ASTHMA

Anticholinergics in the treatment of children and adults with acute asthma: a systematic review with meta-analysis

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Background: Current guidelines recommend the use of a combination of inhaled β_2 agonists and anticholinergics, particularly for patients with acute severe or life threatening asthma in the emergency setting. However, this statement is based on a relatively small number of randomised controlled trials and related systematic reviews. A review was undertaken to incorporate the more recent evidence available about the effectiveness of treatment with a combination of β_2 agonists and anticholinergics compared with β_2 agonists alone in the treatment of acute asthma.
Methods: A search was conducted of all randomised controlled trials published before April 2005.
Results: Data from 32 randomised controlled trials (n = 3611 subjects) showed significant reductions in hospital admissions in both children (RR = 0.73; 95% CI 0.63 to 0.85, p = 0.0001) and adults (RR = 0.68; 95% CI 0.53 to 0.86, p = 0.002) treated with inhaled anticholinergic agents. Combined treatment also produced a significant increase in spirometric parameters 60–120 minutes after the last treatment in both children (SMD = −0.54; 95% CI −0.28 to −0.81, p = 0.0001) and adults (SMD = −0.36; 95% CI −0.23 to −0.49, p = 0.00001).
Conclusions: This review strongly suggests that the addition of multiple doses of inhaled ipratropium bromide to β_2 agonists is indicated as the standard treatment in children, adolescents, and adults with moderate to severe exacerbations of asthma in the emergency setting.

Treatment of acute asthma includes inhaled short acting β_2 agonists, systemic corticosteroids (CCS), and supplemental oxygen.[1 2] In addition, current guidelines recommend the use of a combination of β_2 agonists and anticholinergics, particularly for patients with acute severe or life threatening asthma.[2 3] This statement is based on a relatively small number of randomised controlled trials and related systematic reviews.[4–6] However, new studies have since been published.[7] The aim of this systematic review was to update the evidence on the effectiveness of a combination of inhaled anticholinergics and β_2 agonists compared with β_2 agonists alone for the treatment of children, adolescents, and adults with acute asthma in the emergency department (ED).

METHODS

Search strategy and selection criteria

The search was conducted using five search strategies to identify potentially relevant trials. (1) MEDLINE (1966–April 2005), EMBASE (1974–April 2005) and CINAHL (1982–April 2005) databases were searched using the following MeSH, full text and keyword terms: emergency OR acute asthma OR status asthmaticus OR severe asthma OR wheeze, AND anticholinergics OR ipratropium OR oxitropium, OR glycopirrolate. (2) An advanced search of the Cochrane Controlled Trials Register (first quarter 2005) was completed using the above search strategy to identify any additional trials. (3) References from included studies, reviews, and texts were searched for citations. (4) Hand searching of the top 20 respiratory journals was completed. (5) We made inquires to Boehringer Ingelheim regarding other published or unpublished trials supported by the company. Trials published solely in abstract form were excluded.

Included studies met the following criteria: (1) Target population: children (18 months to 17 years) and adults (≥18 years) with acute exacerbations of asthma presenting to an ED or equivalent care setting. (2) Intervention: single or repeated doses of inhaled anticholinergic agents given in combination with inhaled β_2 agonists compared with inhaled β_2 agonists alone. Studies involving the use of atropine were excluded. (3) Design: randomised and placebo controlled trials without language restriction. (4) Primary outcomes: admission to hospital and spirometric testing (final absolute values or change from baseline 60–120 minutes after the last combined anticholinergic and β_2 agonist inhalation). Because the peak bronchodilator effect after the administration of anticholinergics occurs within 1–2 hours, it is reasonable to expect significant improvement during this time. Secondary outcome measures were clinical score, duration of treatment in the ED, respiratory rate, oxygen saturation, heart rate, and side effects.

Data abstraction and validity assessment

Titles, abstracts, and citations were independently reviewed by two reviewers (GJR and JACR) to assess potential relevance for full review. From the full text, both reviewers independently assessed studies for inclusion based on the criteria for population, intervention, study design and outcomes. Data extraction included the following items: (1) Population: age, sex, number of patients studied, patient demographic data, withdrawals. (2) Intervention: agent, dose, route of delivery, and duration of treatment. (3) Control: concurrent treatments. (4) Outcomes. (5) Design: method of randomisation and allocation concealment. Any disagreement over study inclusion was resolved by consensus. The methodological quality of each trial was evaluated

Abbreviations: CCS, corticosteroids; ED, emergency department; FEV_1, forced expiratory volume in 1 second; NNT, number of patients needed to treat; PEF, peak expiratory flow; RR, relative risk; SMD, standardised mean difference; WMD, weighted mean difference

