Right Dose, Right Now: Randomized Controlled Clinical Trial

Published: 28-05-2018
Last updated: 15-02-2024

To assess the influence of dosing guided by AutoK on achieving PK targets and clinical endpoints in intensive care patients with sepsis.

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

Summary

ID

NL-OMON53354

Source
ToetsingOnline

Brief title
Right Dose, Right Now: Randomized Controlled Clinical Trial

Condition

- Hepatobiliary neoplasms malignant and unspecified

Synonym
blood poisoning, infection, infectious disease, Sepsis

Research involving
Human

Sponsors and support

Primary sponsor: Vrije Universiteit Medisch Centrum
Source(s) of monetary or material Support: ZonMW

Intervention

Keyword: Antibiotics, Personalized medicine, Pharmacometrics, Prediction

Outcome measures

Primary outcome

PK target attainment in the first 24-hours. Targets are 100%-fT>4MIC for the beta-lactam antibiotics, AUC/ MIC>400 for vancomycin and fAUC/MIC *125 for ciprofloxacin.

Secondary outcome

Time to PK target level, PK target attainment during therapy, attainment of clinical cure, length of ICU and hospital stay, delta Sequential Organ Failure Assessment (SOFA) score at 96 hours, days free of ventilator / hemofiltration / other organ support, ICU / hospital / 28 day / 6-month mortality, quality of life at hospital discharge (EQ-5D-5L) and after 6 months, societal costs (iMTA MCQ and iMTA PCQ after 6 months), days free of delirium.

We will assess physician compliance and satisfaction with AutoK and investigate whether its use is associated with an increase in PK/PD knowledge amongst healthcare workers.

Study description

Background summary

Sepsis is a major and growing problem. In the Netherlands alone, around 15.000 patients are diagnosed with severe sepsis each year. Despite major scientific efforts, including many failed clinical trials mainly focusing on inflammatory mediators and the introduction of care bundles, the mortality rate for severe sepsis still remains unacceptably high at around 30%. This is alarming, especially since the incidence of sepsis continues to increase and now exceeds that of colon cancer, breast cancer and AIDS combined.

Antibiotics are essential for treating sepsis. Their early and appropriate use has repetitively been shown to reduce mortality rates. However, achieving adequate antibiotic exposure in critically ill patients is a major challenge due to markedly different pharmacokinetic (PK) profiles in the critically ill. Nevertheless, doctors still rely on standard antibiotic dosing schemes, that were developed based on data from healthy volunteers and non-critically ill patients. Depending on patient characteristics, clinical course and therapy, this strategy may result in underdosing and/or drug-related toxicity during the course of intensive care treatment.

Therefore, we developed AutoKinetics (AutoK) software. AutoK aims to make use of patient data that is available from the electronic patient records, for example about fluid balance and renal function. Using this data, AutoK is able to give fast and precise dosing advice, using published pharmacokinetic models of any drug. AutoK runs on the computer at the bedside. Thus, advice is readily available, even before treatment is started, and is continuously updated as disease and therapy evolve: true personalized dosing.

We hypothesize that AutoK can improve antibiotic dosing, morbidity and mortality for severe sepsis.

Study objective

To assess the influence of dosing guided by AutoK on achieving PK targets and clinical endpoints in intensive care patients with sepsis.

Study design

Multicenter, randomized controlled, two-arm, parallel-group, superiority trial

Intervention

Patients will be randomized to one of two groups.

Group 1 (Control group): standard intravenous antibiotic therapy based on current clinical guidelines and practice. Standard therapy will include TDM for vancomycin, but not for the beta-lactams and ciprofloxacin. The standard antibiotic dosing schemes are:

o OLVG:
* Vancomycin: continuous infusion 1000 mg/24h
* Ciprofloxacin: 2 x 400mg
* Cefotaxim: 4 x 1000mg
* Meropenem: 3 x 1000mg

o VUmc:

* Vancomycin: 1 x 1000 mg
* Ciprofloxacin: 3 x 400 mg
* Ceftriaxon: 1 x 2000 mg
* Meropenem: 3 x 1000 mg

Local standard protocols allow for higher dosing in case of suspicion of atypical pneumonia, central nervous system infection or endocarditis.

Group 2 (Experimental group): Personalized antibiotics dosing guided by AutoK, based on PK models combined with patient data from the electronic patient record.

Study burden and risks

Possible benefits to the subject include improved clinical outcome as a result of improved antibiotic dosing. Further, if feasible and successful, individualized antibiotic dosing could be a major step forward in the treatment of sepsis, which is a significant source of worldwide morbidity and mortality.

Estimated risks are small given AutoK*s safety profile, dose warnings and mandatory dose verification by the treating physician, as explained in the investigational medical device dossier. Burden is limited to extra blood sampling from an existing line (6-10 samples of 4 ml per antibiotic) and participation in follow-up questionnaires.

We therefore believe that the benefits outweigh the risks and burden.

Contacts

Public
Vrije Universiteit Medisch Centrum

De Boelelaan 1117
Amsterdam 1081 HV
NL
Scientific
Vrije Universiteit Medisch Centrum

De Boelelaan 1117
Amsterdam 1081 HV
NL

Eligibility criteria

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

Inclusion criteria

- Age >18 years
- Suspected / confirmed infection
- Suspected / confirmed lactate concentration > 2 mM OR treatment / imminent treatment with vasopressors
- Treatment / imminent treatment with one or more of the following antibiotics: vancomycin, ceftriaxone, meropenem, ciprofloxacine, cefotaxime.

Exclusion criteria

None

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Single blinded (masking used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	19-02-2018
Enrollment:	420
Type:	Actual

Medical products/devices used

Generic name:	AutoKinetics
Registration:	No
Product type:	Medicine
Brand name:	Cefotaxim PCH
Generic name:	Cefotaxime
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Ceftriaxon Hikma
Generic name:	Ceftriaxone
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Ciprofoxacine Kabi
Generic name:	Ciprofloxacin
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Meropenem Fresenius Kabi
Generic name:	Meropenem
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Vancomycin Xelia
Generic name:	Vancomycin
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	11-01-2018
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	25-05-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Approved WMO Date:	29-06-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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	2017-002478-37
CCMO	NL61682.029.17
Other	NTR kandidaat nummer 27792

Study results

Date completed:	02-02-2022
Actual enrolment:	252

Summary results
Trial is onging in other countries