Pharmacokinetics and -dynamics of intrathecal baclofen therapy in patients with spasticity

Published: 06-08-2008
Last updated: 06-05-2024

Primary Objective: Studying the phenomenon of tolerance by evaluating pharmacokinetic- and dynamic parameters, in patients receiving long-term ITB therapy.Secondary Objective(s): 1.To specify the intrathecal pharmacokinetics and -dynamics of...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Movement disorders (incl parkinsonism)
Study type	Interventional

Summary

ID

NL-OMON37169

Source
ToetsingOnline

Brief title
PK/PD of ITB

Condition

- Movement disorders (incl parkinsonism)

Synonym
spasticity, spierspasmen

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Groningen
Source(s) of monetary or material Support: Beurs van de medische faculteit van de RuG voor een MD/PhD project

Intervention

Keyword: baclofen, ITB, spasticity, tolerance

Outcome measures

Primary outcome

The occurrence of tolerance in patients receiving intrathecal baclofen therapy,

determined by baclofen dose and spasticity (MAS) from pump implantation to 1

year after pump implantation

Secondary outcome

-CSF baclofen concentration of patients and the creation of a PK/PD-model for

ITB

-Individual patient characteristics as are described in the protocol.

Study description

Background summary

Intrathecal baclofen therapy (ITB) has been used since many years to treat spasticity that doesn't respond to oral baclofen treatment. ITB has been proven to be safe and effective.
The main problem with ITB therapy is that some of the patients develop tolerance. This means the effect of baclofen is decreasing, while the dose is increasing. After a while the spasticity in these patients doesn't respond to the ITB anymore and returns. It's not clear how tolerance develops, which patients develop it and how it can be treated.

In this study we try to get a better insight in the phenomenon of tolerance by gathering pharmacokinetic en -dynamic data from patients receiving ITB-therapy in combination with baclofen dose and clinical effect. This way we try to understand the development of tolerance and help to treat or prevent it in the future. The pharmacokinetic and -dynamic model can be used to calculate the optimal bolus dose of ITB patients more acurate and more precise, hereby shortening admission time and improving the inital treatment after pump implantation.

Normal procedure before pump implantation is as follows:
Patients who have an indication for ITB-therapy are admitted to the hospital for 2-4 days to test intrathecal baclofen. They receive a bolus of baclofen through an external intrathecal catheter. On the first day they receive a 25 mcg bolus, this dose is increased with 25 mcg every day (day 2: 50 mcg, day 3: 75 mcg, day 4: 100mcg). As soon as the patient reaches a satisfactory spasmolytic effect the patient can go home and does not need any further bolus doses. The patients is put on the list for implantation of the permanent subcutaneous ITB-pump. The most effective bolus dose during test-infusion is used to determine the daily dose after pump implantation (hourly dose = (optimal bolus x 2)/24).
If the patient doesn't reach a satisfactory effect with a bolus of 100 mcg (day 4) the patient isn't suitable for ITB-therapy and therefore won't be put on the list for implantation of the permanent ITB-pump.

After pump implantation the patient receives 3 monthly follow-up appointments. At this appointments the daily dose can be adjusted to the patient's needs.

Study objective

Primary Objective:
Studying the phenomenon of tolerance by evaluating pharmacokinetic- and dynamic parameters, in patients receiving long-term ITB therapy.

Secondary Objective(s):
1.To specify the intrathecal pharmacokinetics and -dynamics of baclofen.
2.To create a model to predict the optimal dose of baclofen after a single bolus of baclofen combined with CSF sampling in candidates for ITB-therapy, hereby shortening the admission time for future ITB-candidates.
3.To study the potency of a fixed bolus dose of baclofen during the first year after pump-implantation.
4.To gain a comprehension of predictive factors for tolerance, by evaluating the clinical and pharmacokinetic and -dynamic data of patients who develop tolerance

Study design

In this study 20 candidates with a clinical indication for ITB therapy will receive a series of test boluses of baclofen to determine the dose with which they reach the most optimal spasmolytic effect. By taking CSF samples after each bolus, the pharmacokinetics and -dynamics of intrathecal baclofen can be studied in detail.