Table 1 Characteristics of trials in children included in the review

Study (year)	Design	Language and country	Jadad score	No (and age) of patients	Mean baseline severity	Dose of β agonist	Dose of anticholinergic	CCS use
Beck *et al* (1985)[12]	R, DB	E, Canada	3	25 (6–17 y)	FEV_1 <50%	S, 0.05 mg/kg q20 min Neb ×6	IB, 0.25 mg Neb ×1	No
Cook *et al* (1985)[13]	R, DB	E, Australia	4	30 (18 m–12 y)	NR	F, 0.125–0.5 ml Neb ×1	IB, 1–2 ml Neb ×1	No
Reisman *et al* 1988)[14]	R, DB	E, Canada	3	24 (5–15 y)	FEV_1 <55%	S, 0.05 mg q20 min Neb ×6	IB, 0.25 mg Neb ×3	No
Watson *et al* (1988)[15]	R, DB	E, Canada	3	31 (6–17 y)	FEV_1 30–70%	F, 0.62 mg q60 min Neb ×2	IB, 0.25 mg q60 min Neb ×2	Yes
Phanichyakam *et al* (1990)[16]	R, DB	E, Thailand	1	20 (4–15 y)	NR	T, 0.5 mg MDI ×1	IB, 0.04 mg MDI ×1	No
Peterson *et al* (1994)[17]	R, DB	E, Canada	5	163 (5–12 y)	FEV_1 <70%	S, 3 mg q45 min Neb ×2	IB, 0.25 mg q45 min Neb ×2	Yes
Schuh *et al* (1995)[18]	R, DB	E, Canada	5	80 (5–17 y)	FEV_1 <50%	S, 0.15 mg/kg q20 min Neb ×3	IB, 0.25 mg Neb ×1 or IB 0.25 mg Neb ×3	No
Qureshi *et al* (1997)[19]	R, DB	E, USA	5	90 (6–18 y)	FEV_1<50%	S, 0.15 mg/kg q30 min Neb ×3	IB, 0.5 mg Neb ×2	Yes
Calvo *et al* (1998)[20]	R, DB	Sp, Chile	3	80 (18–55 y)	PEF <80%	S, 0.2 mg q15 min MDI ×4	IB, 0.04 mg q15 min MDI ×4	Yes
Ducharme *et al* (1998)[21]	R, DB	E, Canada	5	298 (2–18 y)	Mild to moderate	S, 0.07 mg/kg q30 min Neb	IB, 0.25 mg Neb ×1	Yes
Qureshi *et al* (1998)[22]	R, DB	E, USA	5	434 (2–18 y)	Moderate to severe	S, 2.5–5 mg q20 min Neb ×3	IB, 0.5 mg q20 min Neb ×2	Yes
Zorc *et al* (1999)[23]	R, DB	E, USA	5	427 (1–17 y)	Moderate to severe	S, 2.5 mg q20 Neb ×3	IB, 0.5 mg q20 min Neb ×3	Yes
Benito Fernandez *et al* (2000)[24]	R, SB	Sp, Spain	5	102 (5 m–16 y)	Severe	S, 0.2 mg/kg q30 min Neb ×2	IB, 0.25 mg q30 min Neb ×2	Yes
SienraMonge *et al* (2000)[25]	R, DB	Sp, Mexico	2	30 (8–15 y)	Moderate to severe	S, 0.2 mg q10 min MDI ×3	IB, 0.02 mg q10 min MDI ×3	No
Timsit *et al* (2002)[26]	R	F, France	3	114 (2–15 y)	Moderate	S, 0.15 mg/kg q20 min Neb ×6	IB, 0.25 mg q20 min Neb ×3	Yes
Sharma *et al* (2004)[27]	R	E, India	2	50 (6–14 y)	Moderate to severe	S, 0.15 mg/kg q20 min Neb ×3	IB, 0.25 mg q20 min Neb ×3	No

R, randomised; SB, single blind; DB, double blind; E, English; Sp, Spanish; F, French; FEV_1, forced expiratory volume in 1 second; PEF, peak expiratory flow; NR, not reported; S, salbutamol; F, fenoterol; T, terbutaline; IB, ipratropium bromide; CCS, systemic corticosteroids.

using the 5-point scale (0 = worst and 5 = best) described by Jadad *et al*.[8] This instrument assesses the adequacy of randomisation, blinding, and the handling of withdrawals and drop outs.

