Effect of omeprazole on the pharmacokinetics and toxicities of irinotecan in cancer patients: A prospective cross-over drug–drug interaction study ☆

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ABSTRACT

Background: Omeprazole is one of the most prescribed medications worldwide and within the class of proton pump inhibitors, it is most frequently associated with drug interactions. *In vitro* studies have shown that omeprazole can alter the function of metabolic enzymes and transporters that are involved in the metabolism of irinotecan, such as uridine diphosphate glucuronosyltransferase subfamily 1A1 (UGT1A1), cytochrome P-450 enzymes subfamily 3A (CYP3A) and ATP-binding cassette drug-transporter G2 (ABCG2). In this open-label cross-over study we investigated the effects of omeprazole on the pharmacokinetics and toxicities of irinotecan.

Methods: Fourteen patients were treated with single agent irinotecan (600 mg i.v., 90 min) followed 3 weeks later by a second cycle with concurrent use of omeprazole 40 mg once daily, which was started 2 weeks prior to the second cycle. Plasma samples were obtained up to 55 h after infusion and analysed for irinotecan and its metabolites 7-ethyl-10-hydroxycampothecin (SN-38), SN-38-glucuronide (SN-38G), 7-ethyl-10-[4-(1-piperidino)-1-amino]-carbonyloxycamptothecin (NPC) and 7-ethyl-10-[4-*N*-(5-aminopentanoic acid)-1-piperidino]-carbonyloxycamptothecin (APC) by high-performance liquid chromatography (HPLC). Non-compartmental modelling was performed. Toxicities were monitored during both cycles. Paired statistical tests were performed with SPSS.

Results: The exposure to irinotecan and its metabolites was not significantly different between both cycles. Neither were there significant differences in the absolute nadir and percentage decrease of WBC and ANC, nor on the incidence and severity of neutropenia, febrile neutropenia, diarrhoea, nausea and vomiting when irinotecan was combined with omeprazole.

Conclusion: Omeprazole 40 mg did not alter the pharmacokinetics and toxicities of irinotecan. This widely used drug can, therefore, be safely administered during a 3-weekly single agent irinotecan schedule.

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1. Introduction

Drug–drug interactions can cause serious adverse effects, especially in oncology, as a result of the narrow therapeutic window of chemotherapeutic agents. Small changes in the pharmacokinetics or pharmacodynamics of chemotherapy caused by another drug can result in significant changes in its toxicity or efficacy. Because cancer patients often experience disease- and age-related organ failure, they frequently use several other drugs, which put them at risk for drug–drug interactions.[1]

Proton pump inhibitors (PPIs) act as potent blockers of the gastric acid pump without major side effects.[2] They belong to one of the most frequently prescribed medications in the United States (http://www.imshealth.com/deployedfiles/
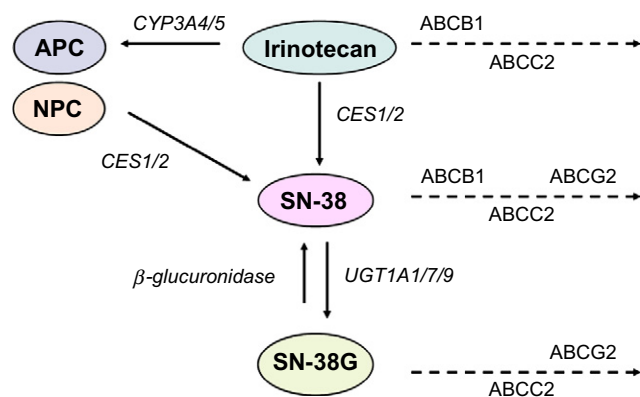
Fig. 1 – Metabolism of irinotecan. The pro-drug irinotecan is metabolised into its active metabolite SN-38 by carboxylesterases type 1 and 2. The affinity for this reaction is low, since only a fraction of irinotecan is directly converted into SN-38. Competing with the formation of SN-38 is the oxidation of irinotecan into the inactive metabolites APC and NPC by CYP3A4 and CYP3A5, which both (partially) can be converted further into SN-38. To facilitate excretion, SN-38 is glucuronidated into its inactive metabolite SN-38-glucuronide (SN-38G) by several UGT1A isoforms; UGT1A1 being the most important. In the intestines, SN-38G can be de-glucuronidated into SN-38 by β-glucuronidase-producing bacteria. Several drug transporters are involved in the elimination of irinotecan and its metabolites. *Abbreviations:* ABCB1, ATP-binding cassette drug-transporter B1, also known as P-glycoprotein; ABCC2, ATP-binding cassette drug-transporter C2, also known as canalicular multispecific organic anion transporter (C-MOAT); ABCG2, ATP-binding cassette drug-transporter G2, also known as Breast Cancer Resistance Protein (BCRP); APC, 7-ethyl-10-[4-N-(5-aminopentanoic acid)-1-piperidino]-carbonyloxycamptothecin, inactive metabolite of irinotecan; CES, carboxylesterase; CYP3A; cytochrome P-450 enzymes subfamily 3A; NPC, 7-ethyl-10-[4-(1-piperidino)-1-amino]-carbonyloxycamptothecin, inactive metabolite of irinotecan; SN-38, 7-ethyl-10-hydroxycampothecin, active metabolite of irinotecan; SN-38G, SN-38-glucuronide, inactive metabolite of SN-38; UGT1A, uridine diphosphate glucuronosyltransferase subfamily 1A.