On the first day of their admission for the test-infusion, all patients will receive two single lumen intrathecal catheters, which are placed using x-ray guidance. One catheter (tip at Th10) will be used to administer baclofen, the

other (tip at Th12) will be used to take CSF samples. Clinical effect will be measured by using the Modified Ashworth Scale (MAS, a spasticity scale) and the Hoffman-reflex (a neurophysiological EMG-test for spasticity). The CSF sample will be used to measure the baclofen concentration in the CSF.

The patients will receive 4 randomized testboluses of baclofen (25,50,75 microgram, and one day when no bolus is given at all) in 4 days (day 2-5 of the admission, day 1 is reserved for catheter placement). Randomization will happen in the hospital pharmacy and is blinded for both patient and physician. All baclofen used during this test-infusion will have a concentration of 0,05 mg / ml (the same as during the normal test-infusion). After each bolus clinical effect is measured (MAS and H-reflex) and 10 liquorsamples will be gathered. These liquorsamples are analyzed for the concentration of baclofen. By combining baclofen concentration, clinical effect and bolus dose it is possible to create a model for the pharmacokinetics and -dynamics of intrathecal baclofen. The model will be cross-validated for each individual patient. The resulting model can be used to improve the admission time and accuracy of future ITB test-infusions.

After a succesfull test-infusion, a permanent subcutaneous ITB-pump is implanted. The pump is filled with baclofen in a concentration of 0,5 mg / ml (the same as during the normal procedure). The first year after pump-implantation all patients will receive 3 monthly follow-up appointments. During this appointments the daily baclofen dose can be altered to the patients needs. Baclofen dose development and clinical effect will be monitored during this first year after impantation.

To study the change of effect of a fixed bolus during the first year, the patient will be admitted to the hospital for 1 day (12-24 hours) at four scheduled time intervals (1 week, 4 weeks, 12 weeks and 1 year after pump implantation). At these admissions their pump will be put into minimal infusion mode, so their spasticity will return shortly. After 5 times the half-life time, all baclofen is washed out of the CSF. At this moment they will receive their optimal bolus dose of baclofen (determined during the test infusion). By measuring clinical effect (MAS, H-reflex) we can determine if the potency of a fixed bolus of baclofen decreases during the first year. The bolus can be given through the implanted pump, so no additional lumbar punctures will be needed.

Intervention

There are several interventions as compared to the normal ITB-test-infusion protocol.

Baclofen test-infusion
•Patients will receive an additional intrathecal catheter, the same catheter that is used during permanent pump-implantation.
•Concerning the boluses of baclofen: The boluses will be (almost) the same as

in the normal test-infusion (25, 50,75 µg (study) vs. 25/50/75/100µg (normal). During the normal test-infusion, the boluses are administered in an increasing order (every day the dose is increased with 25 µg). If the patient reaches a satisfying spasmolytic effect on a dose, this will be considered as the optimal bolus dose and the patient can return home. In this study the order in which the boluses are administered will be randomized in a double-blind setting by the apothecary. Every patient receives each bolus once. One day no baclofen will be administered at al. This will be the negative control. After 5 days the optimal bolus dose will be determined, this is the lowest dose at which a patient reaches optimal spasmolytic effect.
•After each bolus, ten (10 min, 20 min, 40 min, 1 h, 1* h, 2h, 4h, 8h, 12h and 24h after) 1 ml CSF-samples will be gathered, through Th12-catheter. One sample will be taken before the first bolus, this is the negative control sample.
•After each bolus clinical effect will be measured four times (after 1, 2, 4 and 8 hours), using the MAS (Modified Ashworth score) and the H-reflex. During normal procedure the clinical effect is only measured three times after each bolus. Also the H-reflex (a neurophysiological test) is extra as compared with the normal procedure.