Data analysis

The data were combined in the meta-analysis by means of random effects models.[9] Binary outcomes were pooled using common relative risk (RR) and 95% confidence intervals (CI). The number of patients needed to treat (NNT) to prevent the adverse outcome of interest was calculated. For continuous outcomes the weighted mean difference (WMD) (for variables using the same unit of measure) or the standardised mean differences (SMD) (reported in SD units where different units were used) and 95% CI were calculated. We tested for heterogeneity using the DerSimonian and Laird Q statistic and also measured heterogeneity with the I^2 test.[10] Values of 25%, 50%, and 75% represent low, moderate, and high heterogeneity, respectively. Publication bias was evaluated by means of formal statistical analysis.[11] Otherwise, a p value of <0.05 using a two tailed test was considered significant. When heterogeneity was found, subgroup analyses were carried out in an attempt to explain the findings. Sensitivity analysis was performed to identify sources of heterogeneity. These subgroups included: intensity of anticholinergic protocol, baseline severity, co-therapies, and methodological quality of the studies. The meta-analysis was performed using Review Manager 4.2.7 software (Cochrane Review Manager, Cochrane Collaboration, Oxford, UK, 2004).

RESULTS

A total of 88 studies were examined in full text for possible inclusion, 56 of which were excluded for the following reasons: non-randomised trials (n = 4), non-acute asthma (n = 14), anticholinergics alone were studied (n = 6), hospitalised patients (n = 8), use of atropine (n = 5), chronic asthma (n = 18), and use of intravenous route (n = 1). A total of 32 randomised controlled trials (16 including children and adolescents[12–27] and 16 including adults[28–43]) were therefore selected for further analysis (tables 1 and 2). Five studies were supported by Boehringer Ingelheim.[17 18 35–37] Data for 3611 subjects (1564 children and adolescents, 2047 adults) were available for meta-analysis. There was a total agreement between the two independent reviewers on inclusion of studies and Jadad study quality grading. The anticholinergic agent used was ipratropium bromide in 29 studies,[12–32 34–38 40 42 43] oxitropium bromide in two studies,[39 41] and glycopyrrolate in one study.[33] Trials were grouped according to the intensity of the anticholinergic treatment: those testing the addition of a single dose of an anticholinergic agent to β_2 agonist inhalations were named single dose protocols, and those testing more than one dose were grouped as multiple dose protocols. Thirteen studies (five in children[12 13 16 18 21] and eight in adults[28 29 31–33 36 38 43]) tested a single dose protocol and the remaining 19 trials used more than one dose of anticholinergic. Of these, 18 studies tested multiple doses in a predetermined fixed regimen (multiple dose fixed protocol) and one study tested the addition of anticholinergics to every β_2 agonist inhalation, leaving the number of inhalations determined by the patient's needs (multiple dose flexible protocol).[20] One trial tested the first two protocols.[18] Asthma severity was defined at baseline by spirometric testing (forced expiratory volume in 1 second (FEV_1) or peak expiratory flow (PEF) 70–50% of predicted = moderate exacerbation, and FEV_1 or PEF <50% of predicted = severe exacerbation) or different clinical scores. Most enrolled patients with acute asthma had moderate to severe exacerbations, but several studies reported data stratified on asthma severity.[22–24 37 41 42] The most frequently reported outcomes were hospital admission (20 studies) and spirometry (26 studies); respiratory resistance measured by forced oscillation was used

