Anti-Cancer Drugs 2002, **13,** pp. 139–140

Short communication

Altered irinotecan metabolism in a patient receiving phenytoin

Ron HJ Mathijssen,[1] Alex Sparreboom,[1] Herlinde Dumez,[2] Allan T van Oosterom[2] and Ernst A de Bruijn[2]

[1]Rotterdam Cancer Institute (Daniel den Hoed Kliniek), Department of Medical Oncology, 3075 EA Rotterdam, The Netherlands. [2]University Hospital Leuven, UZG/Oncology, 3000 Leuven, Belgium.

The systemic exposure to the anticancer agent irinotecan (CPT-11) and its active metabolite SN-38 were 79 and 92% reduced, respectively, relative to literature data, by concomitant phenytoin therapy. This finding suggests that increased doses of CPT-11 should be given to patients treated simultaneously with these drugs, to achieve adequate levels of SN-38. [© 2002 Lippincott Williams & Wilkins.]

Key words: Irinotecan, metabolism, phenytoin.

CPT-11 is a topoisomerase I inhibitor in use as an anticancer agent with a broad range of activity and has recently been registered for the treatment of advanced colorectal cancer. In humans, the drug is extensively metabolized by a carboxylesterase-mediated hydrolyzation to the highly active metabolite SN-38 which is subsequently extensively conjugated by UDP glucuronosyltransferases to an inactive β-glucuronide (SN-38G).[1] Quantitatively, the most important metabolic pathway of CPT-11 consists of a CYP3A4-mediated oxidation, resulting in the formation of an inactive metabolite identified as APC.[2] In view of the narrow therapeutic index of CPT-11 and the importance of CYP3A4, we evaluated the potential of phenytoin, a known inducer of the CYP3A and CYP2C isozymes,[3] to alter the disposition of CPT-11.

We treated a 28-year-old patient with recurrent malignant glioma receiving CPT-11 administered as a 90-min i.v. infusion once weekly at a starting dose of 125 mg/m^2. During these treatment cycles, the patient also received phenytoin orally at a dose of 3 times daily 100 mg. Drug concentrations in plasma were determined by liquid chromatography with fluorescence detection.[2] The area under the curve (AUC) was estimated by the trapezoidal rule and total plasma clearance (CL) was defined as dose/AUC. Metabolic ratios were calculated as outlined,[4] and included the relative extent of conversion (REC; $AUC_{SN\text{-}38}/AUC_{CPT\text{-}11}$), the relative extent of glucuronidation (REG; $AUC_{SN\text{-}38}/AUC_{SN\text{-}38G}$) and the relative extent of metabolism (REM; $AUC_{APC}/AUC_{CPT\text{-}11}$).

Pharmacokinetic data are summarized in Table 1. In the first course, the CPT-11 plasma clearance was 55.5 l/h/m^2, with an REC of 0.014. This suggests that, compared to data obtained previously in patients not receiving phenytoin,[5] the CPT-11 clearance increased approximately 4-fold, while the relative exposure to the active metabolite decreased more than 10-fold. The low value for the REG suggests that the glucuronidation of SN-38 might be somewhat greater than estimated earlier. As expected, phenytoin also substantially increased the formation of APC, which was the main circulating compound from 5 h onwards after drug administration. In the second course, the CPT-11 dose was increased to 145 mg/m^2 and similar data were obtained relative to the first course.

These are the first data documenting altered CPT-11 disposition given in a weekly regimen when co-administered with phenytoin and suggest that patients receiving this combination should be given an increased CPT-11 dose to achieve adequate levels of SN-38 required for optimal therapeutic effects. Pharmacokinetic-guided dosing may be required to achieve safe and optimal drug levels in plasma.

Correspondence to RHJ Mathijssen, Rotterdam Cancer Institute (Daniel den Hoed Kliniek), Department of Medical Oncology, PO Box 5201, 3008 AE Rotterdam, The Netherlands. Tel: (+31) 10 4391898; Fax: (+31) 10 4391053; E-mail: mathijssen@onch.azr.nl

Table 1. Comparison of pharmacokinetic parameters for CPT-11, SN-38, SN-38G and APC

Parameter	Course 1	Course 2	Control[a]
CPT-11			
dose (mg/m^2)	125	145	125
C_{max} (ng/ml)	745	881	1492 ± 452
AUC (ng · h/ml)	2254	2827	10529 ± 3786
CL (l/h/m^2)	55.5	51.3	13.0 ± 5.55
SN-38			
C_{max} (ng/ml)	8.1	9.2	27.8 ± 11.6
AUC (ng · h/ml)	20.7	13.4	267 ± 115
REC	0.014	0.007	0.033 ± 0.013
SN-38G			
C_{max} (ng/ml)	62.3	77.5	91.7 ± 43.6
AUC (ng · h/ml)	220	351	1270 ± 825
REG	0.16	0.066	0.28 ± 0.177
APC			
C_{max} (ng/ml)	170	145	–
AUC (ng · h/ml)	873	1267	–
REM	0.37	0.43	–

C_{max}, peak plasma concentration; AUC, area under the plasma concentration-time curve from time zero to infinity; CL, total plasma clearance; REC, relative extent of conversion (molar ratio of AUC_{SN-38}/AUC_{CPT-11}); REG, relative extent of glucuronidation (molar ratio of AUC_{SN-38}/AUC_{SN-38G}); REM, relative extent of metabolism (molar ratio of AUC_{APC}/AUC_{CPT-11}).
[a]Data indicate mean values ± SD from 99 patients.

References

1. Mathijssen RHJ, van Alphen RJ, Verweij J, *et al*. Clinical pharmacokinetics and metabolism of irinotecan (CPT-11). *Clin Cancer Res* 2001; **7**: 2182–94.
2. Sparreboom A, de Jonge MJA, De Bruijn P, *et al*. Irinotecan metabolism and disposition in cancer patients (CPT-11). *Clin Cancer Res* 1998; **4**: 2747–54.
3. Tanake E. Clinically significant pharmacokinetic drug interactions between antiepileptic drugs. *J Clin Pharm Ther* 1999; **24**: 87–92.
4. Rivory LP, Haaz MC, Canal P, *et al*. Pharmacokinetic interrelationships of irinotecan (CPT-11) and its three major plasma metabolites in patients enrolled in phase I/II trials. *Clin Cancer Res* 1997; **3**: 1261–6.
5. Schaaf L, Ichhpurani N, Elfring G, Wolf D, Rothenberg M, Von Hoff D. Influence of age on the pharmacokinetics of irinotecan (CPT-11) and its metabolites, SN-38 and SN-38 glucuronide (SN-38G), in patients with previously treated colorectal cancer. *Proc Am Soc Clin Oncol* 1997; **16**: 202a (abstr).

(Received 22 October 2001; accepted 7 November 2001)