

[전문가로부터 배우는 알레르기질환 약물 사용법]

천식 흡입기를 사용할 수 없을 때 사용할 수 있는 약물은? 경구 약물로도 치료가 가능합니다.

김경원

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Allergol Int 2017;66:163-189/ 2017;66:190-204
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 - 류코트리엔 조절제, 테오필린 등 코산틴계 약물, 그 외 기타 약물

천식 치료 약제

- 질병조절제: 천식 조절을 위해서 규칙적으로 사용하는 약제
 - 기도 염증, 천식 증상, 급성 악화와 폐기능 저하의 위험을 감소시킨다.
- 증상완화제: 천식 증상이 발생했을 때 증상 경감을 위하여 필요시 사용할 수 있는 약제
 - 운동 유발 천식을 예방하기 위해 운동 전에 사용할 수도 있다.
 - 증상완화제가 필요하지 않을 정도로 천식 조절상태를 잘 유지하는 것이 천식 치료의 목표이다.

한국 천식진료지침

천식 단계별 치료 (한국 천식진료지침)

6세 이상 소아, 청소년, 성인 5세 이하 소아

단계	단계1	단계2	단계3	단계4
추천 질환조절제	저용량 ICS	저용량 ICS/LABA	중간/고용량 ICS/LABA	중간/고용량 ICS + 류코트리엔 조절제 또는 ICS/항콜린제 또는 ICS/항레프틴제 추가
대체 가능한 질환조절제	저용량 ICS + 류코트리엔 조절제 (또는 ICS/항콜린제 또는 ICS/항레프틴제 추가)	중간/고용량 ICS/LABA + 류코트리엔 조절제 (또는 ICS/항콜린제 또는 ICS/항레프틴제 추가)	중간/고용량 ICS/LABA + 류코트리엔 조절제 (또는 ICS/항콜린제 또는 ICS/항레프틴제 추가)	중간/고용량 ICS + 류코트리엔 조절제 또는 ICS/항콜린제 또는 ICS/항레프틴제 추가
증상완화제	필요시 흡입형 베타2항진제 또는 ICS/항레프틴제	필요시 흡입형 베타2항진제 또는 ICS/항레프틴제	필요시 흡입형 베타2항진제 또는 ICS/항레프틴제	필요시 흡입형 베타2항진제 또는 ICS/항레프틴제

ICS: 흡입 코르티코스테로이드, LABA: 장시간작용 베타2항진제, *ICS/LABA: ICS와 LABA의 복합제, **ICS/항레프틴제: ICS와 항레프틴제의 복합제

천식 단계별 치료 (GINA guidelines)

6세 이상 소아, 청소년, 성인 5세 이하 소아

*Not for children <12 years
*For children 6-11 years, the preferred Step 3 treatment is medium dose ICS
*For patients prescribed SDB/formoterol or BUD/formoterol maintenance and reliever therapy
†Tiotropium by mist inhaler is an add-on treatment for patients ≥12 years with a history of exacerbations

STEP	STEP 1	STEP 2	STEP 3	STEP 4	STEP 5
Preferred controller choice	Low dose ICS	Low dose ICS/LABA	Medium dose ICS/LABA	High dose ICS/LABA	High dose ICS/LABA + LABA or LAMA or both
Other controller options	Low dose ICS + LABA	Low dose ICS + LABA	Low dose ICS + LABA	Low dose ICS + LABA	Low dose ICS + LABA
Reliever	As needed short-acting beta ₂ -agonist (SABA)	As needed SABA or low dose ICS/formoterol	As needed SABA or low dose ICS/formoterol	As needed SABA or low dose ICS/formoterol	As needed SABA or low dose ICS/formoterol