Follow-up phase
•In the follow-up phase all patients will have scheduled 3 monthly appointments. This is the same frequency as for regular ITB therapy patients.
•To study the change of effect of a fixed bolus during the first year, the patient will be admitted to the hospital for 1 day (12-24 hours) at four scheduled time intervals (1 week, 4 weeks, 12 weeks and 1 year after pump implantation). At these admissions their pump will be put into minimal infusion mode, so their spasticity will return shortly. After 5 times the half-life time, all baclofen is washed out of the CSF. At this moment they will receive their optimal bolus dose of baclofen (determined during the test infusion). By measuring clinical effect (MAS, H-reflex) we can determine if the potency of a fixed bolus of baclofen decreases during the first year. The bolus can be given through the implanted pump, so no additional lumbar punctures will be needed..

Study burden and risks

This study protocol closely resembles the protocol of the normal test-infusion phase. The main risk for the patient will be the placement of an extra intrathecal catheter. Since there is always a small chance of infection associated with an external intrathecal catheter, this risk will be doubled for patients in the study. When the catheter is removed within 5 days after placement (as will be done in this study) the risk of infection is minimal. To assure they are placed on the rigth spinal level, both catheter are inserted using x-ray guidance. During this procedure the patient is exposed to a radiation dose of 2mSv.
CSF-sampling will be done through this intrathecal catheter, so this won*t create an extra burden for the patient. After each bolus clinical effect will

be measured 4 times a day, one time more than during standard protocol. Since all patients will receive all bolus doses in a randomized order, the total admission time will be 1-2 days longer as compared to the normal procedure. As a result the patient will also receive 1-2 boluses more than normal.

In the follow-up phase patient are more closely monitored during the first year after pump-implantation. As a result of this, the patients will have to be admitted to the hospital for 1 day at 4 follow-up appointments during this first year.

This study will contribute greatly to the insight in tolerance, a problem that all ITB-patients (including the patients joining the study) can encounter. By joining the study patients will contribute to this insight and possible better treatment option for this problem. Additionaly the patients will contribute to the creation of a model that will make it possible to determine the optimal baclofen dose for future ITB-patients more quickly and more accurate.

In conclusion this means the small risks associated with this study are in proportion to the potential value of the results.

Since the study can only be conducted in patients with spasticity, it is evident that this study could not be conducted without the participation of subjects belonging to the current study population.

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 will have to meet the requirements necessary for implantation of an ITB pump.
-Patients can be monitored regularly (at least once / 6 weeks) during the year after pump implantation.
-Patients details can be taken, including the following details:
o Gender, date of birth,
o Length, weight, blood pressure
o Medication
o Underlying disease, year of onset
o Daily oral baclofen dose and duration of oral baclofen treatment
-Female patients at fertile age need to guarantee adequate anti-conception.

Exclusion criteria

-Patients who have a contra-indication for intrathecal catheter placement:
o Anti-clotting medication
o Low platelet count
o Elevated intracranial pressure
o The presence of another electronic device
-Patients who don*t reach a satisfactory effect in the test-infusion phase.
-Patients experiencing pump failures during the duration of the study
-Patients below the age of 18
-Pregnancy or female patients at fertile age who cannot guarantee adequate anti-conception

Study design

Design

Study phase:	4
Study type:	Interventional
Masking:	Double blinded (masking used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	01-11-2008
Enrollment:	20
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	baclofen intrathecal 0,05 mg / ml
Generic name:	baclofen intrathecal 0,05 mg / ml
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	baclofen intrathecal 0,5 mg / ml
Generic name:	baclofen intrathecal 0,5 mg / ml
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	06-08-2008
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	26-11-2008
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	11-05-2011

Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

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	EUCTR2008-004934-26-NL
CCMO	NL24409.042.08