Amoxicillin-clavulanic acid Levels in Sputum After Nebulization in AECOPD (ALSAN)

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In this study we want to show adequate sputum levels are obtained throughout the day after inhalation of nebulized amoxicillin clavulanic acid in hospitalized AECOPD patients.

Ethical review	Approved WMO
Status	Pending
Health condition type	Bacterial infectious disorders
Study type	Interventional

Summary

ID

NL-OMON53015

Source
ToetsingOnline

Brief title
ALSAN

Condition

- Bacterial infectious disorders
- Respiratory tract infections

Synonym
COPD

Research involving
Human

Sponsors and support

Primary sponsor: Medisch Spectrum Twente
Source(s) of monetary or material Support: subsidie vanuit Stichting Astma Bestrijding,afdelingsbudget desbetreffende afdelingen (apotheek en longafdeling)

Intervention

Keyword: antibiotics, COPD, exacerbation, inhalation

Outcome measures

Primary outcome

Dose exposure data as determined by sputum concentrations of amoxicillin.

Amoxicillin levels in sputum give information on the appropriateness of the

dose given from a calculated time > MIC.

To obtain top, mid and trough sputum levels of amoxicillin between two doses,

patients are asked to give up sputum after inhalation(top), at one point during

the day(mid) and before the next inhalation (trough).

Secondary outcome

A short questionnaire is given to the patient intended to give insight in the

subjective perception of side effects after nebulization (tolerability).

Study description

Background summary

Previous research has shown that an amoxicillin concentration equal or higher than the Minimal Inhibiting Concentration of 90% (MIC90) reduced the mean length of hospitalization during a COPD exacerbation from 11 to 7 days. Furthermore, most patients did not reach amoxicillin levels equal or higher than the MIC90 when amoxicillin clavulanic acid was administered orally or intravenously. [1,2] We hypothesize that more patients will achieve an adequate amoxicillin level in sputum when amoxicillin clavulanic acid is administered locally instead of systemic. Therefore, we want to apply nebulized amoxicillin clavulanic acid by inhalation. The safety and tolerability of four escalation single doses has been investigated in a former study in stable and hospitalized acute exacerbations of COPD (AECOPD) patients. In this study we want to show adequate sputum levels are obtained throughout the day after inhalation of nebulized amoxicillin clavulanic acid in hospitalized AECOPD patients.

Study objective

In this study we want to show adequate sputum levels are obtained throughout the day after inhalation of nebulized amoxicillin clavulanic acid in hospitalized AECOPD patients.

Study design

The study is designed as a single-arm prospective intervention study. Patients willing to participate in this study will follow a schedule with two times daily inhalation of amoxicillin clavulanic acid in a fixed dose during three days of admission (at the third day, only one inhalation takes place). At each day of inhalation a questionnaire will be filled in to obtain insight in the subjective perspective of side effects of inhalation (1 questionnaire per day).

After nebulization sputum samples will be collected through sputum induction. To obtain top, mid and trough sputum levels of amoxicillin between two doses, patients are asked to undergo sputum induction give up sputum after inhalation (top = 30 min after nebulization), at one point during the day (mid) and before the next inhalation (trough). Sputum induction with 3% saline is used (for all patients in this study) since not all patients will be able to spontaneously produce sputum at the described moments. Sputum induction will dilute the sputum samples. This however affects mainly the top concentrations as has been seen in other studies. For amoxicillin, effective by time > MIC, this is not an issue since top levels are expected to be far above the MIC (as seen in previous studies).

Intervention

The included patient will be given amoxicillin clavulanic acid by inhalation twice daily in a concentration of 50/10 mg/ml amoxicillin clavulanic acid in the first two days. The last day only one inhaltion takes place. Patients will nebulize 4 ml solution of 50/10 mg/ml amoxicillin clavulanic acid (200/40 mg amoxicillin clavulanic acid).
After the patient received the first treatment without severe adverse reactions the treatment schedule will be two times daily. (the patient will be questioned on this topic prior to the second nebulization) Adverse reactions will be measured by filling in the questionnaire.

Study burden and risks

Only little is known about the risks and benefits of this product by this route of administration. For oral or intravenous treatment several possible adverse reactions are described in the Summary of Product Characteristics (SPC). There is no reason to suspect other systemic adverse reactions as described in the SPC. Additionally, local effects due to the route of administration such as

cough could occur. The patients reported no side effects in the study Stockley et al performed with nebulization of solely amoxicillin. The STONAC 1 and 2 studies showed that patients experienced only minor side effects due to the inhalation and was well tolerated. None of the 17 patients showed a clinical significant reduction of FEV1 (>20%).
Potential adverse events that might occur is local irritation of the lung tissue which could cause cough and airway narrowing as seen before in the STONAC 1 and 2 studies and seen by other nebulized antibiotics. To prevent airway narrowing bronchodilator therapy is given before starting the inhalation of nebulized amoxicillin clavulanic acid. If airway narrowing occurs after amoxicillin clavulanic acid inhalation (extra) escape medication can be used (bronchodilators).
See IMPD for full text.
Potential Benefits: Previous research has shown that an amoxicillin concentration in sputum higher than the MIC90 reduced the mean length of hospitalization during a COPD exacerbation from 11 to 7 days. We hypothesize that more patients will achieve an adequate amoxicillin level in sputum when amoxicillin clavulanic acid is administered locally instead of systemic and thereby exert a beneficial effect. It is unknown whether or not this effects the clinical response.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

1) A clinical diagnosis of COPD, as defined by GOLD criteria
2) Hospitalized for an acute exacerbation of COPD
3) Admitted to the ward of pulmonary medicine
4) Age 40 years or over
5) Current or former smoker

Exclusion criteria

1) Current pneumonia, defined as an acute respiratory tract illness associated with radiographic shadowing on a X-ray or CT-scan of the chest which was neither pre-existing nor of any other cause.
2) Allergy for penicillin, amoxicillin or clavulanic acid.
3) Recently diagnosed or unresolved lung malignancy
4) amoxicillin or clavulanic acid therapy within 3 days prior to admission,
During the trial the patient cannot be treated with systemic amoxicillin or amoxicillin clavulanic acid.

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL
Recruitment status: Pending

Start date (anticipated):	01-09-2019
Enrollment:	21
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Amoxicillin clavulanic acid
Generic name:	Amoxicillin clavulanic acid
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	23-05-2019
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	06-06-2019
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	25-03-2021
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	09-04-2021
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	21-12-2022
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

Approved WMO Date:	28-12-2022
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

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	EUCTR2015-005391-15-NL
CCMO	NL55935.044.19
Other	NTR24373