Absorption of sublingually delivered fentanyl (Abstral) in head and neck cancer patients treated with curatively aimed chemo-or bioradiotherapy

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Primary Objective: - To study the effect of mucositis on the absorption of sublingually delivered fentanyl (Abstral®) in head and neck cancer patients treated with chemoradiotherapy. Secundary Objective:- To study the effect of xerostomia on the...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Miscellaneous and site unspecified neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON41370

Source
ToetsingOnline

Brief title
Absorption of sublingual fentanyl

Condition

- Miscellaneous and site unspecified neoplasms malignant and unspecified

Synonym
bio-radiotherapy, chemo-radiotherapy, head and neck cancer

Research involving
Human

Sponsors and support

Primary sponsor: Erasmus MC, Universitair Medisch Centrum Rotterdam
Source(s) of monetary or material Support: Prostrakan,Prostrakan, farmaceutisch bedrijf

Intervention

Keyword: abstral, mucositis, pharmacokinetics, sublingual fentanyl

Outcome measures

Primary outcome

Fentanyl pharmacokinetics (i.e.clearance).

Secondary outcome

- side effects according the CTC toxicity criteria

- mucositis according the CTC toxicity criteria and the OMAS

- Painscores according the NRS (in patients with pain)

- Xerostomia scores according the GRIX

Study description

Background summary

In patients with head and neck cancer aggressive treatment strategies, e.g. concurrent treatment with cisplatin or cetuximab and radiotherapy, lead to local tumor control and an improved survival rate in comparison to radiotherapy alone (1, 2). The consequences of this treatment with chemo- or bioradiotherapy, however, are more toxicity problems like mucositis during therapy and an atrophy and dry mouth (xerostomia) following therapy.
Due to the current standard treatment options, the majority of head-and-neck cancer patients treated with curatively aimed chemo-or bioradiotherapy suffer from severe mucositis. In these patients a mean mucositis incidence of 80% is thought to be quite common (3).. Mucositis may lead to severe pain, significant weight loss, need for a feeding tube, hospitalization, and, as a result, increased costs(3, 4). In patients receiving conventionally fractionated radiotherapy (in combination with cisplatin) a median duration of severe mucositis (WHO grade 3-4) of 26 days has been reported. The median time to this severe form of mucositis was found to be 35 days(5). Both the radiotherapy dose

and its localization are correlated with the severity and duration of the mucositis. Cumulative doses in the oral cavity less than 32 Gy were associated with minimal mucositis and doses of 39 Gy and more with a longer duration of mucositis(6).

Besides mucositis, xerostomia is a major problem in head and neck cancer patients treated with radiotherapy. This is due to iradiation of the salivary glands. Xerostomia is the worst six weeks after radiotherapy treatment has finished. Xerostomia improved in time after radiotherapy, in a study during a 5 yr period of follow up, but did not return to baseline (7).

From the third week of radiotherapy, oral pain is getting serious, and will require analgesics(8). Mucositis is increasing in the weeks following and worst at the end of radiotherapy treatment. Despite the wide use of opioids this pain is not always sufficiently controlled(8, 9).

For moderate-severe pain, opioids are indicated. International guidelines advice the use of a combination of slow-release and immediate release opioids; the last ones on demand in case of increasing pain. Because of mucositis, and therefore problems with swallowing, the use of oral medication can be difficult and painful. Transdermal patches like the patches with buprenorfine and fentanyl or subcutaneously delivered morphine or fentanyl are preferred for treatment of continuous pain in mucositis. For the treatment of breakthrough pain several immediate release products are available like short-acting morphine, oxycontin and nowadays several oromucosal fentanyl products.

Fentanyl is one of the most widely used opioids. This drug is highly lipophilic and binds strongly to plasma proteins. In addition, fentanyl is more potent than morphine at equipotent dose levels (10). The metabolism of fentanyl takes place primarily in the liver (11). Fentanyl is mainly oxidized into the inactive metabolite norfentanyl by the CYP3A4 iso-enzyme(12). Less than 1% is metabolized to despropionyl-fentanyl, hydroxyfentanyl, and hydroxynorfentanyl. These metabolites are also inactive. Fentanyl is mainly excreted renally. The large majority of the fentanyl is excreted as metabolites, while 10% is excreted as unchanged drug. A minority of fentanyl is found in the feces, mainly as metabolites (11).

Abstral® is a sublingual form of fentanyl and is one of the new immediate release oromucosal fentanyl products for the treatment of breakthrough pain episodes. Abstral® is placed directly under the tongue, in the deepest part. It will be absorbed by the mucosa. Sublingual fentanyl is well tolerated in patients in a placebo controlled study(13).

Unfortunately, it is unclear if the level and rate of absorption of sublingually administered fentanyl is influenced by mucositis. In healthy subjects, sublingually delivered fentanyl is immediately absorbed by the sublingual mucosa. First detectable plasma concentrations are found around 10

minutes after administration. A part of the dose is absorbed by the gastrointestinal tract. Median Tmax is around 40 minutes(14).

Sublingually delivered fentanyl has not yet been tested in patients with mucositis. Buccally delivered fentanyl was tested in patients with mild mucositis (grade 1) in two small studies, including in total14 (7 patients with mucositis) and 16 (8 patients with mucositis) patients, respectively. In both studies 200 mcg buccal fentanyl was used. In one study patients were opioid naïve. In neither of these studies serious adverse events occurred. These studies showed no difference in fentanyl concentrations between patients with and without mucositis. Besides the small sample size, only inter-patient comparisons (between patients with and without mucositis) were performed and only patients with mild (grade 1) mucositis were included (15, 16). Knowing the inter-patient variability (14, 16) in serum concentrations using the same dose of fentanyl, it is impossible to draw hard conclusions on the influence of mucositis on the absorption of sublingual fentanyl in such small studies. It is also not clear if xerostomia influences absorption of sublingually delivered fentanyl, although the advice is to rinse the mouth with water before taking Abstral ® when suffering from a dry mouth (17).

