Towards dose optimisation through pharcokinetic profiling of piperacillin/tazobactam in critically ill patients

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To assess piperacillin concentrations during continuous dosing of P/T in critically ill patients; to determine PK variables, e.g. creatinine clearance, leading to a predictive mathematical model enabling TDM and ideally establishing better a priori...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Bacterial infectious disorders
Study type	Observational invasive

Summary

ID

NL-OMON39910

Source
ToetsingOnline

Brief title
Pharmocokinetic profiling of piperacillin/tazobactam in the critically ill

Condition

- Bacterial infectious disorders

Synonym
effect, infection

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Groningen

Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: Critical Care, Pharmocokinetic, Piperacillin-tazobactam, Therapeutic drug monitoring

Outcome measures

Primary outcome

Total bound plasma concentrations of piperacillin (and unbound plasma concentrations of piperacillin as well as tazobactam plasma concentrations when feasible in our laboratory); PK parameters; APACHE II; target attainment at different time intervals based on predefined microbiological targets based on MICs of specific micro-organisms; microbiological outcome; clinical outcome

Secondary outcome

- Assessment of relationship between PK parameters and APACHE II score
- To evaluate outcome in terms of ICU-mortality; mortality at day 28 after inclusion; cause of death; microbiological success (eradication of P/T-susceptible micro-organism) or failure (development of P/T-resistance in previously susceptible micro-organism)
- Assessment of reliability of determination of free fraction of P/T from the bound fraction and routinely collected parameters (e.g. serum albumin) - when tazobactam concentration measurements are available.
- Determination of P/T ratio change in organ failure -when tazobactam concentration measurements are available.

Study description

Background summary

Beta-lactams are the most prescribed group of antibiotics in critically ill patients in Dutch intensive care units (ICUs). As suboptimal dosing is unwanted both on an individual level in terms of outcome as well as on a larger scale considering the emerging threat of antimicrobial resistance, ensuring an optimal dosing strategy merits our utmost effort. Recent studies show that conventional intermittent dosing of piperacillin-tazobactam (P/T), the most frequently used β-lactam in our ICU, often leads to insufficient plasma concentrations in the critical care setting. Considering the time-dependent character of P/T, continuous dosing after a loading dose seems more logical, with the potential of better target attainment and outcome. Literature available in this field suggests this point. Given the unpredictable pharmacokinetics of the critical care patient, building a robust pharmacokinetic model on continuous dosing enabling reliable therapeutic drug monitoring (TDM) will likely be of benefit.

Hypothesis: A reliable pharmacokinetic model can be made by assessing drug - concentrations after starting treatment with P/T by continuous infusion in critically ill patients. The purpose of this model will be, in a subsequent study, to enable reliable real-time TDM of continuous P/T dosing in critically ill patients to be introduced in our clinic optimizing treatment with P/T in this patient category.

Study objective

To assess piperacillin concentrations during continuous dosing of P/T in critically ill patients; to determine PK variables, e.g. creatinine clearance, leading to a predictive mathematical model enabling TDM and ideally establishing better a priori dosing through tailoring; to assess inter-individual variability in reaching a steady-state; to assess a relationship between pharmacokinetic (PK) parameters and Acute Physiology and Chronic Health Evaluation II (APACHE II) score; to assess target-attainment based on concentration 4-5 times above a predefined Minimum Inhibitory Concentration (MIC); to assess outcome in terms of ICU-mortality and mortality at day 28; to assess outcome in terms of microbiological success (eradication of P/T susceptible micro-organism) or failure (development of P/T resistence in a priori susceptible micro-organism).

Study design

Prospective, Observational Single Center Cohort study.

Study burden and risks

Blood will be drawn on predefined time points after drug administration (t = 0, t =20 min, 40 min, 1 hour, 2 hours, 4 hours, 8 hours, 12 hours and every 12 hours onwards) at a quantity of 2 ml at a time through an arterial line placed for reasons outside the study protocol. The patients are treated according to the up-to-date standard of care on a recently proposed treatment protocol which propagates the use of continuous infusion of P/T based on well established pharmacokinetic and pharmacodynamic benefits, as alternative for intermittent dosing. Its applicability, however, has not been unanimously adopted worldwide possibly due to lack of evidence in clinical outcome studies; most studies in this field are of small sample size, important case mix variation and resulting poor level of evidence. All studies showed at least non-inferiority in the continuous dosing treatment arm as compared to intermittent dosing. One study showed better clinical outcome, as well as one using extended infusion dosing. In the treatment group there is at least equipoise. For in-depth background information we refer to addendum I, which is a review of available literature in this field, and to chapter I of the protocol.

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

Adult >= 18 yrs
Admiited to the ICU
Proven or suspected infection
Indication for treatment with Piperacillin-tazobactam

Exclusion criteria

Pregnancy
Severe anemia
Contraindication for Piperacillin-tazobactam, including known or suspected allergy
Contraindication for continuous infusion

Study design

Design

Study phase:	4
Study type:	Observational invasive
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	10-12-2013
Enrollment:	40
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Piperacillin-tazobactam
Generic name:	Piperacillin-tazobactam
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	07-06-2013
Application type:	First submission
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	EUCTR2012-004115-30-NL
CCMO	NL42029.042.12