Table 2 Characteristics of trials in adults included in the review

Study (year)	Design	Language and country	Jadad score	No (and age) of patients	Mean baseline severity	Dose of β agonist	Dose of anticholinergic	CCS use
Bryant (1985)[28]	R, DB	E, Australia	2	28 (≥18 y)	FEV_1 <75%	F, 1 mg Neb ×1	IB, 0.5 mg Neb ×1	No
Rebuck *et al* (1987)[29]	MC, R, DB	E, Canada	4	148 (≥18 y)	FEV_1 <70%	F, 1.25 mg Neb ×1	IB, 0.5 mg Neb ×1	Yes
Higgins *et al* (1988)[30]	R, DB	E, England	2	40 (≥18 y)	PEF <30%	S, 5 mg q120 min Neb ×2	IB, 0.5 mg q120 min Neb ×2	Yes
O'Driscoll *et al* (1989)[31]	R, DB	E, England	2	56 (≥18 y)	PEF <35%	S, 10 mg Neb ×1	IB, 0.5 mg Neb ×1	Yes
Summers and Tarala (1990)[32]	R, DB	E, Australia	3	76 (16–70 y)	PEF <60%	S, 5 mg Neb ×1	IB, 0.5 mg Neb ×1	Yes
Cydulka and Emerman (1994)[33]	R, DB	E, USA	3	125 (≥18 y)	FEV_1 <75%	S, 2.5 mg q60 min Neb ×3	Gly, 2 mg Neb ×1	Yes
Rodrigo and Rodrigo (1995)[34]	R, DB	Sp, Uruguay	3	22 (18–50 y)	FEV_1 <50%	S, 0.4 mg q10 min MDI ×3 h	IB, 0.08 mg q10 min MDI ×3 h	No
Karpel *et al* (1996)[35]	MC, R, DB	E, USA	5	384 (18–55 y)	FEV_1 <60%	S, 2.5 mg q45 min Neb ×2	IB, 0.5 mg q45 min Neb ×2	No
FitzGerald *et al* (1997)[36]	MC, R, DB	E, Canada	3	342 (18–50 y)	FEV_1 <70%	S, 3 mg Neb ×1	IB, 0.5 mg Neb ×1	Yes
Garret *et al* (1997)[37]	TC, R, DB	E, New Zealand	4	338 (18–55 y)	FEV_1 <70%	S, 2.5 mg q45 min Neb ×2	IB, 0.5 mg q45 min Neb ×2	Yes
Lin *et al* (1998)[38]	R, DB	E, USA	4	55 (≥18 y)	PEF <200 l/min	S, 2.5 mg q20 min Neb ×3	IB, 0.5 mg Neb ×1	No
Kamei *et al* (1999)[39]	MC, R	E, Japan	3	64 (≥18 y)	FEV_1 <70%	F, 0.2 mg q1 min MDI ×5	OB, 0.1 mg q1 min MDI ×5	Yes
Weber *et al* (1999)[40]	R, DB	E, USA	5	67 (≥18 y)	PEF <70%	S, 10 mg q1 h Neb ×3 h	IB, 1 mg q1 h Neb ×3 h	No
Nakano *et al* (2000)[41]	R, SB	E, Japan	4	74 (≥18 y)	PEF <50%	S, 0.4 mg q20 min MDI ×3	OB, 0.4 mg q20 min MDI ×3	Yes
Rodrigo and Rodrigo (2000)[42]	R, DB	E, Uruguay	5	180 (18–50 y)	FEV_1 <50%	S, 0.4 mg q10 min MDI ×3 h	IB, 0.08 mg q10 min MDI ×3 h	No
Aggarwal *et al* (2002)[43]	R	E, India	2	48 (13–50 y)	PEF <50%	S, 5 mg q60 min Neb ×2	IB, 0.5 mg Neb ×1	No

MC, multicentre; TC, two centre; R, randomised; SB, single blind; DB, double blind; E, English; Sp, Spanish; FEV_1, forced expiratory volume in 1 second; PEF, peak expiratory flow; S, salbutamol; F, fenoterol; IB, ipratropium bromide; OB, oxitropium bromide; Gly, glycopyrrolate; CCS, systemic corticosteroids.

in one trial.[21] One study did not provide spirometric data or admission rates.[13] Clinical scores were used in only a few studies and the reporting of adverse effects was variable.

Hospital admissions

Ten studies accumulating 1786 children and adolescents reported hospital admissions.[14 17–19 21–24 26 27] One study tested two protocols (single and multiple fixed dose)[18] and three trials reported data stratified by asthma severity (moderate and severe patients).[22–24] At the end of treatment patients who received inhaled β_2 agonists and anticholinergics had a significantly lower admission rate (fig 1). The NNT was 13 (95% CI 9 to 28), indicating that 13 children needed to be treated with β_2 agonists and anticholinergics to prevent one admission. There was no evidence of systematic bias identified by the measure of funnel plot asymmetry. Also, no significant heterogeneity was demonstrated, which accepts the null hypothesis of similar treatment effects. Stratification on the basis of baseline severity (moderate *v* severe) and the intensity of the anticholinergic protocol