imshealth/Global/Content/StaticFile/Top_Line_Data/Top%20 Therapy%20Classes%20by%20U.S.Sales.pdf).

Omeprazole was the first registered proton pump inhibitor and is one of the most prescribed drugs worldwide (http://cnnmoney.eu/2009/08/05/news/companies/top_generic_drugs.fortune/index.htm and www.rxlist.com). Although widely used, being approved as over-the-counter product in several countries, and mostly designated as harmless, omeprazole is actually known to be involved in several drug–drug interactions,[3] which could potentially be dangerous when combined with drugs with a narrow therapeutic window, such as chemotherapeutic agents.

Several drug–drug interaction studies with omeprazole have been performed, mainly focusing on interactions on the level of hepatic cytochrome P450 (CYP) enzymes and alteration of the absorption of (oral) drugs via changes in gastric pH. Clinically, the most important drug–drug interaction of omeprazole is a 27–54% reduction in clearance of diazepam due to competitive inhibition of CYP2C19.[4,5] Next to this effect there are *in vivo* and *in vitro* results pointing to induction of UDP-glucuronosyltransferases,[6–8] induction[9,10] and inhibition of cytochrome P-450 enzymes subfamily 3A (CYP3A),[11,12] and inhibition of the ATP-binding cassette drug-transporter B1 (ABCB1)[11,12] and ATP-binding cassette drug-transporter G2 (ABCG2).[13,14] These metabolising enzymes and drug transporters play an important role in the disposition of the topoisomerase-I inhibitor irinotecan (Campto®, Pfizer), which is registered for the treatment of metastatic and/or inoperable colorectal cancer (Fig. 1).

In vitro research of the combination of irinotecan and omeprazole showed an 85% reduction of 7-ethyl-10-[4-(1-piperidino)-1-amino]-carbonyloxycamptothecin (NPC) formation, one of the metabolites of irinotecan, which could potentially lead to increased levels of the active metabolite 7-ethyl-10-hydroxycampothecin (SN-38) and consequently more severe toxicity.[15] We performed comparable *in vitro* experiments and the results led us to initiate a clinical study to investigate the effect of omeprazole on the pharmacokinetics of irinotecan and toxicities in cancer patients.

2. Materials and methods

2.1. *In vitro studies*

In vitro experiments were performed to study the effect of omeprazole on the metabolism of irinotecan. Pooled human liver microsomes (Becton Dickinson Gentest) were incubated for 30 min with irinotecan (10 μM) in the presence or absence of omeprazole (25 μM) or fluconazole (25 μM; CYP3A inhibitor) based on an earlier described method.[16] The experiments were performed on four separate occasions. In each experiment, microsomes (1 mg protein/mL) were incubated in triplicate. In another experiment, microsomes (0.8 mg/mL) were co-incubated for 30 min with SN-38 (5 μM) and omeprazole (25 μM) and ketoconazol (25 μM; uridine diphosphate glucuronosyltransferase subfamily 1A [UGT1A] inhibitor) based on methods described.[17] Experiments were terminated by the addition of perchloric acid/methanol. Irinotecan and metabolite concentrations were analysed based on validated assays.[18,19] HCT116 (colorectal carcinoma) and Caco2

