MEDwave

Living FRIendly Summaries of the Body of Evidence using Epistemonikos (FRISBEE)
*Medwave*2015;15(Suppl 2):e6224 doi: 10.5867/medwave.2015.6224

High-dose inhaled corticosteroids or addition of theophylline in patients with poorly controlled asthma?

Authors: Pilar Celis**[1,2]**, Gabriel Rada**[1,2,3,4,5]**

Affiliation:
[1] Departamento de Medicina Interna, Facultad de Medicina, Pontificia Universidad Católica de Chile, Santiago, Chile
[2] Proyecto Epistemonikos
[3] Programa de Salud Basada en Evidencia, Facultad de Medicina, Pontificia Universidad Católica de Chile, Santiago, Chile
[4] GRADE working group
[5] The Cochrane Collaboration

Celis P, Rada G. High-dose inhaled corticosteroids or addition of theophylline in patients with poorly controlled asthma?. *Medwave*2015;15(Suppl 2):e6224 doi: 10.5867/medwave.2015.6224
Publication date: 19/8/2015

Abstract

There are several management strategies for patients with poorly controlled asthma despite usual treatment. Increasing doses of inhaled corticosteroids or adding theophylline are among the therapeutic alternatives. However, the latter is associated with important adverse effects. Searching in Epistemonikos database, which is maintained by screening 30 databases, we identified only one systematic review including four pertinent randomized controlled trials. We combined the evidence using meta-analysis and generated a summary of findings following the GRADE approach. We concluded it is not clear whether theophylline or high-dose inhaled corticosteroids constitute a better alternative for symptomatic control or reduction in exacerbations in poorly controlled asthmatic patients because the certainty of the evidence is very low.

Problem

There are several management strategies for patients with poorly controlled asthma. Within the therapeutic alternatives are xanthines such as theophylline, or high-dose inhaled corticosteroids. Theophylline exerts its action on the bronchial smooth muscle relaxation, and through its anti-inflammatory and vasodilatory activity. Since theophylline is associated with important adverse effects, it is necessary to assess its potential benefits in symptomatic patients with initial therapy.

Methods

We used Epistemonikos database, which is maintained by screening more than 30 databases, to identify systematic reviews and their included primary studies. With this information we generated a structured summary using a pre-established format, which includes key messages, a summary of the body of evidence (presented as an evidence matrix in Epistemonikos), meta-analysis of the total of studies, a summary of findings table following the GRADE approach and a table of other considerations for decision-making.

Key messages

- It is not clear whether theophylline or high-dose inhaled corticosteroids constitute a better alternative for symptomatic control or reduction of exacerbations in poorly controlled asthmatic patients because the certainty of the evidence is very low.

About the body of evidence for this question

What is the evidence. See evidence matrix in Epistemonikos later	We found one systematic review [1] including four randomised controlled trials [2],[3],[4],[5].
What types of patients were included	All of the studies included patients older than 18 years who had symptomatic asthma. Two studies included patients with forced expiratory volume in 1 second (FEV1)> 50% [2],[4], one study with peak expiratory flow (PEF)> 50%, [3] and one study did not limit for lung function. Two of the studies specified there was no use of oral corticosteroids in the three weeks prior to intervention [2],[5]. The baseline therapy in all the studies was low-dose inhaled corticosteroids and short-acting inhaled beta agonists.
What types of interventions were included	All of the studies consisted of one arm receiving low-dose inhaled corticosteroids associated with theophylline and another arm receiving double dose of corticosteroids without theophylline. The dose of theophylline varied between 200 and 375 mg twice daily (depending on body weight). Two studies reported median plasma levels of theophylline (8.7 to 10.1) [2],[4]. High-dose of inhaled corticosteroids corresponded to twice the standard dose in all studies. In three studies the corticosteroid was beclomethasone (400-500 ug/day) [3],[4],[5] and in one study budesonide 400 ug/day [2].
What types of outcomes were measured	The systematic review meta-analyzed the following outcomes: change in morning PEF, change in evening PEF and predicted FEV1. Although symptomatic scores were reported in all studies, these results were not considered in the systematic review. Neither mortality, exacerbations nor hospitalizations were reported.

