Influence of Medicinal Cannabis (Bedrocan) on the pharmacokinetics of irinotecan and docetaxel in cancer patients (METC 2003-171 Erasmus MC).

No registrations found.

Ethical review	Positive opinion
Status	Recruitment stopped
Health condition type	-
Study type	Interventional

Summary

ID

NL-OMON24424

Source
NTR

Brief title
N/A

Health condition

Cancer

see also inclusion criteria:

1. Histological or cytological confirmed diagnosis of any form of (metastatic) cancer;

1.1 which is refractory to conventional treatment; or

1.2 for which no other (effective) treatment options are available.

Sponsors and support

Primary sponsor: Erasmus MC- Daniel den Hoed Kliniek, afdeling Interne Oncologie.
Source(s) of monetary or material Support: Erasmus MC -Daniel den Hoed kliniek, afdeling Interne Oncologie.

Intervention

Outcome measures

Primary outcome

Irinotecan and metabolite pharmacokinetics, course 1 and 2
Docetaxel pharmacokinetics, course 1 and 2.

Secondary outcome

Hematological toxicity course 1 and 2.

Study description

Background summary

For the past 4,000 years, 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 vomiting, and palliation. However, largely due to the lack of well designed clinical trials, much controversy remains regarding the claimed benefits.
Until recently, the only FDA-approved medicinal cannabis product was an oral formulation containing dronabinol (Marinol®; Solvay Pharmaceuticals Inc, Marietta, GA, USA), the synthetic version of delta9-tetrahydrocannabinol (THC), the main pharmacologically active cannabinoid. 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 a oromucosal spray called Sativex® (GW Pharm Ltd, Salisbury, United Kingdom) containing both THC and cannabidiol (CBD) in April 2005. However, many patients claim (subjectively), that a whole or partially purified extract of Cannabis sativa L. offers advantages over a single isolated ingredient. In The Netherlands, the unavailability of a legal product forced patients to frequent ‘coffeeshops’, 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, while simultaneously offering patients access to a prescription product meeting pharmaceutical quality standards (standardised content; free of microbiological impurities), a legal medicinal cannabis product was introduced in The Netherlands However, as it is not an officially registered drug, pharmacokinetic drug-interactions have not been evaluated as recommended for new drug applications. Yet it has previously been shown that pharmacokinetic drug-interactions, with herbal products (increasingly used by cancer patients), can result in under- or overdosing.

Cannabinoids appear able to modulate the catalytic activity of several hepatic cytochrome

P450 (CYP) isozymes, including isozyme 3A, responsible, in part, for the metabolism of 37% of all currently FDA-approved anticancer drugs. The majority of in vitro and animal data suggest an inhibitory effect on CYP3A-mediated metabolism, yet induction of CYP3A has been observed after repeated administration. In vivo data are also contradictory; both CYP3A inhibition and induction 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.

We anticipated that the introduction of a legal cannabis product in The Netherlands would result in increased use of medicinal cannabis concomitant with cytotoxic drugs, many of which are highly toxic and characterised 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 The proposed trial will allow us to report on the plasma pharmacokinetics of irinotecan and docetaxel after intravenous infusion to cancer patients, with and without concomitant oral medicinal cannabis administration.

Study objective

To determine the influence of oral medicinal cannabis on the pharmacokinetics of irinotecan and docetaxel and their respective metabolites in cancer patients.

Study design

N/A

Intervention

Course 1 irinotecan: patients will be treated with 600 mg irinotecan given as a 90-minute intravenous infusion in 250 ml NaCl 0.9% (t=0, day 1, course 1).

Course 1 docetaxel: patients will be treated with 180 mg docetaxel given as 1-hour intravenous infusion in 250 ml NaCl 0.9% (t=0, day 1, course 1).

As an (extra) safety assessment, pharmacokinetic profiles will be determined before day 7 of course 1. Only patients who do not develop abnormal toxicity or an abnormal pharmacokinetic profile and for whom no dose reduction due to an increased risk for toxicity would have been necessary (if a second course of irinotecan or docetaxel without cannabis were to be given), will be further treated according to the study protocol. The decision to further treat a patient according to the study protocol will be made by the responsible physician and the study coordinators and will take prior to the start of the medicinal cannabis treatment). Patients who remain included in the study will receive medicinal cannabis during

15 days, as described [25], starting on day 10, course 1. On day 1, course 2 (i.e. day 22) the second course of docetaxel or irinotecan will be given. The last 3 days of medicinal cannabis will thus be given during the second course of chemotherapy (i.e. day 1-3, course 2).

Course 2 irinotecan: patients will be treated with 450 mg irinotecan given as a 90-minute intravenous infusion in 250 ml NaCl 0.9% (t=0, day 1, course 2).

Course 2 docetaxel: patients will be treated with 135 mg docetaxel given as 1-hour intravenous infusion in 250 ml NaCl 0.9% (t=0, day 1, course 2).