(colorectal adenocarcinoma) cells were cultured in Hepes-buffered RPMI 1640 medium supplemented with Glutamax™, 10% foetal bovine serum (Gibco), 100 U/mL penicillin and 100 μg/mL streptomycin at 37 °C in a humidified atmosphere containing 5% CO_2. Cells were cultured for 24 h in the presence of 25 μM omeprazole or 0.1% (v/v) DMSO as solute control. After 24 h, total RNA was extracted using RNA-Bee (Tel-TEST Temco, Inc.). Relative UGT1A1 expression levels were measured by real time RT-PCR using Taqman Universal Master mix and Assay-On-Demand products from Applied Biosystems (UGT1A1 assay ID: Hs02511055-s1). The human glyceraldehyde-3-phosphate dehydrogenase (GAPDH assay ID: 4310884E; VIC/TAMRA) was used for normalisation. Reactions were run on an ABI PRISM 7900 sequence detector system (Applied Biosystems) using the following cycling conditions: 50 °C for 2 min, 95 °C for 10 min followed by 40 cycles of 95 °C for 15 s, and 60 °C for 1 min.

2.2. Patients

Nineteen patients were included in this open-label cross-over interaction study. Inclusion criteria were: (1) histological or cytological confirmed diagnosis of any form of (irresectable and/or metastatic) cancer, which was thought to be sensitive to irinotecan-treatment; (2) age ≥ 18 years; (3) WHO performance score ≤ 1; and (4) adequate haematological, renal and hepatic function. Starting 2 weeks before irinotecan administration, patients were not allowed to use grapefruit, star fruit, dietary supplements, St. John's wort, herbal tea and herbals or any other known inhibitor and/or inducer of CYP3A and ABCB1. In addition, the use of proton pump inhibitors was prohibited. Specific exclusion criteria were: (1) any form of anti-cancer treatment within 4 weeks of start of irinotecan administration; (2) unresolved bowel obstruction or chronic colic disease; and (3) any form of illness that would prohibit the process of understanding and giving of informed consent. All patients gave written informed consent and the local institutional review board approved the clinical protocol, which was written in accordance with the declaration of Helsinki.

2.3. Treatment

All patients received their first cycle of irinotecan (Campto®, Pfizer) without and their second cycle with concomitant omeprazole (Losec®MUPS®, AstraZeneca). Fourteen days before the start of the second cycle, patients started with omeprazole 40 mg once daily until the third day after the second administration. Irinotecan was administered intravenously over 90 min at a flat-fixed dose of 600 mg during both cycles.[20] All patients received a standard anti-emetic regimen of intravenous granisetron (1 mg) and dexamethason (10 mg) 30 min before the administration of irinotecan and atropine (0.25 mg, subcutaneously) prior to irinotecan infusion, to prevent an acute cholinergic syndrome. For the treatment of irinotecan-induced diarrhoea, patients received treatment with loperamide and, when necessary, antibiotics. A dose-reduction of 25% was performed at the discretion of the physician when necessary. Patients were asked to record side-effects, the intake of any other drugs during both treatment cycles and the time of intake of omeprazole in a specific diary.

2.4. Pharmacokinetic analyses of irinotecan

Pharmacokinetic analyses of irinotecan and its main metabolites SN-38, SN-38G, APC and NPC were performed during both treatment cycles. Blood samples (5 mL; lithium-heparine) were collected prior to infusion, 30 min after the start of infusion, at the end of infusion, as well as 10, 20 and 30 min, and 1, 1.5, 2, 3, 4, 5, 6, 22.5, 30, 46.5 and 53.5 h post-infusion. Samples were centrifuged for 10 min at 2860g (4 °C) and plasma was stored at –80 °C until analysis by validated reversed-phase high-performance liquid chromatography assays with fluorescence detection, as described elsewhere.[18,19,21] Pharmacokinetic parameters of irinotecan and its metabolites were calculated using weighted non-compartmental analyses with WinNonLin 5.2 (Pharsight Corp., Mountain View, CA).