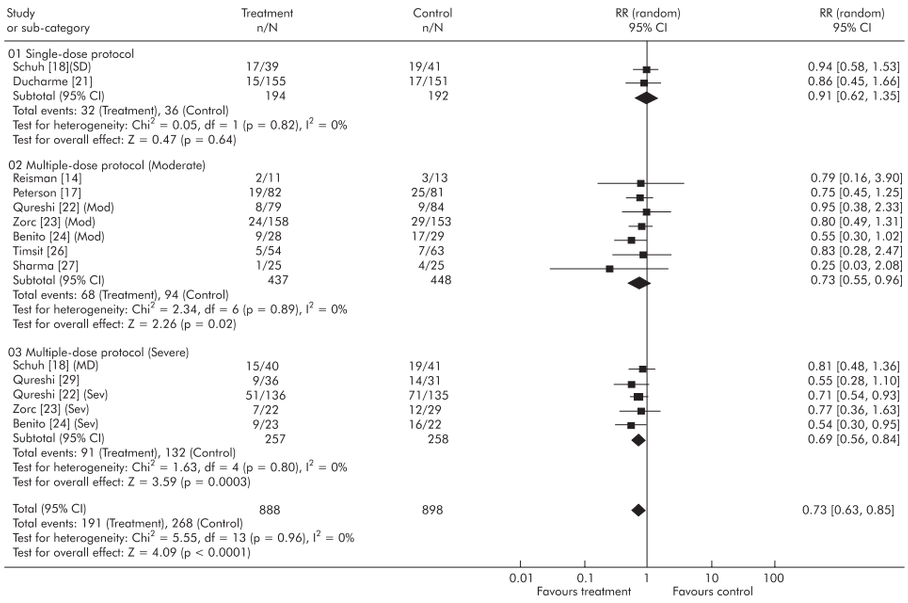

Figure 1 Pooled relative risk for hospital admission (with 95% confidence interval) of eligible studies in children comparing the addition of anticholinergic agents to β_2 agonists (treatment) with β_2 agonists alone (control). Trials stratified according to intensity of anticholinergic treatment (single or multiple fixed dose protocols) and asthma severity (moderate or severe patients).

(single *v* multiple fixed dose protocol) suggested a trend towards a reduced risk of admission in children with the most severe asthma attack and treated with multiple doses of anticholinergics. The NNT to prevent one admission among severe patients was 7 (95% CI 4 to 16). The hospital admission rate did not change when we excluded studies without explicit admission criteria (RR = 0.73; 95% CI 0.62 to 0.85, $I^2 = 0\%$). The use of systemic CCS did not modify this outcome (RR = 0.69; 95% CI 0.58 to 0.81).

Nine trials totalling 1556 adults with acute asthma reported hospital admissions.[33–38 40–42] One trial reported data stratified on asthma severity (moderate and severe patients).[42] There was a significant reduction in the hospital admission rate favouring anticholinergic use (fig 2). The NNT was 14 (95% CI 9 to 30). There was no evidence of systematic bias identified by the measure of funnel plot asymmetry. Again, no significant heterogeneity was demonstrated. Stratification on the basis of baseline severity (moderate *v* severe) and the intensity of the anticholinergic protocol (single *v* multiple fixed dose) suggested a trend towards a reduced risk of admission in adults with the most severe asthma attack and treated with multiple doses of anticholinergics (fig 2). Intensity of anticholinergic treatment greatly influenced the reduction in hospital admission; a greater reduction was seen in trials using three or more doses of anticholinergic agents (RR = 0.53; 95% CI 0.36 to 0.76, p = 0.0006; NNT = 6; 95% CI 4 to 13). These results did not change when only studies with explicit admission criteria were pooled (RR = 0.58; 95% CI 0.38 to 0.87, $I^2 = 28\%$) or when systemic CCS were used (RR = 0.74; 95% CI 0.48 to 1.14).

Spirometric testing

Nine studies examined the response to treatment in children and adolescents with acute asthma using spirometry.[12 14–16 18 19 22 25 27] Five trials reported the percentage change in FEV_1,[12 14–16 25] three reported the percentage change in PEFR,[19 22 27] one reported the change in percentage predicted FEV_1,[18] and one study reported the percentage change in respiratory resistance.[21] One trial tested two protocols[18] (single and multiple fixed dose) and one study presented data stratified by severity of obstruction (moderate and severe).[22] Data were recorded 60–120 minutes after the last combined treatment. When all the studies were pooled a significant improvement in spirometric parameters favoured the combination treatment (SMD = −0.54; 95% CI −0.28 to −0.81, p = 0.0001). However, there was significant heterogeneity ($\chi^2 = 23.41$, df = 10, $I^2 = 57.3\%$, p = 0.009). When we pooled the seven studies that reported FEV_1 data (change in percentage predict or percentage change)[12 14–16 18 25 27] stratified by the intensity of anticholinergic treatment (one or two doses *v* more than two doses), homogeneity was achieved (fig 3). The use of more than two doses of anticholinergics showed more benefit than lower doses. There was no evidence of systematic bias. Patients treated with one or two doses of anticholinergic agents had a mean difference of change in FEV_1 of 12.4% (95% CI 5.4 to 19.4) compared with those who did not receive anticholinergics, while those who received more than two doses had a mean difference of 16.3% (95% CI 8.2 to 24.5).

