Addition of Tobramycin inhalation antibiotic treatment to standard IV antibiotic treatment for ventilator-associated pneumonia

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Does addition of inhalation tobramycin to standard IV treatment result in a higher clinical cure rate than standard IV antibiotic treatment alone in patients with ventilator-associated pneumonia.The initial response to treatment will be evaluated...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Respiratory tract infections
Study type	Interventional

Summary

ID

NL-OMON40796

Source
ToetsingOnline

Brief title
Vaporise study

Condition

- Respiratory tract infections

Synonym
pneumonia caused by mechanical ventilation

Research involving
Human

Sponsors and support

Primary sponsor: Erasmus MC, Universitair Medisch Centrum Rotterdam

Source(s) of monetary or material Support: Ministerie van OC&W,industrie stelt de medicatie en placebo beschikbaar

Intervention

Keyword: antibiotic, Inhalation, tobramycin, VAP

Outcome measures

Primary outcome

The initial response to treatment will be evaluated after 3 days of

antimicrobial treatment (between 72 and 96 hours after start treatment).

Nonresponse is considered when at least one of the following criteria is

present:

(1) No improvement of the arterial O2 tension to inspired O2 fraction ratio

(2) Persistence of fever (>=38°C) or hypothermia (<35.5°C) together with purulent

respiratory secretions

(3) increase in the pulmonary infiltrates on chest radiograph of greater than

or equal to 50%

(4) occurrence of septic shock or multiple organ dysfunction syndrome, defined

as three or more organ system failures not present on Day 1

Secondary outcome

- clinical response at end of treatment (after 8 or 14 days)

- 20-day and 90- day mortality rate

- length of stay

- ICU survival

- Number of days without mechanical ventilation

- duration of mechanical ventilation

- discharge from the ICU

- adverse events

- day of normalisation of CRP, procalcitonin (PCT) and chest X-ray

- eradication of pathogens (especially pseudomonas), defined as three negative

cultures until day 90

- Clinical Pulmonary Infectious Score; APACHE II score; multiple organ

dysfunction score (MODS); SOFA score; Lung injury score

Study description

Background summary

INTRODUCTION AND RATIONALE

Approximately 9-27% of mechanically ventilated patients in the intensive care unit (ICU) develop ventilator-associated pneumonia (VAP). Patients in whom VAP develops have a higher mortality rate up to 50%, stay longer in the intensive care unit (ICU), and require more resources than those without the disease. Despite the availability of modern ICU care and modern antibiotics, the overall clinical cure rate for VAP in randomized clinical trials is only 40%. The cure rate for Pseudomonas aeruginosa is even lower (9). It is unclear why VAP cure rates are so low.

There is a disappointing amount of data in the medical literature about the effect of inhalation antibiotics. Almost all of the studies were observational and did not have control groups
In one study, 38 patients were randomized to receive either endotracheally (ET) sisomicin (aminoglycoside) or placebo added to systemic β-lactam/aminoglycoside therapy. The cure rate was significantly better in the ET group (77 vs 45%). This study from 1979 remains the largest randomized, placebo-controlled trial of aerosolized antibiotics for treating VAP. Another prospective randomized trial has also examined the impact of the adjunctive use of locally instilled tobramycin with intravenous therapy in the treatment of VAP. Although the addition of endotracheal tobramycin did not improve clinical outcome compared with placebo, microbiologic eradication was significantly greater in the patients receiving aerosolized antibiotics. The small number of patients in this study suggests that more data are needed on this type of therapy before determining its value.

The relatively poor response rates seen with intravenous therapy of VAP and the emergence of MDR organisms makes new treatment options desirable. The ATS/IDSA VAP guidelines recommend that *adjunctive therapy with an inhaled aminoglycoside or polymyxin (colistin) for MDR Gram-negative pneumonia should be considered, especially in patients who are not improving*. The recommendations by the Society of Infectious Diseases Pharmacists are similar.

Study objective

Does addition of inhalation tobramycin to standard IV treatment result in a higher clinical cure rate than standard IV antibiotic treatment alone in patients with ventilator-associated pneumonia.
The initial response to treatment will be evaluated after 3 days of antimicrobial treatment at day 4.

Study design

A prospective double-blind randomized controlled trial
comparing Tobramycin inhalation antibiotic treatment and standard IV antibiotic treatment with standard IV antibiotic treatment alone for ventilator-associated pneumonia

Intervention

Patients will receive Tobramycin inhalation (Bramitob) 300 mg 2 times daily or placebo inhalation (identically packaged sterile saline) 2 times daily besides IV antibiotic treatment

Study burden and risks

A number of pulmonary adverse events such as coughing and bronchospasm can occur with outpatient use of aerosolized antibiotics. The only adverse events reported in the aminoglycoside VAP studies were coughing and dizziness in four patients. No other adverse events were reported. The vast majority of aminoglycoside VAP reports used the intravenous formulation. A preservative-free formulation of tobramycin for inhalation used in cystic fibrosis may theoretically provide a better safety profile, but this has not been studied widely in VAP patients.

Serumconcentrations need to be controlled in patients with renal dysfunction. Tobramycin inhalation treatment needs to be stopped until trough level is < 2 microgram/ml (2 mg/l).When a patient is known to have a renal dysfunction, is using nefrotoxic medication, has a serum creatinine level of > 180 micromol/l, or in case of acute renal insufficiency or on dialysis than a trough level will be determined. When the trough level is > 1 mg/l than tobramycin will not be

given until the trough level is < 1mg/l.

Benefit: possible reduction in mortality, length of treatment, improvement of other important clinical outcome parameters, like clinical cure rate and improved eradication of microorganisms.

Contacts

Public
Erasmus MC, Universitair Medisch Centrum Rotterdam

's Gravendijkwal 230
Rotterdam 3000 ca
NL
Scientific
Erasmus MC, Universitair Medisch Centrum Rotterdam

's Gravendijkwal 230
Rotterdam 3000 ca
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Patients older than 18 years
admitted to these ICUs for 48 hours or more
with clinical suspicion of VAP.
VAP is diagnosed in patients with previous invasive Mechanical ventilation for 48 hours or more .;The clinical suspicion of pneumonia is based on the ATS criteria:

- new or progressive radiologic pulmonary infiltrate
Together with at least two of the following three criteria:
- temperature >38°C
- leukocytosis >12,000/mm3 or leucopenia <4,000/mm3
- purulent respiratory secretions

Exclusion criteria

patients with allergy to tobramycin; pregnancy; expected to die within 72 hours after enrollment

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Single blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	26-03-2015
Enrollment:	42
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Tobramycin (Bramitob)
Generic name:	Tobramycin
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	05-08-2014
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	21-01-2015
Application type:	First submission
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	EUCTR2014-001406-17-NL
CCMO	NL48009.078.14