2.5. Toxicities

During both cycles, patients were seen weekly at the outpatient clinic for physical examination, toxicity screening and laboratory tests. Leucopenia, neutropenia, diarrhoea, nausea and vomiting were graded using the Common Terminology Criteria for Adverse Events (CTC) version 3.0 (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf), and were also classified into severe (grade 3–4) and not severe (grade 0–2). In addition, leucopenia and neutropenia were evaluated as absolute nadir and as percentage decrease at nadir from baseline which was calculated as percentage decrease = [baseline value – nadir value]/baseline value × 100%. Toxicity analyses were only performed in the group of patients who received two full dose cycles of irinotecan (600 mg; N = 12).

2.6. Genotyping

In all patients, UGT1A1-genotype analyses were performed for the UGT1A1*28 ((TA)$_6$ → (TA)$_7$) and UGT1A1*93 (–3156G>A) polymorphisms as described.[22] In addition, patients were screened for being an ultra-rapid metabolizer of CYP2C19 (CYP2C19*17),[23] which may result in a sub-therapeutic exposure to omeprazole.[23,24]

2.7. Statistics

The primary objective of this study was to investigate the influence of omeprazole on the plasma pharmacokinetics of irinotecan and its metabolites in cancer patients. To detect a 25% difference in SN-38 AUC between the cycles with and without concomitant omeprazole with a two-sided significance level of 5% and a power (1-β) of 90%, a sample size of at least 14 patients was required. For the sample size calculation, data were used from patients who received two subsequent cycles of irinotecan at a flat-fixed dose of 600 mg.[22] Dose-reduced patients were excluded from this analysis. The secondary objective was to compare side effects, especially

leucopenia and neutropenia, and late-onset diarrhoea, in the presence and absence of omeprazole.

Data are presented as mean values with 95% confidence intervals unless stated otherwise. To compare pharmacological parameters and nadir and percentage decrease of neutrophils and leucocytes between the cycle with and without omeprazole, paired t-tests were used. For the comparison of the CTC-graded toxicities between both cycles, Mc Nemar's test was used. Statistical tests were calculated two-sided and P-values of less than 0.05 were regarded as statistically significant. All statistical calculations were performed with SPSS version 15.0 (SPSS Inc., Chicago, IL).

3. Results

3.1. In vitro experiments

As shown in Fig. 2, co-incubation of human liver microsomes with irinotecan and omeprazole resulted in an 80% inhibition on NPC formation and a 75% inhibition on APC formation, which was comparable with results with the CYP3A inhibitor fluconazole (78% and 74% inhibition, respectively). Although in vitro no effect of omeprazole was seen on the formation of SN-38, the inhibition of both NPC and APC formation could potentially lead to higher SN-38 levels in vivo.
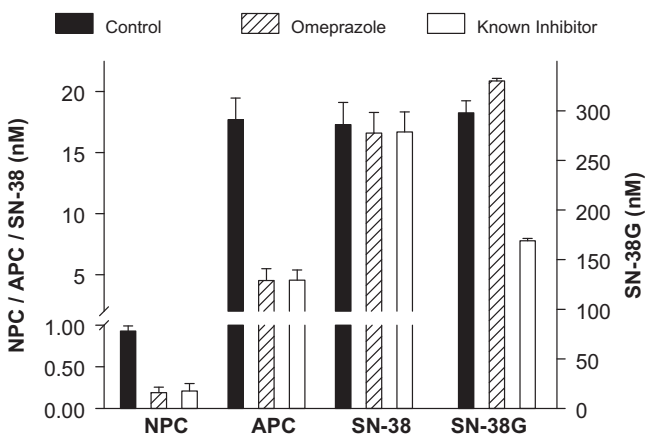
Fig. 2 – Omeprazole affects the metabolism of irinotecan in vitro. Effect of omeprazole (striped bars) and CYP3A inhibitor fluconazole (open bars) on the formation of NPC, APC and SN-38 during incubation of human liver microsomes with irinotecan and effect of omeprazole (striped bars) and UGT1A1 inhibitor ketoconazole (open bars) on the formation of SN-38G during incubation with SN-38. The black bars represent the formation of metabolites in the absence of a potential inhibitor. Depicted are the mean values of the formed metabolite + SD. Abbreviations: APC 7-ethyl-10-[4-N-(5-aminopentanoic acid)-1-piperidino]-carbonyloxycamptothecin, inactive metabolite of irinotecan; CYP3A; cytochrome P-450 enzymes subfamily 3A; NPC, 7-ethyl-10-[4-(1-piperidino)-1-amino]-carbonyloxycamptothecin, inactive metabolite of irinotecan; SN-38, 7-ethyl-10-hydroxycampothecin, active metabolite of irinotecan; SN-38G, SN-38-glucuronide, inactive metabolite of SN-38; UGT1A1, uridine diphosphate glucuronosyltransferase subfamily 1A1.

