

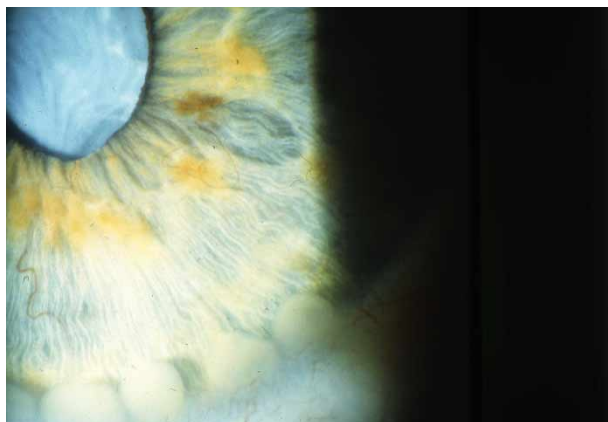


Figure 1. Slit-lamp examination of the eye showing small pearls in the anterior chamber

exceedingly rare [5,6]. Previously existing retinomas or reactivation of a previous spontaneously-arrested retinoblastoma have been suggested as etiological factors [7] ; 2) None of the tumors reported in the literature exhibited the diffuse infiltrating pattern [5,6] ; 3) Despite this usually chemoresistant subtype of retinoblastoma, the combination of an active chemotherapy regimen with high-dose ifosfamide and radical surgery allowed prolonged disease-free survival in this patient. Some tumor regressions have been reported in advanced retinoblastoma with conventional cytotoxic agents such as vincristine, doxorubicin and cyclophosphamide, or more recently with combination carboplatin and etoposide [8]. In conclusion: this variant of diffuse retinoblastoma was initially misdiagnosed because of the involvement of anterior ocular structures with mini-

mal involvement of the retina. Retinoblastoma should be considered in the differential diagnosis of chronic uveitis in any age group.

Conflict of interest

We declare no conflicts of interest.

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Irinotecan-induced central nervous system toxicity. Report on two cases and review of the literature

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To the Editor

The topoisomerase I inhibitor irinotecan is a widely used cytotoxic drug [1]. The most frequent side effects of irinotecan include acute cholinergic syndrome (ACS), delayed-onset diarrhoea, and bone-marrow suppression [1]. Much more unusual is the occurrence of irinotecan-induced central nervous system (CNS) toxicity with dysarthria as the predominant symptom. Given its rarity and sometimes impressive and threatening appearance, it is conceivable that the occurrence of irinotecan-induced CNS toxicity might lead to termination of further treatment with this drug. In order to improve the acquaintance of this untoward event and to elucidate a potential mechanism, we here report two patients experiencing CNS toxicity during irinotecan infusion in whom pharmacokinetic (PK)-analysis as well as diffusion-weighted Magnetic Resonance (MR) imaging of the brain were performed. In addition, the literature on this particular adverse event is reviewed.

Case reports

A 34-year old man was diagnosed with metastatic small blue round cell sarcoma for which he was previously treated with chemotherapy resulting in a partial remission. During follow-up, a colon carcinoma with liver metastases was found. Treatment with capecitabine combined with oxaliplatin was initiated, followed by irinotecan at subsequent progression. Prior to the first irinotecan infusion, a 90-minutes infusion at a dose of 350 mg/m² (550 mg) per 3 weeks, serum bilirubin was slightly elevated (18 µmol/L; reference value 0–16 µmol/L) while all other liver enzyme levels were within normal ranges. He used oxycodone as concurrent medication. Granisetron and dexamethasone were administered as premedication. Fifteen minutes after starting irinotecan infusion he developed a slurred speech that gradually increased in severity and lasted for 4 hours (with ultimately full recovery). On neurological examination a cerebellar dysarthria was present. No other neurological abnormalities or signs of ACS were found. Interrupting the irinotecan infusion for 15 minutes and administering atropine did not decrease the symptoms. Hereafter, it was decided to re-initiate the irinotecan infusion at the standard infusion-rate. The second administration was given at a reduced dose (75%), because of the previous occurrence of dysarthria. To exclude a possible role of ACS, atropine was added. All laboratory values, including bilirubin, were within normal ranges. During the second irinotecan infusion (without interruption), the symptoms were

identical, although somewhat less in intensity. On neurological examination he again had a mild cerebellar dysarthria. MR images of the brain, including diffusion-, T2- and T1- weighted images with gadolinium, performed during the dysarthria in the second cycle were normal. He regained normal speech again after 3 hours. No further irinotecan infusions were given because of progressive disease.

