done on interactions. In clinical oncology, an understanding of the implications of concomitant prescription of drugs is important, because most anticancer drugs are highly toxic, have a narrow therapeutic index, and are metabolized by readily modulated pathways, in particular, CYP3A. Consequently, pharmacokinetic drug interactions, even with herbal supplements/products (which are increasingly being used, in particular by cancer patients [16]), can result in under- or overdosing [18–20]. Our study shows that medici-

Table 4. Summary of irinotecan ($n = 7$) and docetaxel ($n = 6$) hematologic pharmacodynamics in the absence (−) and presence (+) of medicinal cannabis for patients who received two full-dose treatments

Parameter[a]	Cannabis − Irinotecan	Cannabis + Irinotecan	*p*-value[b]	Cannabis − Docetaxel	Cannabis + Docetaxel	*p*-value[b]
Leukocytes						
% decrease WBC	38.8 (20.2–57.4)	23.5 (11.1–35.8)	.04	82.6 (75.2–90.1)	80.6 (73.2–88.0)	.75
Nadir, $\times 10^9$/l	4.8 (3.1–6.4)	4.6 (3.2–6.0)	.69	1.14 (0.61–1.67)	1.47 (0.95–1.98)	.17
Neutrophils						
% decrease ANC	44.4 (22.0–66.7)	25.4 (10.9–40.0)	.03	91.3 (85.7–96.8)	92.0 (87.4–96.5)	.75
Nadir, $\times 10^9$/l	3.0 (1.91–4.0)	2.9 (1.91–3.9)	.60	0.41 (0.13–0. 69)	0.49 (0.15–0.84)	.75

% decrease WBC and ANC are defined as [(pretreatment value − nadir value)/(pretreatment value)] × 100%; nadir is defined as the absolute lowest point during follow-up.
[a]Values are reported as mean with 95% confidence interval in parentheses.
[b]Nonparametric paired analysis for those patients for which the doses for the first and second treatment were identical (i.e., 600 mg for irinotecan and 180 mg for docetaxel).
Abbreviations: ANC, absolute neutrophil count; WBC, white blood cell count.

nal cannabis (variety Bedrocan®)—ingested as an herbal tea for 15 consecutive days, starting 12 days before i.v. administration of irinotecan or docetaxel, two anticancer drugs for which CYP3A is a major route of metabolism—does not influence the systemic pharmacokinetics and does not negatively affect the hematological toxicity of these drugs. Furthermore, besides being inactivated by CYP3A, irinotecan is subject to carboxylesterase-mediated activation, resulting in SN-38. SN-38 is subsequently detoxified in the liver to its glucuronide SN-38G by UDP glucuronosyltransferase 1A isoforms, in particular UGT1A1 [55]. Since both exposure to and clearance of SN-38 and SN-38G, as well as the metabolic conversion ratios for these two irinotecan metabolites, were equal for the first and second treatments, it seems unlikely that the evaluated variety of medicinal cannabis affects these enzyme systems. We have no indications that patients were nonadherent, which could have explained the lack of a drug interaction.

Several aspects regarding the observed lack of a (statistically) significant and clinically relevant effect of medicinal cannabis on the pharmacokinetics of irinotecan and docetaxel require attention. First, our conclusions apply specifically to the investigated medicinal cannabis variety. In The Netherlands, medicinal cannabis is currently available in two varieties (Bedrocan® and Bedrobinol®), both containing a standardized content of THC (18% and 13%, respectively) and CBD (0.8% and 0.2%, respectively). At present, there are plans to introduce a third variety with a significantly higher content of CBD, claimed to be beneficial for syndromes associated with spasticity. To what extent a higher exposure to CBD (recently shown to inhibit the transporter protein P-glycoprotein ABCB1 in vitro [56]) influences the pharmacokinetics of concomitantly prescribed drugs remains to be investigated. Although it was anticipated that the availability of medicinal cannabis in Dutch pharmacies would decrease the need to resort to "coffee shops," more than 80% of patients still frequent the illegal circuit [57]. The high price in pharmacies, complaints of lower effectiveness, and the hesitation of physicians to prescribe medicinal cannabis seem to be the major reasons underlying this finding. Because our conclusions do not apply to illegal products, oncologists should recommend that patients who wish to use cannabis for medicinal purposes resort to prescription-based, legally produced cannabis, instead of cannabis of unknown origin and quality.

Second, the evaluated dose is the initial recommended dose, which may be increased according to an individual's need. Again, it is possible that a higher cannabinoid exposure might yet result in an undesirable drug interaction. Third, we have evaluated orally administered medicinal cannabis. An alternative recommended route of administration is inhalation [15]. Because of extensive first-pass metabolism and high lipid solubility, only 10%–20% of orally administered THC reaches the systemic circulation unchanged [58]. In contrast, up to 50% of THC can be absorbed from the lungs, resulting in higher systemic exposure. From our data, we cannot draw justified conclusions regarding the potential effects of inhaled medicinal cannabis on the pharmacokinetics of concomitantly administered irinotecan and docetaxel, or other (anticancer) drugs.

The lower percentage decrease in WBC and ANC in patients administered irinotecan concomitant with medicinal cannabis observed in our exploratory evaluation is not necessarily attributable to a pharmacodynamic interaction—given the fact that nadir values of WBC and ANC were

almost identical for the two treatments—yet, it is most likely to be of multifactorial origin or related to the limited sample size. Indeed, the study was not designed to detect statistically significant differences in pharmacodynamic parameters. Furthermore, the observed differences do not translate into different grades of neutropenia [43].

Conclusion

Despite the low prescription rate of legal medicinal cannabis, there remains a need for clinical trials to evaluate the efficacy and safety of medicinal cannabis for specific indications and in combination with other drugs with a narrow therapeutic index, as well as research into adequate dosage forms. If, in the meantime, cancer patients wish to use medicinal cannabis (variety Bedrocan®, orally administered as recommended) concomitantly with irinotecan or docetaxel, or other drugs primarily detoxified by CYP3A, we do not recommend any dose adjustments a priori.

Acknowledgments

This work was presented in part at the 96th Annual Meeting of the American Association for Cancer Research (abstract # 3985), April 16–20, 2005, Anaheim, California, and at the 3rd Conference of the International Association for Cannabis as Medicine, September 9–10, 2005, Leiden, The Netherlands. The authors wish to thank Lena E. Friberg for the irinotecan pharmacokinetic analysis. The first and second authors contributed equally to the study.

Disclosure of Potential Conflicts of Interest

The authors indicate no potential conflicts of interest.

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