Dexamethasone infusion in community-acquired pneumonia

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Primary objective:1. Reduction of hospitality duration in patients with CAP treated with intravenous dexamethasone. Secondary objective:1. Reduction of the use of intravenous antibiotics in patients with CAP treated with intravenous dexamethasone.2...

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

Summary

ID

NL-OMON35460

Source
ToetsingOnline

Brief title
Ovidius study

Condition

- Hepatobiliary neoplasms malignant and unspecified

Synonym
CAP, lung infection

Research involving
Human

Sponsors and support

Primary sponsor: Sint Antonius Ziekenhuis
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: CAP, community-acquired pneumonia, corticosteroids, dexamethasone

Outcome measures

Primary outcome

- length of hospital stay

Secondary outcome

- admission to ICU, inflammation markers and health performance

- length of treatment with intravenous antibiotics

- side-effects

- lung function

- mortality

- prognostic value of serum ACE activity

- analysis of cost savings and effectiveness

- coagulation cascade in patients with CAP (pulmonary en intravascular)

Study description

Background summary

Community-acquired pneumonia (CAP) is common and approximately 20 percent of all episodes of pneumonia result in hospitalization. It is the leading cause of community-acquired infection requiring ICU admission. Especially elderly patients may have a severe illness with a high morbidity and mortality rate. In pulmonary infections, the release of cytokines and other inflammatory mediators from alveolar macrophages serves as a useful mechanism in the elimination of invading pathogens. However, this natural reaction can be potentially harmful when excessive release of circulating inflammatory cytokines causes damage to the patient, particularly the lung.
Interest in the role of corticosteroids in the pathophysiology of critical illness has existed since the early part of the 20th century. On ICU, early treatment with corticosteroids to attenuate systemic inflammation is

widespread. At the same time, outside the ICU little evidence is available on the effect of treatment with corticosteroids in patients diagnosed with CAP. Hypothetically, early initiated administration of corticosteroids in the course of a CAP can lower systemic and pulmonary inflammation. This may lead to earlier resolution of pneumonia and a reduction of complications (sepsis, mortality).

In 2004 Confalonieri et al. evaluated 24 patients with a severe CAP who received hydrocortisone 10 mg/hour for 7 days compared to 24 patients who received placebo. The hydrocortisone group had a significant reduction in CRP levels over time, a significant improvement in PaO2:FiO2 and reduction of incidence of delayed septic shock. This is the only study evaluating infusion of hydrocortisone in patients with a CAP outside the ICU. Monton et al. evaluated the role of glucocorticoids on the ICU in mechanically ventilated patients with a severe pneumonia. Eleven of the 20 patients received methylprednisolone for 9±7 days. In this study there was a consistent trend for an attenuated inflammatory respons, however the clinical efficacy was not assessed. Meduri et al. found improvement in lung injury and multiple organ dysfunction syndrome in 16 ICU patients with unresolving acute respiratory distress syndrome (ARDS). These patients received methylprednisolone 2 mg/kg per day for 32 days. In addition, no increase of infections was found in the intervention group.

Unfortunately, some adverse side effects have been attributed to corticosteroids, like hyperglycaemia or opportunistic infections. However, in severe COPD exacerbation, short-term administration of systemic corticosteroids has proved to be safe, with no clinically important side effects. Niewoenher et al. found a moderate improvement in clinical outcomes among patients hospitalized for exacerbations of COPD treated with systemic glucocorticoids. Hyperglycaemia of sufficient severity to warrant treatment was the most frequent complication. Other adverse effects, for example secondary infection, did not differ significantly among the groups.

Inflammation and coagulation are closely related. Inflammation activates the coagulation system, while several components of the coagulation cascade have proinflammatory effects.37 This results in ongoing inflammation and deposition of fibrin in intravascular and extravascular spaces. Several studies have demonstrated the interaction between inflammation and coagulation activation in lung diseases. It is known that coagulation is both activated in the intravascular compartment, as in the pulmonary compartment in animals with CAP, in patients with ventilator associated pneumoniae, in patients with sepsis and in healthy humans pulmonary challenged with bacterial products.38-40 The relevance of the activation of the coagulation system has recently become more obvious. A randomized clinical trial in sepsis patients treated with placebo or recombinant activated protein C (APC), a coagulation inhibitor, demonstrated a statistically significant 6.1% absolute reduction in all-cause mortality at 28 days for patients receiving APC.41 A retrospective analysis of this trial

showed a relative risk reduction in 28 days mortality of 28% in patients with severe CAP.42

There is little information about the coagulation system in patients with CAP. This study gives us a unique opportunity to investigate the possible intravascular and pulmonary activation of the coagulation system in these patients. It also gives us, due to the existing study design and protocol, the opportunity to investigate the interaction between inflammation and coagulation and to investigate the effect of dexamethasone on both systems.

