Effect of body mass index (BMI) and cigarette smoking on the pharmacokinetics of fentanyl

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Primary Objective: to study the influence of a BMI < 20 or a BMI > 25 on the clearance of fentanyl, in patients using a stable dose of the fentanyl patch (Durogesic ®).to study the effects of smoking on the clearance of fentanyl, in patients...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Miscellaneous and site unspecified neoplasms benign
Study type	Observational invasive

Summary

ID

NL-OMON40075

Source
ToetsingOnline

Brief title
Factors influencing fentanyl PK

Condition

- Miscellaneous and site unspecified neoplasms benign

Synonym
cancer, pain

Research involving
Human

Sponsors and support

Primary sponsor: Erasmus MC, Universitair Medisch Centrum Rotterdam
Source(s) of monetary or material Support: stichting Nuts Ohra

Intervention

Keyword: body mass index, cigarette smoking, fentanyl, pharmacokinetics

Outcome measures

Primary outcome

Farmacokinetic parameters (i.e. clearance, AUC)

Secondary outcome

NA

Study description

Background summary

Pain is a common problem in cancer patients, occurring both in curative settings as well as in palliative settings. Opioids are often used to treat cancer pain. Fentanyl is one of the most widely used opioids.

Several preparations of fentanyl are currently available (1). The transdermal fentanyl patch is developed for maintenance medication in chronic pain and is the most commonly used form. Patches are available in different sizes, consistent with specific delivery doses of these patches (12ug/hr, 25ug/hr, 50ug/hr, 75ug/hr or 100ug/hr). Fentanyl is absorbed through the intact skin and a constant dose of drug is absorbed. Two different patches have been developed; a reservoir patch and a matrix patch. These patches differ in the way fentanyl is stored. However farmacokinetically, they are comparable (2, 3). Nowadays, only the matrix patch is used in clinical practice.

After placement of the patch, the plasma fentanyl concentration gradually increases. After 72hrs the patch has to be changed for a new one, as a stable diffusion of the drug through the skin is no longer guaranteed. Steady state concentrations are approached when a second transdermal fentanyl patch is sticked on the skin (4). Removing the patch will not immediately lead to diminished fentanyl concentrations because of the amount of fentanyl stored in subcutaneous depots, and therefore systemic concentrations will gradually decrease.

Fentanyl is a drug that is highly lipophilic and binds strongly to plasma proteins. Fentanyl is more potent than morphine at equipotent dose levels (5). The metabolism of fentanyl takes place primarily in the liver (6). Fentanyl is

mainly oxidized into the inactive metabolite norfentanyl by the CYP3A4 iso-enzyme (7). Less than 1% is metabolized to despropionyl-fentanyl, hydroxyfentanyl, and hydroxynorfentanyl, which are also inactive metabolites. Fentanyl is mainly excreted renally and for a minor part through the feces. The large majority of the fentanyl is excreted as the metabolites mentioned; 10% as unchanged drug (6).

Unfortunately there is a wide pharmacokinetic intra- and interpatient variability in patients using a fentanyl patch. It is largely unclear which factors contribute to this variability (8, 9). It is crucial to know which factors influence fentanyl concentrations because of the risk of over- and underdosing of fentanyl. An overdose of fentanyl could lead to serious complications, including respiratory depression or ultimately death, while underdosing fentanyl may lead to inadequate pain relief.

Fentanyl is dosed by titration. When pain is inadequately treated and side effects are manageable the fentanyl dose is usually increased. Dose finding by titration cannot be used in patients who switch from another opioid to fentanyl. Usually these patients start with more or less the equi-analgetic dose of fentanyl. Especially in these cases it would be extremely helpful if could be predicted if these patients are at risk for under- or overdosing of fentanyl.

Fentanyl is highly liphophilic and will be absorbed by the subcutaneous fat-tissue. We hypothesize that higher fentanyl concentrations will be reached when the patch is used by patients with thicker subcutaneous fat layers, represented by patients with a higher body mass index (BMI). Most farmacokinetic studies with fentanyl are performed in healthy volunteers or in patients undergoing elective surgery. Unfortunately, not all studies reported the BMI of the included patients. In studies with healthy volunteers BMI was under 30kg/m2 (10, 11) or mean weight between 70 and 80 kg (3, 10, 12). Most studies in patients undergoing surgery only included patients with a weight under 100kg (13-16). Just a few studies have studied fentanyl farmacokinetics in cancer patients. One of these studies showed significantly lower fentanyl concentrations in cachectic patients (mean BMI 16 kg/m2) than in normal weigth patients (mean BMI 23 kg/m2) using a fentanyl patch for 48 - 72hr (17). Two other farmacokinetic studies in cancer patients did not show significant differences between normal weight patients compared to cachectic patients (8, 9). However, in these studies patients in the lowest BMI group had a BMI <= 18.5 instead of a BMI of 16 in the study of Heiskanen (17).

Another factor that can be of influence on the pharmacokinetics of medication is cigarette smoking. As 25% of the population in the Netherlands smokes cigarettes, male vs female is 27% -23 %, probably a significant part of the fentanyl users also are smokers (18).. .

The polycyclic aromatic hydrocarbons in cigarette smoke are believed to be

responsible
for the induction of cytochrome P450.(19, 20). A study with erlotinib showed a significantly decreased AUC in smokers compared to nonsmokers (21). Both erlotinib and fentanyl are mostly metabolized by CYP 3A4. A small part of the metabolism of erlotinib is also influenced by CYP 1A1. Cigarette smoke induces CYP 1A1 and can lead to a cascade, which also involves CYP 3A4, thereby influencing the clearance of erlotinib (21). Probably, it also influences the metabolism of fentanyl. A study from our group with irinotecan showed a lower exposure to SN-38 (the active irinotecan metabolite) in smokers compared to non-smokers. The hypothesis was that irinotecan is highly sensitive to CYP3A induction and that this is modulated by cigarette smoking (22).. Possible influence of smoking on clearance of fentanyl is important to know. Terminally ill patients often change their habits in the last part of life. Heavy smokers are physically not able to smoke as much as they did before, or occasional smokers smoke more because of stress. Both scenarios can potentially influence the fentanyl clearance. This may result in over- or underdosing of fentanyl, causing intoxication or ineffective pain treatment.

As a result of these earlier publications, in this study we want to determine which patient characteristics influence the pharmacokinetics of fentanyl.

Study objective

Primary Objective:
to study the influence of a BMI < 20 or a BMI > 25 on the clearance of fentanyl, in patients using a stable dose of the fentanyl patch (Durogesic ®).
to study the effects of smoking on the clearance of fentanyl, in patients using a stable dose of the fentanyl patch (Durogesic ®).

Stable dose is defined as using the same dose of fentanyl during at least 8 days.

Study design

This is a multicenter pharmacokinetic cohort study. The trial will be performed at the Erasmus MC Cancer Institute, department of Medical Oncology.

Patients with a stable dosage of fentanyl used through a patch can be included. Stable dose is defined as at least 8 days using a stable fentanyl dosage. Blood samples are always taken on the 2nd day of the used patch.

Patients will be asked to stick a fentanyl patch (Durogesic ®) during 3 periods at the upper arm. During the third period, 1 venous blood sample will be collected.

After taking the blood sample the patient has finished the study.

Study burden and risks

NA

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

use of fentanyl patch

Exclusion criteria

use of fentanyl rescue medication

Study design

Design

Study type: Observational invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	01-04-2014
Enrollment:	80
Type:	Actual

Ethics review

Approved WMO Date:	25-03-2014
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	31-07-2014
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

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
CCMO	NL41937.078.13