Spirometric data were reported by 16 studies in adult subjects.[28–43] Two trials showed data stratified by severity of obstruction (moderate and severity).[41 42] Eight trials reported FEV_1 (l),[28 29 34–37 39 42] 11 reported PEFR (l/min),[29–32 34 38–43] and one reported FEV_1 (% predicted).[33] Combined treatment produced a significantly greater increase in spirometric parameters than β_2 agonists alone (SMD = −0.36; 95% CI −0.23 to −0.49, p = 0.00001). There was a significant heterogeneity between trials ($\chi^2 = 25.5$, df = 15, $I^2 = 41.3\%$, p = 0.04). Homogeneity was achieved when studies that reported PEFR (l/min) were stratified by intensity of anticholinergic treatment (fig 4).[29–32 34 38–43] Again, the use of more than two doses of anticholinergics produced a greater benefit than one or two doses and there was no evidence of systematic bias. As previously observed for PEFR, patients treated with more than two doses of anticholinergics had a significant difference in FEV_1 of 0.44 l (95% CI 0.25 to 0.63) while those treated with one or two doses had a difference of only 0.15 l (95% CI 0.05 to 0.24).

Other outcomes

Three paediatric studies[21 22 24] reported a significant reduction in the clinical score after combined treatment (SMD = −0.29;

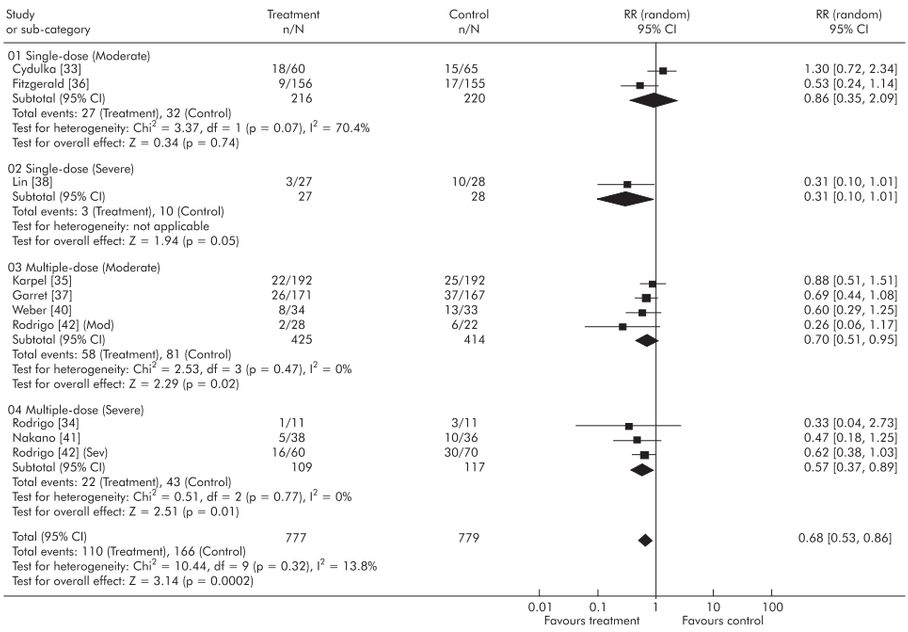

Figure 2 Pooled relative risk for hospital admission (with 95% confidence interval) of eligible studies in adults comparing the addition of anticholinergic agents to β_2 agonists (treatment) with β_2 agonists alone (control). Trials stratified according to intensity of anticholinergic treatment (single or multiple fixed dose protocols) and asthma severity (moderate or severe patients).

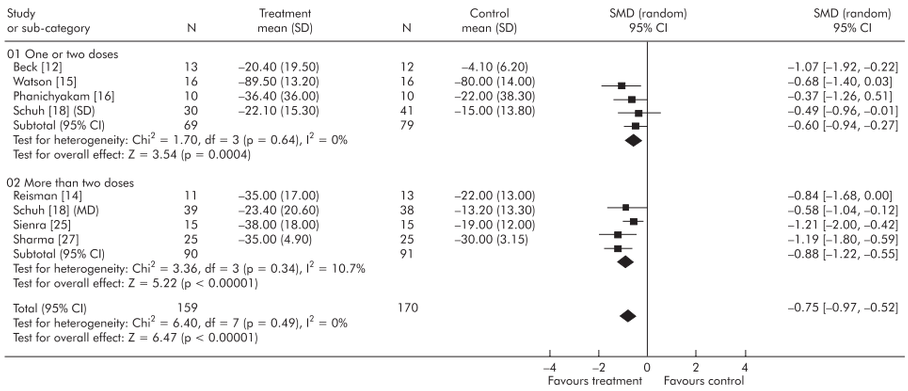

Figure 3 Pooled standardised mean difference (with 95% confidence interval) in forced expiratory volume in the first second (change in percentage predicted or percentage change) of children studies comparing the addition of anticholinergic agents to β_2 agonists (treatment) with β_2 agonists alone (control). Trials stratified according to the intensity of anticholinergic treatment (one or two doses *v* more than two doses).