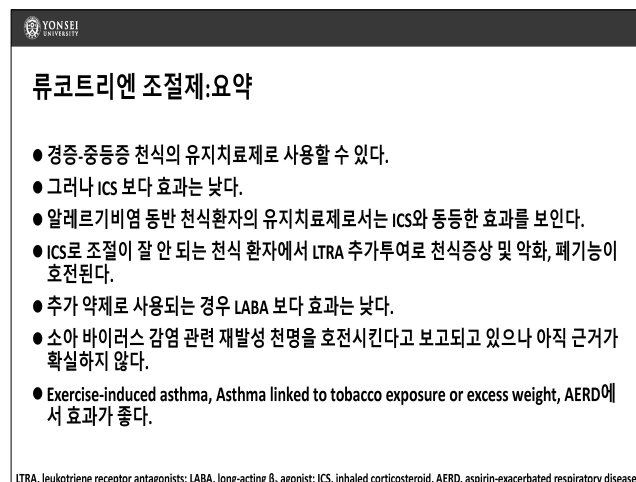
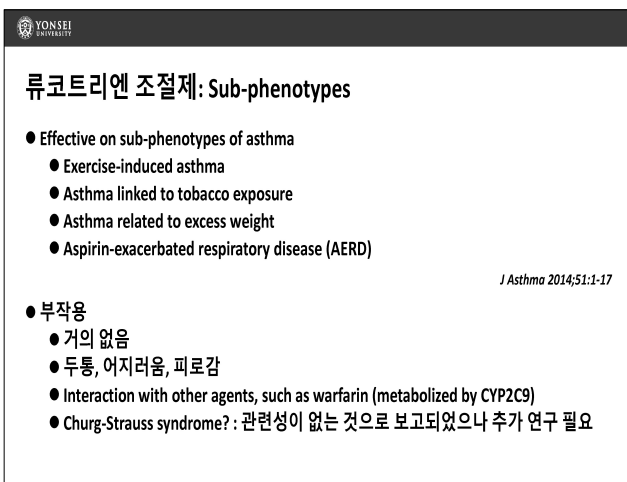
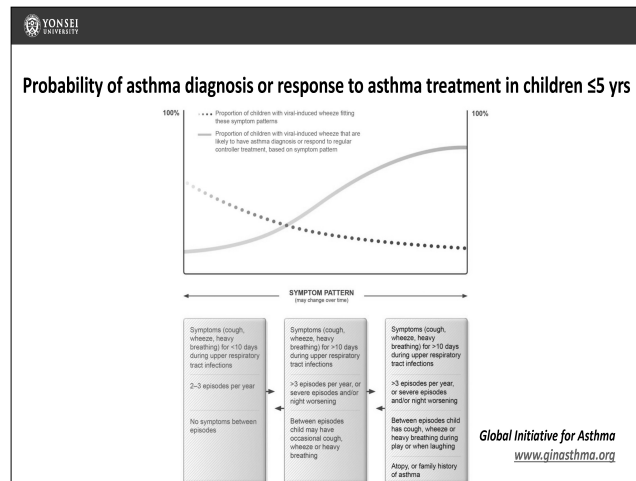
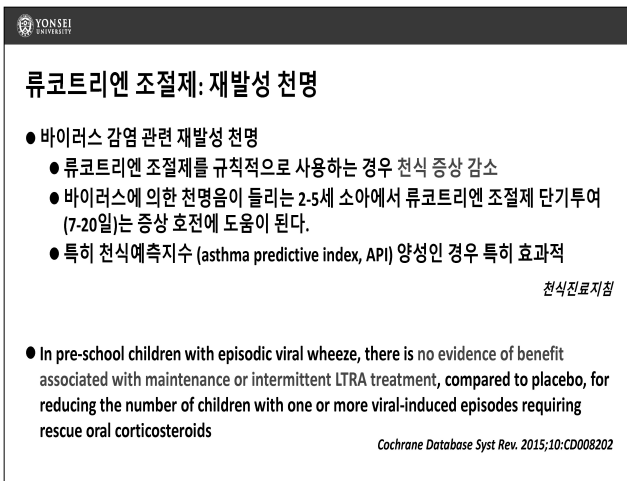
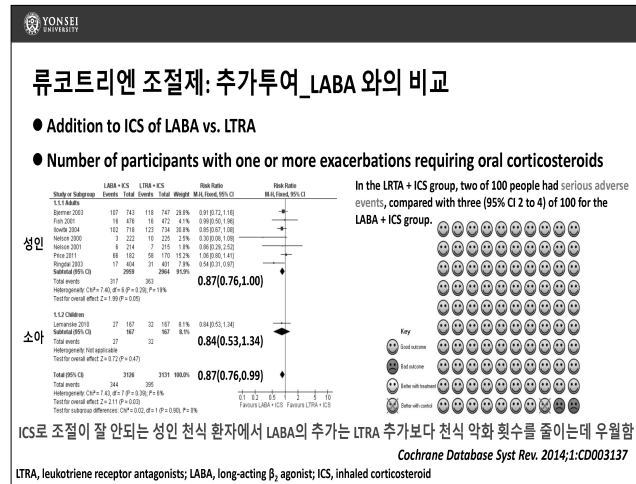
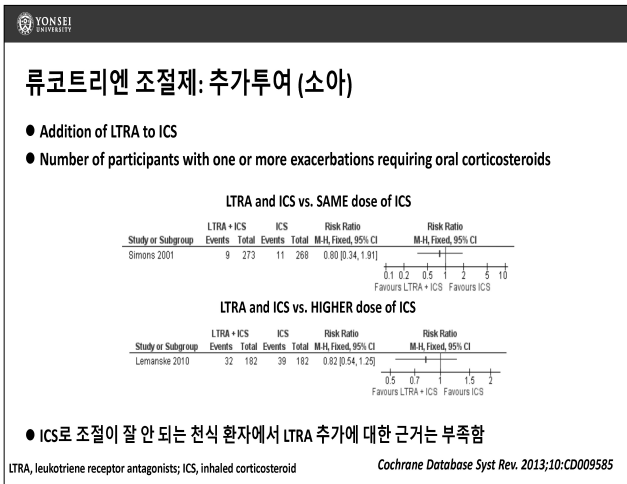
Consider this step for children with:

- Intermittent wheezing and/or few mild symptoms
- Symptoms consistent with asthma and asthma symptoms not well-controlled, or <3 exacerbations per year
- Symptoms not consistent with asthma but wheezing episodes occur frequently, e.g. every 4-6 weeks. Give diagnostic trial for 3 months.

Not well-controlled on low dose ICS

First check diagnosis, inhaler skills, adherence, exposure

김경원 천식 흡입기를 사용할 수 없을 때 사용할 수 있는 약물은? 경구 약물로도 치료가 가능합니다.



- 2018 대한천식알레르기학회 제53차 교육강좌

테오필린 등 크산틴계 약물, Sustained-release theophylline

- Long-acting bronchodilator with anti-inflammatory effects
- 역할
 - 기관지확장제
 - 저용량: 항염증 작용
- 부작용
 - 구역, 구토 등의 위장관 증상, 무른변, 부정맥, 경련발작, 사망
 - 발열, 임신, 항결핵제는 테오필린 혈중농도 감소
 - 간질환, 심부전, 씨메티딘, 퀴놀론계 일부, 마크롤라이드계 일부는 부작용 위험 증가
 - 저용량의 테오필린은 부작용이 적다

테오필린 등 크산틴계 약물: 단독투여

- Budesonide 800 mg bd, budesonide 200 mg bd, or theophylline (Theo-Durs®) 300mg bd
- Double-blind, double-dummy, and randomized, in a parallel group design for 9 months

The efficacy of ICS was superior to oral theophylline

ICS, inhaled corticosteroid

Respir Med 2002;96:432-8

테오필린 등 크산틴계 약물: 단독투여

- A randomized, double-masked, placebo controlled trial in 489 participants with poorly controlled asthma randomly assigned to placebo, theophylline (300 mg/d), or montelukast (10 mg/d).

