Medical Clinic II

Department Pneumology / Allergology / Sleepmedicine

1,8-Cineole in asthma and COPD - from bench to bedside

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Therapy options for phytopharmaceuticals in acute and chronic respiratory diseases

Natural Substances and Mixtures

Well known:
- secretolytic effects
- antiinfectious
- antioxidant
- bronchodilatory
- systemic availability
- good compatibility

New Approach:
- Longterm Co-medication:
  - Optimisation of guideline therapies by availability + synergy
    - Reaching the lung periphery
    - Control of systemic Inflammation
  - Control of exacerbations
    - Improvement of steroid resistance
  - New interactions with VD3-levels?

Juergens, Bonn 2015
Mechanisms of the antioxidative effects of 1,8-Cineole in FCS-stimulated human monocytes in vitro

O$_2^-$ → SODs → H$_2$O$_2$ → Inflammation

Inhibition of control (mean±SEM)

- **p<0.05
- **p<0.004

Juergens, Bonn 2007
Cough and sputum production correlate with increased risk of exacerbations

Patients WITH chronic cough and sputum

Frequent Exacerbations

Patients WITHOUT chronic cough and sputum

Number of Exacerbations per patient per year

Chronic Cough and Sputum

Chronic Inflammation

COPD-Phenotype: Exacerbations, Prognosis und Therapeutic needs

COPD-Subgroups

- ECLIPSE
  - 2,138 Pat.
  - 3 Years

Increase in Exacerbationen:
- Severity
- Health Status
- History of Reflux
- Leukocytosis (Granulocytes)

Hazard Function of Successive Hospitalised Chronic Obstructive Pulmonary Disease

Decreasing inhibition of superoxides by combined incubation with Formoterol (F) + Budesonide (BUD)

% Inhibition of LPS-control (mean±SEM)

* p=0.0059 vs. FCS-control

p=0.0604

p=0.0588

p=0.0693

Juergens, Bonn 2009
Inhibition of cytokine production by 1,8-cineole in LPS-stimulated human monocytes in vitro

Juergens, Bonn 2012
Antiinflammatory Synergies: 1.8-Cineol+Budesonide

**IL-6**

- **Bud alone**
- **+C2x10^-6M**

**IL-8**

- **Bud alone**
- **+C2x10^-6M**
- **+C4x10^-6M**
- **+C6x10^-6M**

Juergens, Bonn 2008
Co-medikation with 1,8-cineole (Soledum® forte Capsl.) for intensification of guideline therapies in COPD and Asthma

Juergens, Bonn 2013
Increase of system inflammation according to GOLD Stage

**CRP**

- **GOLD III/IV**
- **GOLD II**
- **GOLD I**
- **Gesunde Kontrolle**

**Serum C-Reactive Protein (mg/L)**

**TNF-α**

- **GOLD III/IV**
- **GOLD II**
- **GOLD I**
- **Gesunde Kontrolle**

**Serum TNF-Alpha (pg/mL)**

Anti-inflammatory systemic effects of 1,8-cineole (3x200mg) in steroid-dependent Asthma and healthy subjects in monocytes ex vivo


Asthma: n=10; NS: n=12
Reduction of exacerbations in COPD (GOLD II-III) by co-medications with 1.8-Cineol (Soledum\textsuperscript{R} forte)

Patients (n=242) with COPD GOLD II-III
FEV1 57.5 ± 31%
Pack-yrs 31.4±17

- 1.8-Cineol 3x200mg/day
- Placebo

2x3months

Exacerbations
- Frequency, Severity, Duration,
- Lungfunction
- Quality of life [AQLQ]

Reduction of exacerbation compared to placebo

\begin{itemize}
  \item Anzahl: -38.5\%^{*}
  \item Schwere: -42.5\%^{*}
  \item Dauer: -25.8\%^{*}
  \item SGRQ: -13.4\%^{**}
\end{itemize}

\textsuperscript{*}p<0.036
\textsuperscript{**}p=0.0619

Worth H et al., Respiratory Research 2009,10:69
Reduction of exacerbations in COPD

Clinical Studies in COPD:

1. Tiotropium 18μg (UPLIFT):

2. Roflumilast 500μg (Mw von 2 Studien):
   Calverly PMA et al., Lancet 2009

3. Tiotropium 18μg:
   Niewoeheer DE et al., An Int Med, 2005

4. FP 2x500μg (Mw von 3 J.):
   Burge PS et al., (ISOLDE), BMJ 2000

5. 2x F 4.5μg+BUD 160μg:
   Szafranski W et al., Eur Respir J 2003

6. 2x F 4.5μg+BUD 400μg:
   Calverley PMA et al., Eur Respir J 2003

7. 2x SFP 50/500μg (TORCH)
   Calverley PMA et al., N Engl J Med 2007

8. 1.8-Cineol 3x200mg:
   Worth H et al., Respiratory Research 2009

% Reduction of exacerbations compared to placebo

Clinical studies

Juergens, Bonn 2011
Improvement of asthma control by co-medication with 1,8-cineole (Soledum\textsuperscript{R} forte)

Patients (n=247) with persistent Asthma (FEV1 82%)
Design: PC,R,DB,MZ

- 1.8-Cineol 3x200mg/Day
- Placebo

6-months

Primary Endpoint
- Lung-function
- Frequency of night symptoms
- Quality of life [AQLQ]

FEV1

\[ \Delta \text{FEV1} (l) \]

\[ \begin{array}{c}
0.31 \\
0.20 \\
0.05 \\
0.00 \\
\end{array} \]

\[ p = 0.0398 \]

Nocturnal dyspnea

\[ \text{Summenscore (nächtliches Asthma)} \]

\[ \begin{array}{c}
3.1 \\
5.2 \\
1.0 \\
0.0 \\
\end{array} \]

\[ p = 0.0327 \]

Asthma-Quality of Life

\[ \Delta \text{AQLQ} \]

\[ \begin{array}{c}
5.2 \\
2.6 \\
1.0 \\
0.0 \\
\end{array} \]

\[ p = 0.0475 \]

Worth H et al., J of Asthma 2012, Oct;49(8):849-853
Synergistic anti-inflammation of VD3 and 1.8-Cineol

Inhibition of TNF-α

p<0.004 für Vit.D3, C, Vit.D3+C vs. LPS-Kontrolle
*p<0.08 vs LPS-Kontrolle
**p<0.007 für C2x10⁻⁶+Vit.D3 vs Vit.D3 alleine
p<0.004 für C4x10⁻⁶+Vit.D3 vs. Vit.D3 alleine

Juergens, Bonn 2011
Working principle of 1.8-cineole: control of inflammation as cause of hypersecretion

Thank you for your attention!