The second patient was a 63 year old woman diagnosed with a disseminated adenocarcinoma of an unknown primary. She was treated in the context of a research protocol with single agent irinotecan at a fixed dose of 520 mg. At base-line, all liver enzymes were within normal ranges. This patient used acebutolol for several years; granisetron and dexamethasone were administered as premedication. Thirty minutes after initiating the first irinotecan infusion, she developed dysarthria that lasted for 2.5 hours. The irinotecan infusion was not interrupted. No other abnormalities were found at neurological examination. Apart from CNS toxicity she experienced an ACS for which atropine was administered. At each subsequent irinotecan infusion, atropine premedication prevented occurrence of ACS but not the dysarthria, which recurred during each administration, but less intense and of shorter duration with each subsequent cycle (during cycle 2 the dysarthria was present for 2 hours, and during cycle 8 only for a few minutes).

Pharmacokinetic analysis

In both patients intensive sampling for PK-analysis was performed (in patient 1 only during the second cycle, in patient 2 during the first two cycles) as described in detail elsewhere [2]. Plasma levels of irinotecan and its active metabolite SN-38 (Figures 1 and 2) were within normal ranges as reported in a larger population [3]. In addition, while dysarthria severity decreased, there were no clear differences in terms of irinotecan and SN-38 plasma concentrations between both cycles in the second patient.

Literature review and discussion

Five cases with this particular toxicity have been described until now [4–8]. In all cases, CNS toxicity already occurred during the first administration with neurological symptoms always being reversible (Table I). None of the described patients had CNS-metastases. In all cases dysarthria occurred despite the administration of atropine.

CNS toxicity induced by irinotecan is characterised by the development of dysarthria within the 90 minutes after initiation of infusion. Currently, its exact pathogenesis is unknown. In view of our

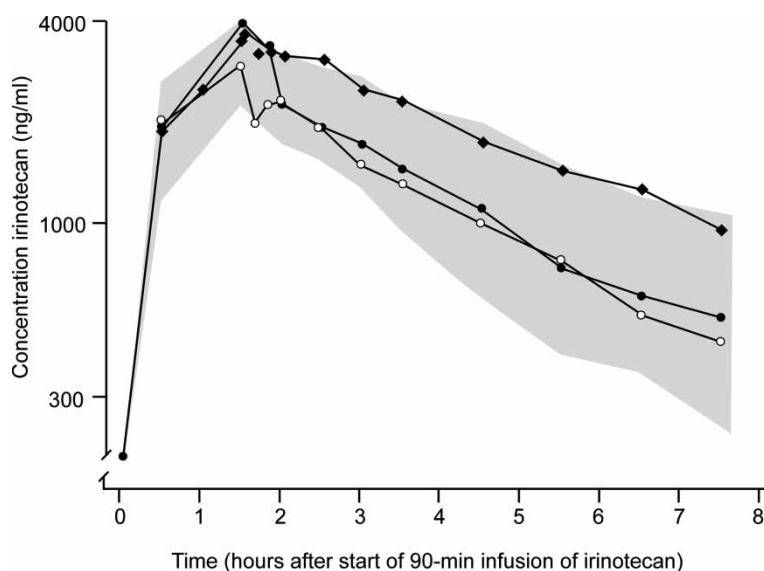


Figure 1. Plasma levels of irinotecan during irinotecan infusions in patient 1 (squares; 1 cycle of 500 mg) and patient 2 (circles; 2 cycles of 520 mg). The grey background depicts the dose-adjusted population interval ± 1 SD [3].

findings several potential underlying mechanisms are less likely. As shown, altered systemic clearance of irinotecan or SN-38 is probably not involved, because PK data were in line with the findings in a large cohort. Furthermore, although a decline in severity and duration occurred, no changes in plasma concentrations of irinotecan or SN-38 were found at a subsequent administration of irinotecan. Whether one of the other reported metabolites plays a role is currently unknown. The lack of an apparent relationship between infusion duration and dose (and thus peak level) on one hand and the time of appearance and duration of the side effect on the other, is also suggestive for other than PK causes.

Another potential cause accounting for irinotecan-induced CNS toxicity might be that for some reason the blood-brain-barrier was disrupted in these patients allowing an increase in irinotecan and/or SN38 levels in the cerebrospinal fluid (CSF). Indeed, low irinotecan levels (14% of the plasma level) have been detected in the CSF of non-human primates with an intact blood-brain barrier [9]. In rats with a brain tumour, the tissue irinotecan level within the brain tumour reached peak levels approximately 15 minutes after bolus injection of irinotecan (at the maximum tolerated dose), but still was only 6% of the plasma level of irinotecan. No SN-38 was found in plasma, CSF or brain tumour tissue [10]. There-