Study objective

Primary objective:
1. Reduction of hospitality duration in patients with CAP treated with intravenous dexamethasone.

Secondary objective:
1. Reduction of the use of intravenous antibiotics in patients with CAP treated with intravenous dexamethasone.
2. What is the effect of intravenous dexamethasone in patients with a CAP on admission to ICU, inflammation markers and health performance?
3. Toxicity of dexamethasone in patients with CAP.
4. What is the effect of intravenous dexamethasone in patients with a CAP on lung function?
5. Mortality in patients with CAP treated with or without dexamethasone.
6. Prognostic value of serum ACE activity on pneumonia outcome
7.· Analysis of cost savings and effectiveness of the use of intravenous dexamethasone in patients with a CAP.·
8 Is the coagulation cascade activated in the intravascular compartment in patients with CAP?
9 Is the local pulmonary coagulation cascade activated in patients with CAP?
10 Relation between causative micro-organism and coagulation activation.
11 Evaluation of the effect of administered dexamethasone on the coagulation activation

Study design

randomized placebo controlled trial

Intervention

intervention:
On ER: bolus 5 mg (1 ml) dexamethasondisodiumphosphate
5 mg (1 ml) dexamethasonedisodiumphosphate once a day for three days

control:

On ER 1 ml sterile water
1 ml sterile water once a day for three days.

Study burden and risks

risks of the use of dexamethasone:
Hypokalemia
Fluid volume shift
Skin thinning and purpura
Cushingoid appearance
Alopecia
AcneHirsutism
Posterior subcapsular cataract
Elevated intraocular pressure/glaucoma
Hypertension
Arrhythmias with pulse infusions
Gastritis
Peptic ulcer disease
Pancreatitis
Amenorrhea/infertility
Osteoporosis
Avascular necrosis
Myopathy
Euphoria
Dysphoria/depression
Psychosis
Diabetes mellitus
Hypothalamic-pituitary-adrenal insufficiency
Heightened risk of typical infections
Opportunistic infections
Herpes zoster

Benefits:
reduction in time of hospital stay

Contacts

Public
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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 aged 18 to 100 years with a community-acquired pneumonia.
Criteria to determine a community-acquired pneumonia:
Chest radiograph showing new opacities
In combination with two of the following findings:
· Cough
· Production of sputum
· Temp >38,0 °C or <36,0 °C
· Audible abnormalities by chest examination compatible with pneumonia
· Leukocytosis (>10.000 cells/mm3), leftward shift (>10%) or leukopenia (<4000 cells/mm3)
· CRP > 15 mg/l (three times upper limit of normal)

Exclusion criteria

Immunocompromised patients:
· Patients with a known congenital or achieved immunodeficiency.
· Patients who received chemotherapy less than 6 weeks ago.
· Patients who received corticosteroids in the last 6 weeks.
· Patients who received immunosuppressive medication in the last 6 weeks. (like cyclosporine, cyclofosfamide, azathioprine)
· Patients with COPD who are on systemic corticosteroids for COPD.

· Patients who require ICU treatment.
. Patients who received a 13-valent pneumococcal conjugate vaccine within the last 30 days.

Study design

Design

Study phase:	4
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	27-11-2007
Enrollment:	300
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Dexamethasonedisodiumphosphate
Generic name:	Dexamethasonedisodiumphosphate
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	02-07-2007
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United

	(Nieuwegein)
Approved WMO Date:	14-09-2007
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	20-11-2007
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	14-12-2007
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	14-10-2008
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	21-09-2009
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	09-03-2010
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	EUCTR2007-002612-25-NL
ClinicalTrials.gov	NCT00471640
CCMO	NL17866.100.07