Also shown in Fig. 2, co-incubation of human liver microsomes with SN-38 and omeprazole did not result in reduced formation of SN-38G, whereas the formation of SN-38G was reduced with 57% when SN-38 was co-incubated with the UGT1A1 inhibitor ketoconazole.

A 24-h exposure of the colorectal carcinoma cell lines HCT116 and Caco2 to 25 μM omeprazole resulted in a two-fold upregulation of UGT1A1 mRNA levels as determined by quantitative RT-PCR.

3.2. Patients

Nineteen patients were included in the clinical study. Two patients did not start treatment after registration; one due to the diagnosis of a second malignancy, the other due to progressive liver failure. One patient did not receive a second administration of irinotecan because of severe toxicity during the first cycle (grade 4 diarrhoea and haematological toxicity). One patient was not evaluable for pharmacokinetics due to ascites with possible third space pharmacokinetics.

Table 1 – Patient characteristics.[a]				
Characteristics	N	%	Median	Range
Age (years)			65	26–74
BSA (m²)			1.87	1.59–2.38
Sex				
Male	9	64%		
Female	5	36%		
Tumour type				
Colorectal	4	29%		
Pancreatic	4	29%		
(A)CUP	2	14%		
Miscellaneous[b]	4	29%		
Smoking status				
Smoker	1	7%		
Non-smoker	13	93%		
*UGT1A1*28 genotype*				
TA6/TA6 (wildtype)	7	50%		
TA6/TA7	7	50%		
TA7/TA7	0	0%		
*UGT1A1*93 genotype*				
GG (wildtype)	9	64%		
GA	5	36%		
AA	0	0%		
*CYP2C19*17 genotype*				
CC (wildtype)	5	36%		
CT	7	50%		
TT	2	14%		

Abbreviations: (A)CUP, (adeno)carcinoma of unknown primary; BSA, body surface area; UGT1A1*28, polymorphism for an additional (seventh) repeat in the TATA box of the promotor region of UGT1A1 leading to reduced UGT1A1 formation; UGT1A1*93, polymorphism in the UGT1A1 gene, also known as –3156G>A, resulting in less functional UGT1A1; CYP2C19*17, polymorphism in CYP2C19 gene (–806C>T and –3402C>T), resulting in more functional CYP2C19 (ultra rapid metabolizer).
[a] N = 14, patients evaluable for two treatment cycles.
[b] Including primitive neuro-ectodermal tumour (1), cholangiocarcinoma (1), jejunal carcinoma (1) and breast cancer (1).

Another patient was not evaluable due to problems with pharmacokinetic sampling. Of the 14 evaluable patients for pharmacokinetics, two patients were not evaluable for toxicity analysis due to 25% dose reduction during their second cycle because of severe toxicity (grade 4 haematological toxicity plus grade 3 gastro-intestinal toxicities and grade 3 hepatological toxicity, respectively). The pharmacokinetics of these dose-reduced cycles was extrapolated to full-dose pharmacokinetics, since the pharmacokinetics of irinotecan and its metabolites are linear in this dose range.[25] Patient demographics are stated in Table 1.

3.3. Irinotecan pharmacokinetics

As shown in Table 2, there was no significant difference in the area under the curve (AUC) and maximum concentration (C_{max}) of irinotecan ($P > 0.24$), SN-38 ($P > 0.63$), SN-38G ($P > 0.07$), APC ($P > 0.07$) and NPC ($P > 0.13$) between the cycles with and without omeprazole. Similar results were obtained when the two ultra-rapid metabolizers of CYP2C19 (CYP2C19*17/*17) were left out of analysis ($P > 0.06$). Fig. 3 shows the time versus plasma-concentration curves of irinotecan and its metabolites as well as the intra-individual AUCs with and without concomitant omeprazole.