In studies with buccally and sublingually delivered fentanyl in healthy volunteers, doses up till 200 mcg were studied without significant side effects and safety problems (9). When more than 200 mcg fentanyl was used, naltrexone was co-administered(18) . Co-administration of naltrexone minimizes the opioid receptor mediated effects of fentanyl. This combination of drugs would not be expected to affect the pharmacokinetics of fentanyl because fentanyl is a substrate of CYP3A4 and naltrexone is not (19). Other studies with buccally and sublingually delivered fentanyl were done in opioid tolerant patients.

Study objective

Primary Objective:
- To study the effect of mucositis on the absorption of sublingually delivered fentanyl (Abstral®) in head and neck cancer patients treated with chemoradiotherapy.

Secundary Objective:
- To study the effect of xerostomia on the absorption of sublingually delivered fentanyl (Abstral®).
- To study the relation between radiotherapy dose sublingual and the changes in pharmacokinet ics

Study design

This is a single-center pharmacokinetic study. The trial will be performed at

the Erasmus MC-Daniel den Hoed Cancer Center, Department of Medical Oncology. Patients will be given a single dose of Abstral® 200 mcg sublingually. Pharmacokinetics of sublingually delivered fentanyl will be measured at 4 different time points: at or within 3 days before start of the radiotherapy (T=0), 18-21 days after starting radiotherapy (T=1), 39-42 days after starting (T=2) and six weeks after the end of the chemo- or bioradiotherapy (T=last). For patients* convenience, and therefore feasibility of the study, study procedures will be planned as far as possible at days patients are visiting the hospital for treatment, information or other reasons.
Pharmacokinetic samples will be taken pre-dosing, at 10, 20, 30, 40, 50, 60, 90, 180 and 360 minutes after the single Abstral ® l dose.

Radiotherapy: Patients will be given 70 Gy to the primary tumor and clinically positive nodes, given in 35 fractions of 2 Gy each over a seven-week period (elected lymph node areas are irradiated with a minimum of 46 Gy). The radiotherapy dose in the sublingual area will be measured by the radiation oncologist.

Patients treated with cisplatin stay in the hospital during 24 hrs. Cisplatin (100 mg/m2) solved in natriumchloride 3% is given in 3 hours. For anti-emetic prophylaxis patients receive a regimen consisting of oral aprepitant 125 mg plus i.v. dexamethasone 10 mg and i.v. granisetron 1 mg on day 1 15 minutes before the administration of cisplatin, aprepitant 80 mg and oral dexamethasone 6 mg once daily on day 2-3, and dexamethasone 6 mg on day 4. Patients are pre- and posthydrated with glucose 2.5%, natriumchloride 0.45% in combination with potassiumchloride during 24hrs.

Patients treated with cetuximab stay in the hospital during 4 hrs. Patients receive a loading dose of 400mg/m2 i.v 1 week prior to radiotherapy and then seven weekly infusions of 250 mg/m2 during radiotherapy, the first 250 mg/m2 infusion at the start of radiotherapy. For anti-allergy prophylaxis patients receive clemastin 1mg prior to cetuximab treatment.

Pain scores will only be documented when patients have pain at the start of the pharmacokinetic sampling. In these patients pain will be scored again 1 hour after administration of Abstral. Pain will be scored according the Numeric Rating Scale (NRS).

General toxicity will be scored before the pharmacokinetic sampling and 1 hour after administration of Abstral Toxicity will be scored according te NCI-CTC v 4.3 toxicity criteria (Appendix B).

Mucositis will be scored according the NCI-CTC v 4.3 toxicity criteria (Appendix C) and the Oral Mucositis Assessment Scale, OMAS. The OMAS is easy to use and showed a high interobserver reproducibility (correlation coefficient >0.92),(20) Appendix D).

Xerostomia will be scored according the Groningen Radiotherapy-induced Xerostomia questionnaire (GRIX). The Grix is a validated questionnaire (21) (Appendix E).

When patients need analgesics they can use all opioids except immediate and slow release fentanyl. For continuous pain the buprenorfine is preferred because of the transdermal administration route. Oxynorm and oramorph can be used for breakthrough pain. Otherwise, subcutaneous morphine can be used in case of side effects or inadequate pain relief on buprenorphine. When fentanyl is deemed necessary, patients will get off study.
General toxicity will be scored according the NCI-CTC toxicity criteria, before taking Abstral ® and 30 and 60 minutes after taking Abstral ®.
Naltrexone is available for use in case of rare serious side effects.

Intervention

- administration of sublingual fentanyl

Study burden and risks

low

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

- patients with head and neck cancer and planned treatment with chemo-radiotherapy or radiotherapy in combination with cetuximab
- written informed consent
- age > or = 18
- no serious psychiatric illness, confusion or intellectual disability

Exclusion criteria

- use of fentanyl medication within one week before inclusion in the study (other opioid and non-opioid analgesics are allowed)
- opioid intolerance
- former allergic reactions to opioids
- the use of cytochrome P450 (CYP) inhibitors or inducers is not an exclusion criterion by itself. However, the patient should not change its use during the sampling periods, to exlude altered CYP function on the PK of Abstral

Study design

Design

Study type: Interventional

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	05-12-2014

Enrollment:	13
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Abstral
Generic name:	Fentanyl
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	18-12-2013
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	22-04-2014
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	24-08-2015
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	09-10-2015
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
EudraCT	EUCTR2013-003707-18-NL
CCMO	NL46205.078.13