Summary of findings

The information on the effects of adding oral theophylline compared to the use of high-dose inhaled corticosteroids is based on four randomised controlled trials including 318 patients. All studies measured symptoms, and change in morning and evening PEF as outcomes. Three studies measured change in predicted FEV1 [1],[2],[4]. No study measured exacerbations, hospitalizations or mortality.

- It is not clear whether theophylline or high-dose inhaled corticosteroids achieve better symptomatic control or reduction of exacerbations in poorly controlled asthmatic patients because the certainty of the evidence is very low.
- No studies were found that evaluated the impact of theophylline compared with high-dose inhaled corticosteroids on mortality.
- The studies identified did not report adverse effects.

Adding theophylline versus high-dose inhaled corticosteroids for poorly controlled asthma				
Patients	Adults with symptomatic asthma despite treatment with inhaled corticosteroids and on-demand short-acting beta agonists			
Intervention	Adding oral theophylline			
Comparison	High-dose inhaled corticosteroids			
Outcomes	Absolute effect*		Relative effect (95% CI)	Certainty of the evidence (GRADE)
	WITH high-dose corticosteroids	**WITH theophylline**		
Symptoms or exacerbations	The only systematic review we identified did not analyze symptoms, although individual studies concluded there are no differences between the two alternatives. There was no difference in the morning or evening PEF, or the change in predicted FEV1 as indirect evidence about this outcome.		--	⊕◯◯◯[1,2,3,4] Very low
Mortality	The review did not mention mortality			No studies
Adverse effects	The review did not mention adverse effects			No studies

RR: Risk ratio.
Margin of error = 95% confidence interval (CI).
GRADE: evidence grades of the GRADE Working Group (see later in this article).

* The risk **WITH HIGH DOSE CORTICOSTEROIDS** is based on the risk in the control group of the trials. The risk **WITH THEOPHYLLINE** (and its margin of error) is calculated from relative effect (and its margin of error).

1 The certainty of the evidence was downgraded in two levels because of the use of a surrogate outcome, which is very indirect evidence of the effect on the critical outcome for decision making.
2 The certainty of the evidence was diminished in one level because of the possibility of publication bias, since the search of the systematic review is five years old and there could be further studies.
3 The certainty of the evidence was diminished in two levels because of inconsistency: the effect on surrogate outcomes in different studies is highly heterogeneous.
4 The certainty of the evidence was diminished based on imprecision because the confidence interval includes both superiority and inferiority of the intervention.

About the certainty of the evidence (GRADE)*

⊕⊕⊕⊕
High: This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different† is low.

⊕⊕⊕◯
Moderate: This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different† is moderate

⊕⊕◯◯
Low: This research provides some indication of the likely effect. However, the likelihood that it will be substantially different† is high.

⊕◯◯◯
Very low: This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different† is very high.

*This concept is also called 'quality of the evidence' or 'confidence in effect estimates'.
† Substantially different = a large enough difference that it might affect a decision.

Other considerations for decision-making

To whom this evidence does and does not apply
• The evidence presented in this summary comes from adult patients with asthma treated with inhaled corticosteroids and short-acting inhaled beta agonists on demand that remain symptomatic. Most patients at this stage use long-acting beta agonists, so it is debatable if this evidence can be extrapolated.
About the outcomes included in this summary
• The systematic review assessed only lung function outcomes as measure of effectiveness. Such outcomes should be considered as surrogates for those critical for decision making, such as symptomatic control, exacerbations, hospitalizations or mortality.
Balance between benefits and risks, and certainty of the evidence
• It is difficult to make a risk/benefit analysis of the use of theophylline in symptomatic asthma given the very low certainty about its benefits. However, if the gain was of little or no relevance, it would seem reasonable to lean towards the use of high-dose inhaled corticosteroids, given there is information about the adverse effects of theophylline (gastrointestinal, neurological and cardiovascular) that could limit its use.
Resource considerations
• There are no major costs differences between theophylline and high-dose inhaled corticosteroids. However, it is not possible to make a balance between costs and benefits/risks, due to the very low certainty of the evidence.
Feasibility
• Both therapies are easily accessible, however the use of theophylline needs to be monitored with plasma levels to allow a safe use, which implies greater difficulties in its practical application.
Differences between this summary and other sources
• The key message of this summary is partially consistent with the conclusion of the systematic review which is more optimistic about the effectiveness of theophylline in controlling asthma symptoms, without considering the low certainty of the evidence. • The conclusions of this summary are consistent with the available clinical guidelines for asthma [6],[7] that suggest other therapeutic alternatives in stage 3 or higher before the addition of theophylline, such as high-dose inhaled corticosteroids, long-acting beta agonists, leukotriene receptor antagonists or combinations of these strategies.
Could this evidence change in the future?
• The likelihood that this information change in the future if new studies become available is very high, because the certainty of the evidence is very low. • According to the records of the International Controlled Trials Registry Platform of the World Health Organization, there are no additional published or ongoing studies answering this question.