3.4. Toxicities

No statistical differences were seen in the absolute nadir and percentage decrease of leucocytes and neutrophils after irinotecan treatment with or without omeprazole ($P > 0.34$; Table 3). In addition, no differences were seen in the incidence of severe leucopenia and neutropenia ($P = 1.0$). Overall, the incidence of severe (grade 3–4) gastro-intestinal toxicities was low in our study. Only 2 patients suffered from grade 3 or 4 diarrhoea, nausea and vomiting.

4. Discussion

Here we investigated the possible drug–drug interaction between the proton pump inhibitor omeprazole and irinotecan. No effect of the co-administration of omeprazole on the pharmacokinetics and toxicities of irinotecan and its metabolites was seen. Two patients in our study were characterised as CYP2C19-ultra rapid metabolizers, which could have influenced our results as they could have had suboptimal levels of omeprazole. However, when these patients were excluded from analysis, there still was no significant influence of omeprazole on the pharmacokinetics and toxicities of irinotecan and its metabolites.

Since irinotecan has a complex disposition profile involving several drug metabolising enzymes and drug transporters, drug–drug interactions can occur at several levels. In recent years, several herbs and drugs were combined with irinotecan to investigate the possibility of a drug interaction, potentially explaining the occurrence of treatment failure or severe side effects, such as neutropenia and late-onset diarrhoea. For example, a reduced exposure to irinotecan and its potent metabolite SN-38, was seen when irinotecan was combined with the CYP3A inducer phenytoin.[26,27] Concomitant smoking also resulted in reduced plasma-concentrations of irinotecan and SN-38.[28] Reduced levels of SN-38 were seen when irinotecan was combined with valproic acid,[29] and with St. John's wort.[30] Higher levels of SN-38 were seen in combination with lopinavir/ritonavir and the combined CYP3A and UGT1A

| Parameter[a]	Omeprazole (–)	Omeprazole (+)	Ratio[b]	P
Table 2 – Pharmacokinetics of irinotecan and its metabolites without (–) and with (+) concomitant use of omeprazole.				
Irinotecan				
AUC_{0-55h} (ng·h/mL)	24,498 (16,186–32,811)	23,472 (16,195–30,748)	0.97 (0.92–1.02)	0.24
C_{max} (ng/mL)	3700 (2998–4401)	3585 (2814–4355)	0.97 (0.90–1.04)	0.34
SN-38				
AUC_{0-55h} (ng·h/mL)	439 (346–533)	453 (354–551)	1.05 (0.92–1.19)	0.63
C_{max} (ng/mL)	41.9 (29.9–53.9)	43.0 (31.7–54.3)	1.09 (0.87–1.31)	0.81
SN-38G				
AUC_{0-55h} (ng·h/mL)	2913 (1874–3953)	3167 (1963–4371)	1.08 (0.96–1.19)	0.15
C_{max} (ng/mL)	209 (155–264)	228 (165–291)	1.09 (1.00–1.19)	0.07
APC				
AUC_{0-55h} (ng·h/mL)[c]	7471 (4944–9998)	6438 (5016–7859)	0.94 (0.80–1.07)	0.15
C_{max} (ng/mL)[c]	587 (393–781)	476 (378–575)	0.90 (0.77–1.04)	0.07
NPC				
AUC_{0-55h} (ng·h/mL)	189 (114–265)	154 (119–189)	0.92 (0.75–1.09)	0.25
C_{max} (ng/mL)	19.9 (12.5–27.3)	15.0 (12.5–17.5)	0.89 (0.72–1.05)	0.13