CHANGE IN ASTHMA SYMPTOM SCORES BY TREATMENT ASSIGNMENT

Change from Baseline Score	No. Participants	Treatment Assignment, mean (95% CI)		
		Theophylline	Montelukast	Placebo
AQOL score	408	0.7 (0.4, 0.9)	0.8 (0.4, 1.0)	0.8 (0.4, 1.0)
ASR score	462	0.10 (0.07, 0.12)	0.10 (0.06, 0.12)	0.08 (0.05, 0.10)
ACQ	462	-0.7 (-0.8, -0.6)	-0.7 (-0.8, -0.6)	-0.7 (-0.8, -0.5)

Definition of abbreviations: ACQ = Asthma Control Questionnaire; AQOL = Asthma Quality-of-Life Questionnaire; ASR = Asthma Symptom Utility Index; CI = confidence interval.
For the AQOL and ASR scores, a positive value indicates improvement. For the ACQ, a negative value indicates improvement.
p values for treatment effects, mean questionnaire scores, and 95% confidence intervals were estimated from linear regression models with robust variance estimation and adjusted for visit, where appropriate (i.e., for repeated measures of AQOL and ACQ).
None of the treatments were significantly different from placebo or from each other.

Low dose theophylline was beneficial in those patients who had not been prescribed ICS.

ICS, inhaled corticosteroid

Am J Respir Crit Care Med 2007;175:235-42

테오필린 등 크산틴계 약물: 추가투여

- Patients with moderate asthma and persistent symptoms (N=62)
- In a double-blind, placebo-controlled trial for 3 months
- 400 mg of inhaled budesonide (low-dose) with 250 or 375 mg of theophylline (depending on body weight) or 800 mg of inhaled budesonide (high-dose)

Geometric mean ratio: 1.07, 1.02, 1.06, 1.03
95% Confidence interval: 0.99-1.15, 0.94-1.10, 0.98-1.13, 0.95-1.12

N Engl J Med 1997;337:1412-8

테오필린 등 크산틴계 약물: 추가투여

- Multicentre, randomised, double-blind, double-dummy, parallel-group study
- Salmeterol/fluticasone propionate combination (SFC) 50 mg/250 mg+1 placebo tablet vs. fluticasone propionate 250 mg+1 sustained release theophylline 200 mg (SR-T+FP), twice daily for 8 weeks
- LABA was associated with greater improvements in lung function than theophylline.

Res Med 2008;102:1055-64

- A LTRA (N=33) and a sustained released theophylline (Theo, N=34), with a moderate dose of ICS for 4 weeks
- The effects of both medications were comparable.
- For asthmatic patients even on a moderate dose of ICS, the addition of either LTRA or sustained released theophylline does not improve asthma-related symptoms but significantly and equally increases PEF.

Allergy Asthma Proc 2005;26:287-91

LTRA, leukotriene receptor antagonists; LABA, long-acting β_2 agonist; ICS, inhaled corticosteroid; PEF, peak inspiratory flow

테오필린 등 크산틴계 약물: 요약

- 경증-중등증 천식의 유지 치료제로 사용할 수 있다. 그러나 ICS 보다 효과는 낮다.
- ICS 보다 효과는 약하므로 ICS를 사용하기 어려운 경우 사용하는 것이 좋다.
- ICS로 잘 조절되지 않는 천식에서 테오필린을 추가 약제로 사용할 수 있다.
- 추가 약제로 사용되는 경우 LABA 보다 효과는 낮다.
- 추가 약제로 사용되는 경우 LTRA와 효과는 비슷하다.
- 경증-중등증 소아 천식의 유지 치료제로 사용할 수 있다.(일본)
- 경증-중등증 소아 천식의 유지 치료제로 권장하지 않는다.(한국 천식진료지침 및 GINA guidelines)
- Step 4 소아 천식의 추가 약제로서 사용한다.(일본)
- Step 4 소아 천식의 추가 약제로서 사용하지 않는다. (한국 천식진료지침 및 GINA guidelines)

Cochrane Database Syst Rev. 2006;1:CD002885

LTRA, leukotriene receptor antagonists; LABA, long-acting β_2 agonist; ICS, inhaled corticosteroid

김경원 천식 흡입기를 사용할 수 없을 때 사용할 수 있는 약물은? 경구 약물로도 치료가 가능합니다.

