Influence of intravenous versus oral administration, arterial versus venous sampling and gender on pharmacokinetic-pharmacodynamic modelling of morphine and morphine-6-glucuronide-induced pain relief in healthy volunteers.

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This study is designed to get a full PK/PD characteristic of the opioid analgesic morphine and its active metabolite M6G after oral and iv infusion and to test wether sex differences exist in the analgesic behaviour of both opioids.

Ethische beoordeling	Positief advies
Status	Werving gestopt
Type aandoening	-
Onderzoekstype	Interventie onderzoek

Samenvatting

ID

NL-OMON28632

Bron
NTR

Verkorte titel
N/A

Aandoening

Post-operative pain

Ondersteuning

Primaire sponsor: Leiden University Medical Center
Overige ondersteuning: CeNes Ltd, Cambridge UK (provide the M6G)

Onderzoeksproduct en/of interventie

Uitkomstmaten

Primaire uitkomstmaten

Pain relief related parameters (VAS to heat pain) in males vs females.

Toelichting onderzoek

Achtergrond van het onderzoek

Morphine is a potent opioid used for the treatment of acute and chronic pain.
After morphine infusion a small part (6 to 10%) is metabolized to the active component morphine-6-glucuronide (M6G). Both morphine and M6G act at the mu-opioid receptor causing analgesia and side effects, such as respiratory depression, sedation, itching, orthostatic hypotension, blurred vision, delayed gastric emptying, etc.
Recent studies indicate, however, that the side effect profiles of different opioids differ significantly.
For example, our own studies indicate that M6G displays favorable pharmacodynamics over morphine with respect to respiratory depression. It is therefore to be expected that M6G will be available for the treatment of acute postoperative and chronic cancer pain in the near future (M6G is currently undergoing phase III studies).

Intravenous versus oral administration:

In previous studies we assessed the pharmacokinetics and pharmacodynamics of intravenous morphine and M6G.
This resulted is reliable pharmacokinetic/ pharmacodynamic (PK/PD) models which may be used to predict morphine and M6G concentrations and pain relief after an intravenous infusion.
While for treatment of acute pain opioids are predominantly administered via the intravenous route, chronic and cancer pain treatment is often performed via non-intravenous routes, e.g., sublingual, rectal, transcutaneous and oral routes.
Good PK/PD models of these non-iv routes are currently not available. Furthermore it may be argued that M6G will undergo de-glucuronization in the gut and hence its bio-availability may be reduced after oral administration.
This would profoundly increase clinically relevant doses of M6G, and restrict its clinical utility while concomitantly increasing its side-effect liability.

Sex differences:

Previously we observed important sex differences in the pharmacodynamics of morphine with greater morphine potency in women.
The end-point of that study was pain tolerance to an electrical noxious stimulus. Interestingly, no sex differences in M6G's analgesic potency were observed in later studies. However, opioid analgesic efficacy/potency has been demonstrated t be pain modality specific.
Thus, we remain uninformed whether the observed sex differences in morphine's analgesic properties were related to the pain modality measured or can be generalized to other pain modalties.

Arterial versus venous sampling:

In previous studies we determined arterial blood concentrations of morphine and M6G after intravenous infusions of these opioids and linked the measured concentrations to the pharmacodynamic end-point (electrical pain relief) using standard PK/PD modeling techniques.
We prefer arterial blood samples over venous samples. However, it may be argued –taken into account the elimination half-life of these drugs- that similar results may be obtained when using venous samples, assuming that a rapid equilibration between venous and arterial blood is obtained. Since there are currently no studies exploring the effect of arterial versus venous sampling on the kinetics and dynamics of morphine and M6G, there are currently no data to substantiate either position.

Doel van het onderzoek

This study is designed to get a full PK/PD characteristic of the opioid analgesic morphine and its active metabolite M6G after oral and iv infusion and to test wether sex differences exist in the analgesic behaviour of both opioids.

Onderzoeksopzet

N/A

Onderzoeksproduct en/of interventie

Drug administration (blinded): morphine or M6G.

Contactpersonen

Publiek

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Deelname eisen

Belangrijkste voorwaarden om deel te mogen nemen (Inclusiecriteria)

1. Healthy volunteers;

2. Aged 18+.

Belangrijkste redenen om niet deel te kunnen nemen (Exclusiecriteria)

1. BMI>30;

2. Pregrancy or lactation;

3. Presence of medical disease;

4. Presence of psychiatric disease;

5. Allergy to study medication;

6. History of drugs or alcohol abuse.

Onderzoeksopzet

Opzet

Type:	Interventie onderzoek
Onderzoeksmodel:	Parallel
Toewijzing:	Gerandomiseerd
Blindering:	Dubbelblind
Controle:	Geneesmiddel

Deelname

Nederland

Status:	Werving gestopt
(Verwachte) startdatum:	01-11-2005
Aantal proefpersonen:	60
Type:	Werkelijke startdatum

Ethische beoordeling

Positief advies

Datum:	06-09-2005
Soort:	Eerste indiening

Registraties

Opgevolgd door onderstaande (mogelijk meer actuele) registratie

Geen registraties gevonden.

Andere (mogelijk minder actuele) registraties in dit register

Geen registraties gevonden.

In overige registers

Register	ID
NTR-new	NL192
NTR-old	NTR229
Ander register	: N/A
ISRCTN	ISRCTN80473151

Resultaten

Samenvatting resultaten
N/A