Abbreviations: APC, 7-ethyl-10-[4-N-(5-aminopentanoic acid)-1-piperidino]-carbonyloxycamptothecin, inactive metabolite of irinotecan; AUC_{0-55h}, area under the concentration–time curve from timepoint 0 to 55 h; C_{max}, maximum concentration; NPC, 7-ethyl-10-[4-(1-piperidino)-1-amino]-carbonyloxycamptothecin, inactive metabolite of irinotecan; SN-38, 7-ethyl-10-hydroxycamptothecin, active metabolite of irinotecan; SN-38G, SN-38-glucuronide, inactive metabolite of SN-38.
[a] Data presented as mean with 95% confidence interval in parentheses.
[b] Ratio of mean pharmacokinetic parameters of irinotecan with and without omeprazole [ratio = with omeprazole/without omeprazole].
[c] N = 13, data on pharmacokinetics of APC missing in one patient.
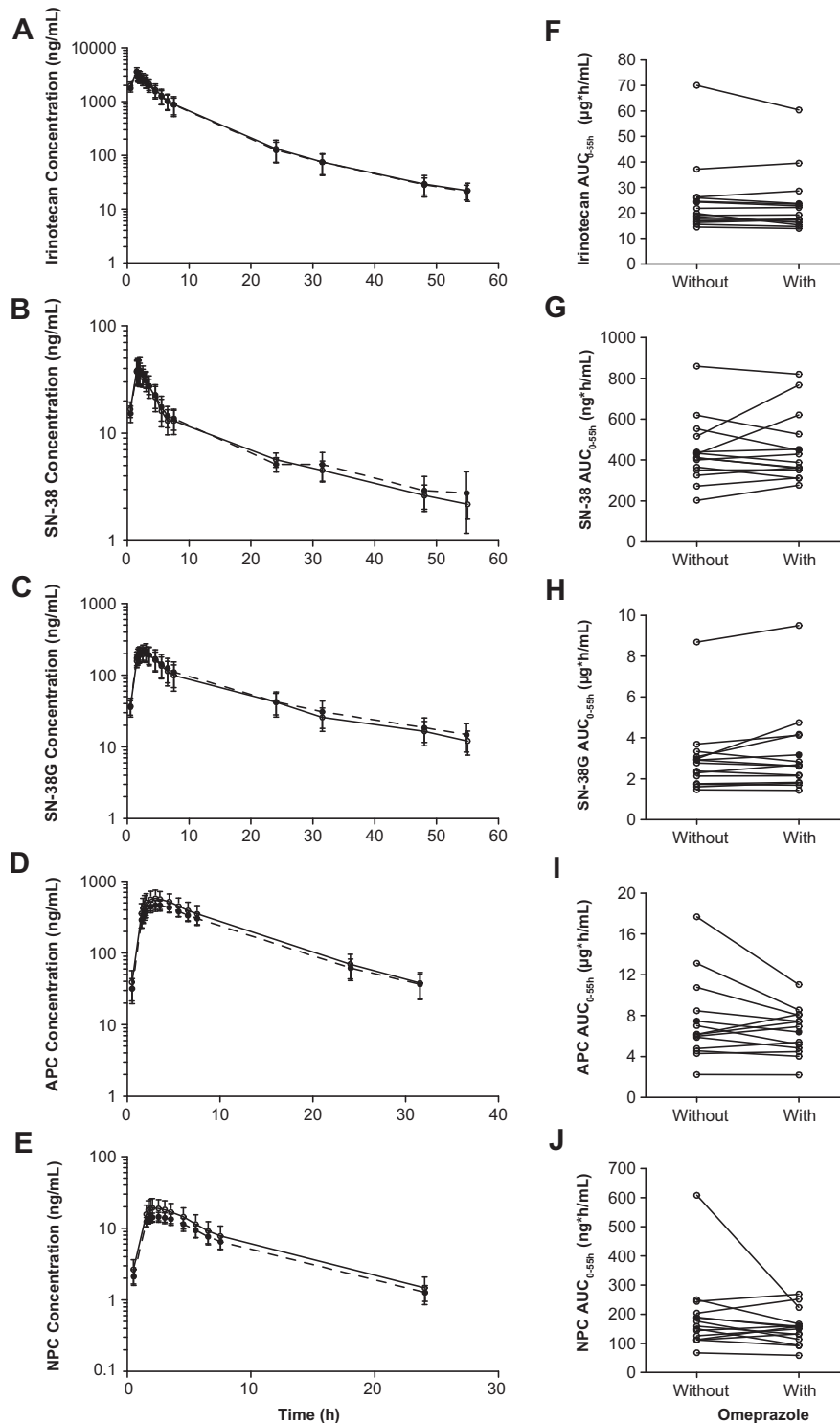
Fig. 3 – (A–J) Pharmacokinetics of irinotecan with and without concomitant omeprazole. (A–E) Mean (±95% confidence interval) time versus plasma-concentration curves of irinotecan (A), SN-38 (B), SN-38G (C), APC (D) and NPC (E) in 14 cancer patients after intravenous infusion of 600 mg irinotecan, with (closed circles) and without (open circles) concomitant use of omeprazole 40 mg once daily. (F–J) Intra-individual (open circles) and mean (closed circle) area under the curve (AUC) of irinotecan (F), SN-38 (G), SN-38G (H), APC (I, N = 13) and NPC (J) of 14 cancer patients treated with irinotecan 600 mg intravenously with and without concomitant use of omeprazole 40 mg once daily. *Abbreviations:* APC, 7-ethyl-10-[4-N-(5-aminopentanoic acid)-1-piperidino]-carbonyloxycamptothecin, inactive metabolite of irinotecan; NPC, 7-ethyl-10-[4-(1-piperidino)-1-amino]-carbonyloxycamptothecin, inactive metabolite of irinotecan; SN-38, 7-ethyl-10-hydroxycamptothecin, active metabolite of irinotecan; SN-38G, SN-38-glucuronide, inactive metabolite of SN-38.