Cromones (nedocromil sodium and sodium cromoglycate, SCG)

- 경증-중등증 소아 천식의 유지 치료제로 사용할 수 있다.

Cochrane Database Syst Rev. 2006;3:CD004108

- 소아와 성인의 지속성 천식에서 유지치료제로 사용할 수 있다.
- 소아와 성인 천식에서 폐기능 호전과 천식 조절에 ICS가 SCG보다 우월하다.

Cochrane Database Syst Rev. 2006;2:CD003558

Other oral medications from Japanese guidelines (adult asthma)

1. Corticosteroids 1) Inhaled corticosteroids i) Beclomethasone dipropionate ii) Fluticasone propionate iii) Budesonide iv) Ciclesonide v) Mometasone furoate 2) Oral corticosteroids 2. Long-acting β_2-agonists 1) Inhalants Salmeterol xinafoate 2) Patch Tiotropium 3) Oral medicines Procaterol hydrochloride Clenbuterol hydrochloride Formoterol fumarate Tiotropium hydrochloride Mabuterol hydrochloride 3. Combination inhaler of corticosteroid/long-acting β_2-agonist 1) Combination inhaler of fluticasone propionate/salmeterol xinafoate 2) Combination inhaler of budesonide/formoterol fumarate 3) Combination inhaler of fluticasone propionate/formoterol fumarate 4) Combination inhaler of fluticasone furoate/vilanterol trifenatate	4. Leukotriene receptor antagonists 1) Pranlukast hydrate 2) Mometasone sodium 5. Theophylline sustained-release preparation 6. Long-acting muscarinic receptor antagonist Tiotropium bromide hydrate 7. Anti-IgE Antibody Omalizumab 8. Anti-allergics other than leukotriene receptor antagonists 1) Mediator antileukotrienes Sodium cromoglycate, tranilast, amlexanox, repirinast, ibudilast, tazanast, and pemirolast potassium 2) Histamine H_1 receptor antagonists Ketotifen fumarate, azelastine hydrochloride, oxatomide, mequitazine, and epinastine hydrochloride 3) Thromboxane inhibitors i) Thromboxane- A_2 synthesis inhibitor Ozagrel hydrochloride ii) Thromboxane- A_2 receptor antagonist Seratrodast Suplatast tosilate 9. Other agents and therapies (Chinese medicines, specific immunotherapy, and non-specific immunotherapy)
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Allergol Int 2017;66:163-89

Choosing between controller options for population-level decisions

- Choosing between treatment options at a population level
- The 'preferred treatment' at each step is based on:
 - Efficacy
 - Effectiveness
 - Safety
 based on group mean data for symptoms, exacerbations and lung function (from RCTs, pragmatic studies and observational data)
- Availability and cost at the population level

Global Initiative for Asthma www.ginasthma.org

Choosing between controller options for individual patients

- Use shared decision-making with the patient/parent/carer to discuss the following:
 1. Preferred treatment for symptom control and for risk reduction
 2. Patient characteristics (phenotype)
 - Does the patient have any known predictors of risk or response? (e.g. smoker, history of exacerbations, blood eosinophilia)
 3. Patient preference
 - What are the patient's goals and concerns for their asthma?
 4. Practical issues
 - Inhaler technique - can the patient use the device correctly after training?
 - Adherence: how often is the patient likely to take the medication?
 - Cost: can the patient afford the medication?

Global Initiative for Asthma www.ginasthma.org