How we conducted this summary

Using automated and collaborative means, we compiled all the relevant evidence for the question of interest and we present it as a matrix of evidence.

Starting from any systematic review, Epistemonikos builds a matrix based on existing connections in the database.
The author of the matrix can select relevant information for a specific health question (typically in PICO format) in order to display the information set for the question.
The *rows* represent systematic reviews that share at least one primary study, and *columns* display the studies.
The boxes in green correspond to studies included in the respective reviews.

Follow the link to access the **interactive version:** Increasing dose of inhaled corticosteroids or adding theophylline for unresponsive asthma

Notes

The upper portion of the matrix of evidence will display a warning of "new evidence" if new systematic reviews are published after the publication of this summary. Even though the project considers the periodical update of these summaries, users are invited to comment in *Medwave* or to contact the authors through email if they find new evidence and the summary should be updated earlier. After creating an account in Epistemonikos, users will be able to save the matrixes and to receive automated notifications any time new evidence potentially relevant for the question appears.

The details about the methods used to produce these summaries are described here http://dx.doi.org/10.5867/medwave.2014.06.5997.

Epistemonikos foundation is a non-for-profit organization aiming to bring information closer to health decision-makers with technology. Its main development is Epistemonikos database (www.epistemonikos.org).

These summaries follow a rigorous process of internal peer review.

Conflicts of interest
The authors do not have relevant interests to declare.

References

1. Wang Y, Lin K, Wang C, Liao X. Addition of theophylline or increasing the dose of inhaled corticosteroid in symptomatic asthma: a meta-analysis of randomized controlled trials. Yonsei Med J. 2011 Mar;52(2):268-75. | CrossRef | PubMed |
2. Evans DJ, Taylor DA, Zetterstrom O, Chung KF, O'Connor BJ, Barnes PJ. A comparison of low-dose inhaled budesonide plus theophylline and high-dose inhaled budesonide for moderate asthma. N Engl J Med. 1997 Nov 13;337(20):1412-8. | PubMed |
3. Lim S, Jatakanon A, Gordon D, Macdonald C, Chung KF, Barnes PJ. Comparison of high dose inhaled steroids, low dose inhaled steroids plus low dose theophylline, and low dose inhaled steroids alone in chronic asthma in general practice. Thorax. 2000 Oct;55(10):837-41. |PubMed |
4. Ukena D, Harnest U, Sakalauskas R, Magyar P, Vetter N, Steffen H, Leichtl S, Rathgeb F, Keller A, Steinijans VW. Comparison of addition of theophylline to inhaled steroid with doubling of the dose of inhaled steroid in asthma. Eur Respir J. 1997 Dec;10(12):2754-60. |PubMed |
5. Wang Y, Wang CZ, Lin KX, Qian GS, Zhuo WL, Li SP, et al. Comparison of inhaled corticosteroid combined with theophylline and double-dose inhaled corticosteroid in moderate to severe asthma. Respirology. 2005 Mar;10(2):189-95. | PubMed |
6. Executive Committee GEMA 2009. GEMA 2009 (Spanish guideline on the management of asthma). J Investig Allergol Clin Immunol. 2010;20 Suppl 1:1-59. | PubMed |
7. GINA. Global strategy for asthma management and prevention 2015. ginasthma.org [on line]. | Link |

Author address:
[1] Facultad de Medicina
Pontificia Universidad Católica de Chile
Lira 63
Santiago Centro
Chile