Table 3 – Toxicities of irinotecan without (–) and with (+) concommitant use of omeprazole of patients who received two full-dose treatments (N = 12)[a].			
Parameter	Omeprazole (–)	Omeprazole (+)	P
Leucocytes			
Nadir (×10^{9})	2.79 (2.00–3.59)	3.01 (2.07–3.95)	0.46
Decrease (%)[b]	46.8 (31.3–62.4)	40.3 (17.6–63.0)	0.34
Severe leucopenia (grade 3–4)[c]	5 (42%)	4 (33%)	1.00[d]
Neutrophils			
Nadir (×10^{9})	1.47 (0.86–2.08)	1.43 (0.88–1.98)	0.87
Decrease (%)[b]	57.4 (41.8–73.1)	49.6 (25.3–74.0)	0.35
Severe neutropenia (grade 3–4)[c]	4 (33%)	5 (42%)	1.00[d]

[a] Two patients were excluded from this analysis because of dose reduction during the second cycle due to severe toxicities during the first cycle.
[b] Percentage decrease compared with baseline, [baseline value – nadir value]/baseline value × 100%.
[c] Number of patients with percentage in parentheses.
[d] Mc Nemar test.

inhibitor ketoconazole,[17,31,32] and when irinotecan was combined with tacrolimus.[33] However, no effect was seen when irinotecan was combined with medicinal cannabis.[34]

We detected a modest two-fold increase in *UGT1A1* mRNA levels when colorectal carcinoma cell lines were cultured with omeprazole for 24 h. Similarly Donato et al. reported a six-fold induction of UGT1A1 activity in HepG2 cells when they were cultured in the presence of 50 μM omeprazole for 72 h.[8] This can be explained by the agonistic effect of omeprazole on the Ah-receptor,[35] which is known to be involved in transcription of the *UGT1A1* gene.[36] However, *in vivo* omeprazole had no significant inducing effect on the glucuronidation of SN-38, possibly because *in vivo* lower concentrations of the drug are present.

Our results complement outcomes of other drug–drug interaction studies with omeprazole and anti-cancer drugs. For example, no effect of omeprazole was seen on the pharmacokinetics of the CYP3A-substrates imatinib and bortezomib.[37,38] However, the exposure to dasatinib was reduced in combination with omeprazole (http://www.clinicalstudyresults.org/documents/company-study_1477_2.pdf). The mechanism for this effect could be CYP3A4 induction or reduced gastric acid secretion which influences the absorption of dasatinib. As irinotecan is administered intravenously, the latter cannot play a role in a possible interaction. And, in contrast with dasatinib, where only CYP3A4 is thought to play an important role in its metabolism,[39] irinotecan has multiple enzymes that are involved in its disposition.

A limitation of our study might be the fixed-sequence design instead of a randomised design. We chose this design to avoid a possible influence of the different sequences on the pharmacokinetics of irinotecan and to avoid treatment delay due to the 2-weeks induction-period for omeprazole. Although the sample size was large enough to detect a possible difference in pharmacokinetics according to the power analysis, this was a small study and the study was not powered to detect differences in toxicity outcome.

To conclude, our results indicate that omeprazole 40 mg once daily can be safely combined with a single agent irinotecan schedule, administered once every 3 weeks. Since other proton pump inhibitors have a different potential for drug–drug interactions,[40] effect of other proton pump inhibitors on the pharmacokinetics and toxicities of irinotecan should be further investigated, before they might be safely combined with irinotecan.

Conflict of interest statement

The authors have no conflicts of interest.

Clinical trial

Registration number: NTR1179 (www.trialregister.nl)

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