For safety reasons, a 25% dose reduction will be applied during the combination therapy in at least the first three irinotecan and the first three docetaxel patients. A safety evaluation will be performed after these first three patients in each chemotherapy arm have been treated to evaluate safety (i.e. toxicity). Based upon this evaluation, the chosen dose reduction of 25% will be re-adjusted or maintained. Not before this safety (i.e. pharmacokinetic/pharmacodynamic) evaluation has been performed, will the study be continued.

Medicinal cannabis treatment: patients will receive a standardized dose of once daily (in the evening) 200 ml medicinal cannabis tea (1g/L). This is the recommended therapeutical dose of orally administered medicinal cannabis (oral information BMC: Mr. Scholten; www.maripharm.nl). The tea will be brewed using a standardized medicinal cannabis extract, Bedrocan, which is standardized at 21.8% delta-9-THC, 189 mg/100g CBD and 3.2 mg/100g CBN. The medicinal cannabis extract (Bedrocan) is produced by BMC-licensed and approved cultivators according to Good Manufacturing Practice (GMP) and will be purchased from the Bureau for Medicinal Cannabis (BMC).

Contacts

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Eligibility criteria

Inclusion criteria

1. Histological or cytological confirmed diagnosis of any form of (metastatic) cancer;

1.1 which is refractory to conventional treatment; or

1.2 for which no other (effective) treatment options are available.

2. Age 18 years and older.

3. WHO performance 2 or less (see appendix).

4. Adequate hematological functions (absolute neutrophil count > 2.0x109/L, platelets > 100x109/L).

5. Adequate renal and hepatic functions: bilirubin < 1.25xULN; SGOT and SGPT < 2.5xUNL, in case of liver metastasis < 5xUNL; serum creatinine < 1.25xULN; AP £ 5xULN; patients with SGPT and/or SGOT > 1.5xULN associated with AP > 2.5xULN are not eligible for the docetaxel arm.

6. Written informed consent.

7. Complete initial work-up within two weeks prior to chemotherapy.

8. Willingness to abstain from grapefruit, grapefruit juice, herbal dietary supplements, and herbal tea during the study period (starting 3 weeks before the first course).

9. Willingness to abstain from alcohol, car-driving, use of dangerous instruments and machinery or engagement in hazardous activity during the time of medicinal cannabis-use because of (non-excludable) interference with logical thinking, ability to concentrate, and response speed.

Exclusion criteria

1. Pregnant or lactating patients; patients with reproductive potential must use a reliable method of contraception (excluding oral contraceptives), if required.

2. Symptomatic CNS metastases.

3. Other serious illness or medical unstable condition requiring treatment or history of psychiatric disorder that would prohibit the understanding and giving of informed consent.

4. Time between last anti-tumor chemotherapy treatment and first day of irinotecan or docetaxel therapy less than 4 weeks, provided that the patient has recovered from all relevant toxic effects.

5. Radiotherapy within the last 4 weeks before chemotherapy, unless < 20% of the bone marrow area is involved.

6. Major surgery within 4 weeks before study entry (to be determined by an MD).

7. History of alcohol or drug abuse, including current substance dependence, methadone maintenance.

8. Use of St John’s wort and/or other herbal medicines within 4 weeks before study entry.

9. Current cannabis use and/or history of marijuana/cannabis abuse.

10. (Chronic) use of CYP3A inhibiting medication, dietary supplements or other inhibiting compounds.

11. (Chronic) use of CYP3A inducing medication, dietary supplements or other inducing compounds.

12. Unwillingness to change medication, or no adequate alternatives available, when drugs known to interact with CYP3A isozymes, are taken.

13. History of serious depression, schizophrenia, or psychosis.

Additionally for irinotecan patients:

1. Unresolved bowel obstruction or chronic colic disease.

2. Radiotherapy at abdomen.

Study design

Design

Study type:	Interventional
Intervention model:	Crossover
Masking:	Open (masking not used)
Control:	N/A , unknown

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	01-01-2004
Enrollment:	24
Type:	Actual

Ethics review

Positive opinion

Date:	26-09-2006
Application type:	First submission

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
NTR-new	NL772
NTR-old	NTR783
Other	: N/A
ISRCTN	ISRCTN72088851

Study results

Summary results

1. Oncologist. 2007 Mar;12(3):291-300.

2. de Jong FA, Engels FK, Sparreboom A, Loos WJ, de Bruijn P, Friberg LE, Mathôt RAA, Verweij J, Mathijssen RHJ. Influence of medicinal Cannabis on the pharmacokinetics of Docetaxel and Irinotecan. Proc Amer Assoc Cancer Res 2005; 46:[Abstract 3985].

3. de Jong FA, Engels FK, Verweij J, Mathijssen RHJ. Influence of medicinal cannabis on the pharmacokinetics of the anticancer drugs irinotecan and docetaxel. 3rd Conference of the International Association for Cannabis as Medicine, 2005.