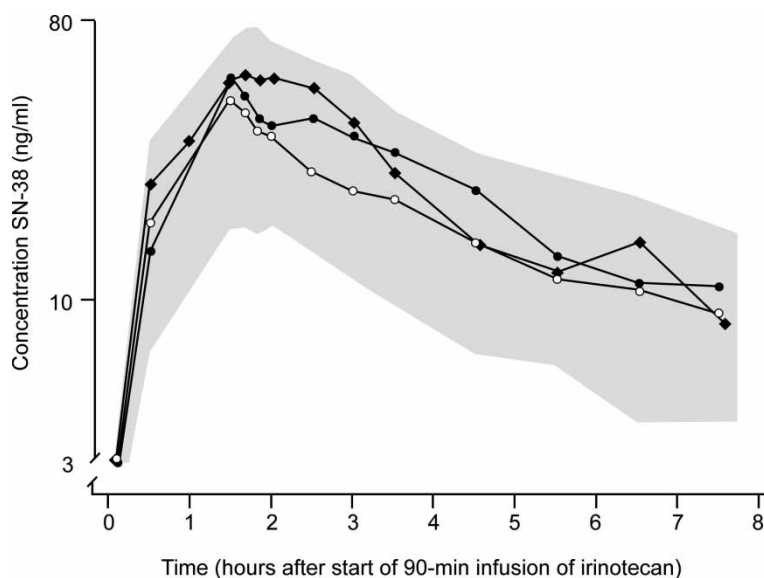


Figure 2. Plasma levels of SN-38 during irinotecan infusions in patient 1 (squares; 1 cycle of 500 mg) and patient 2 (circles; 2 cycles of 520 mg). The grey background depicts the dose-adjusted population interval ± 1 SD [3].

Table I. Reported cases of irinotecan-induced central nervous system toxicity [4–8].

Ref	Dosage irinotecan	Duration infusion	CNS symptoms	Initiation of CNS symptoms	Duration of CNS symptoms	CNS symptoms reversible?	Reoccurrence of CNS toxicity	Tachyphylaxis in toxicity?	ACS?	Premedication	Concurrent medication
Sevilla	350 mg/m ²	60 minutes	Dysarthria	Shortly after start of infusion	2 hours	Yes	Yes	Unknown	No	Granisetron	Prednisone Diclofenac Metamizole Famotidin Tramadol
Baz	150 mg/m ²	30 minutes	Dysarthria/ motor aphasia	Few minutes after start of infusion	45 minutes	Yes	Yes	Unknown	Unknown	Ondansetron Dexamethasone Atropine	5-Fluorouracil Fentanyl Diazepam Amitriptyline
Ceccaldi	180 mg/m ²	90 minutes	Dysarthria	1 hour	15–20 minutes	Yes	Yes	No	No	Ondansetron Metoclopramide Atropine*	Nicardipine
DeMarco	180 mg/m ²	60 minutes	Dysarthria/ motor aphasia	30 minutes	15 minutes	Yes	Unknown	Unknown	No	Ondansetron Dexamethasone Atropine	Tramadol
Hamberg	350 mg/m ² (550 mg)	90 minutes	Dysarthria/ ataxia	90 minutes	8 hours	Yes	Yes	Yes	No	Granisetron Dexamethasone Atropine	Ibuprofen Paracetamol
This report patient 1	350 mg/m ² (550 mg)	90 minutes	Dysarthria	15 minutes	4 hours	Yes	Yes	Yes	No	Granisetron Dexamethasone Atropine*	Oxycodone
This report patient 2	520 mg	90 minutes	Dysarthria	30 minutes	2.5 hours	Yes	Yes	Yes	Yes	Granisetron Dexamethasone Atropine*	Acebutolol

Ref: reference.

CNS: central nervous system.

ACS: acute cholinergic syndrome.

*: also dysarthria in cycles without atropine.

fore, it would be informative to perform PK-analysis of the CSF during an episode of dysarthria but both patients declined consent to a lumbar puncture. In contradiction with this hypothesis is the finding that no CNS-toxicity is reported in over 140 irinotecan-treated patients with brain tumours, despite the presence of a clearly disrupted blood-brain barrier in these patients [11–13].

Cytotoxic oedema is unlikely to play an important role in irinotecan induced CNS toxicity since normal diffusion-weighted MR images of the brain were found in one of our patients while experiencing dysarthria. It is also unlikely that irinotecan-mediated CNS toxicity occurs in the context of ACS. Dysarthria can occur in patients without ACS, while administration of atropine does not appear to prevent its (re-)occurrence whereas it effectively deals with ACS.

Of importance, pre-clinical toxicology never revealed any CNS-toxicity (Pfizer, data on file) rendering it difficult if not impossible to further study this side effect in animal models.

In conclusion, the exact cause of irinotecan-induced CNS toxicity remains unravelled and plasma pharmacokinetics also do not provide an explanation. Therefore, a specific treatment cannot be recommended. Most importantly, since in all cases CNS toxicity was fully reversible, was not exaggerated by rechallenge with irinotecan, and can even decline in severity at repeated exposure; CNS toxicity is not a reason to discontinue irinotecan treatment despite its sometimes impressive and threatening appearance.

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Pancreatic ascites due to rupture of a mucinous cystic neoplasm

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