95% CI −0.51 to −0.07, p = 0.01). No significant heterogeneity was demonstrated ($\chi^2 = 1.33$, df = 3, p = 0.72, $I^2 = 0\%$). There was no apparent increase in the occurrence of side effects among subjects treated with either single or multiple dose protocols. Thus, there was no significant difference between groups in the five studies in children that reported the presence of tremor (RR = 1.15; 95% CI 0.79 to 1.69, p = 0.46).[13 14 17 18 27] An identical pattern was seen in three adult studies that reported the same variable (RR = 1.28; 95% CI 0.92–1.78, p = 0.14).[31 35 42] Six adult trials that evaluated the effect of treatment on heart rate did not find a difference between groups (WMD = −2.07; 95% CI −4.35 to 0.21, p = 0.07).[28 29 31 34 35 42] There was insufficient information to pool outcomes such as oxygen saturation due to the insufficient number of trials reporting this outcome. Analysis of the only trial which tested the administration of multiple inhalations of combined treatment until a satisfactory clinical response was achieved (multiple dose flexible protocol) showed a significant decrease in the clinical score at 30–45 minutes between patients treated with salbutamol and ipratropium and those treated with salbutamol alone.[20]

DISCUSSION

This systematic review constitutes an effort to incorporate the best evidence available up to April 2005 on the role of inhaled anticholinergic agents added to β_2 agonists in children, adolescents, and adults with acute asthma in the ED setting. New data were found which we added to previous review.[3 5] Thus, 10 new randomised trials (four in children[24–27] and six in adults[33 34 39 41–43]) with a total of 809 patients have been added, representing an increase of 22% on the previous sample. Unlike the previous reviews, this study has enabled analysis of the effect of cumulative doses, particularly in adult studies. Several important conclusions can be made. Overall, our analysis confirmed that early administration of inhaled anticholinergic agents with β_2 agonists lead to a reduction in admission rates of both children and adults of 30%. Baseline severity and the intensity of the anticholinergic protocol clearly influenced the magnitude of the benefit. Thus, anticholinergic agents are particularly beneficial in patients with moderate to severe obstruction (FEV_1 <70% of predicted) treated with multiple dose fixed protocols consisting of three or more doses of an anticholinergic. These patients had a reduction in the hospital admission rate of 30–45% and only 6–14 subjects need to be treated to prevent one hospital admission. This is a very relevant finding since hospital admissions count for the largest part of direct health costs for asthma in most countries, and children or adults with more severe asthma attacks are more prone to be admitted to hospital. However, this review did not identify any beneficial effects of anticholinergic agents in patients with mild acute asthma. The fact that the use of systemic CCS

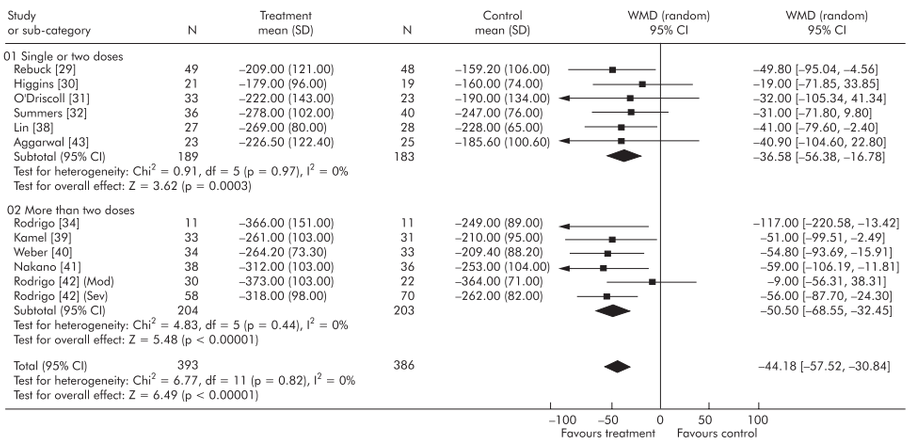

Figure 4 Pooled weighted mean difference (with 95% confidence interval) in peak expiratory flow (l/min) of studies in adults comparing the addition of anticholinergics to β_2 agonists (treatment) with β_2 agonists alone (control). Trials were stratified by intensity of anticholinergic treatment (one or two doses *v* more than two doses).

has not shown a significant effect is in agreement with the evidence that they require 6–12 hours to modify outcomes such as hospital admission or spirometric parameters.[44 45] The short duration of the study period in all trials made it unlikely that these drugs would have a significant contribution.

Significant differences favouring the combination treatment were observed on spirometric data in both children and adults. Again, there was a dose-response relationship, with a greater benefit being achieved in patients treated with more than two doses of anticholinergic agents in combination with a β_2 agonist. In adults, treatment with more than two doses produced clinically significant improvements in both FEV_1 (0.44 l) and PEFR (50.5 l/min).[46]

In our meta-analysis we also looked at secondary outcomes and side effects but these were difficult to analyse because there was insufficient information to be pooled. A few of the studies in children reported a significant reduction in different clinical scores after combined treatment. There was no apparent increase in the occurrence of side effects such as tremor or heart rate among subjects treated with single or multiple dose protocols.

Strengths and limitations of the study

This study met most of the methodological criteria suggested for scientific reviews.[47] Similar to all systematic reviews, this meta-analysis is limited by the quality and quantity of existing research and how data are reported. A comprehensive search of the published literature for potentially relevant studies was conducted using a systematic strategy to avoid bias. All of the 32 trials were randomised, and 26 were double blind. Exclusion of trials with lower methodological quality did not affect the conclusions. Assessment of the consistency of effects across studies is an essential part of the review to determine the generalisability of the findings; low values of heterogeneity (<15%) were obtained in all group and subgroup comparisons. The generalisability of study results to different countries should also be considered, particularly with regard to the hospital admission criteria. The decision to admit patients is based on many factors including past asthma and current exacerbation histories and spirometric test results, as well as clinical factors. Important variations in admission criteria could therefore influence the results. However, the results did not change when we analysed only studies with explicit criteria for admission to hospital.

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GJR has received fees for speaking from Boehringer Ingelheim.

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LUNG ALERT

Nitric oxide protects against airway hyperresponsiveness

▲ Que LG, Liu L, Yan Y, *et al*. Protection from experimental asthma by an endogenous bronchodilator. *Science* 2005;**308**:1618–21

Nitric oxide (NO) is a highly active endogenous bronchodilator and, although increased levels are found in asthmatic lungs, the link between NO and asthma has remained elusive. NO is short lived in vivo but it reacts with cysteine sulphurs (thiols) in proteins to form more stable *S*-nitrosothiols (SNOs) which act as a source of bioactive NO. *S*-nitrosoglutathione (GSNO) is the most abundant SNO found in the airways where its levels are governed by the enzyme GSNO reductase (GSNOR). However, GSNO is depleted in asthmatic airways, suggesting a protective role.

In this study the authors showed that GSNOR levels were raised in the lungs of mice exposed to the allergen ovalbumin (OVA), probably due to lysis of airway epithelial cells and leucocytes. SNO levels were depleted. GSNOR gene knockout mice exposed to OVA had raised levels of SNOs in the airway, reduced basal airway tone, and no response to methacholine. Levels of type II inducible NO synthase were similar to wild type mice, as was the inflammatory response measured by bronchoalveolar fluid cell counts and IL-13, serum total IgE, and mucus metaplasia. Tracheal rings from wild type mice became desensitised to repeated β adrenergic stimulation, whereas GSNOR knockout mice did not and so retained the capacity to relax.

This is the first study to show a definitive link between NO and airway hyperresponsiveness (AHR). NO, when present as SNOs, protects against AHR through modulation of β adrenoreceptor function. SNO levels are regulated by GSNOR which is raised in asthmatic airways, and the resulting lack of SNOs promotes AHR.

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the UK may not see a single case of tuberculosis in several years.

Nevertheless, given the consequence of pulmonary tuberculosis to the individual and society, it is appropriate for clinicians and general practitioners to ensure that tuberculosis is among the differential diagnoses in patients with relevant symptoms and signs and to investigate for tuberculosis fairly promptly. Every attempt should be made to obtain a microbiological diagnosis. As Jolobe points out, it is also true that patients with smear-negative culture-positive tuberculosis can transmit infection, although less so than those who have a positive smear from direct sputum examination.[4] Exclusive extrapulmonary tuberculosis is, however, not infectious and the suggestion to the contrary is erroneous.

In view of the current rise in the incidence of tuberculosis, without high case detection and the adequate treatment of cases, tuberculosis may not remain an uncommon illness in the UK. Vigilance for both pulmonary and extrapulmonary tuberculosis is required.

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CORRECTION

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The paper entitled "Anticholinergics in the treatment of children and adults with acute asthma: a systematic review with meta-analysis" by G J Rodrigo and J A Castro-Rodriguez (Thorax 2005;**60**:740–746. doi:10.1136/thx.2005.047803) was published twice online first, on one of those occasions with an incorrect DOI (doi:10.1136/thx.2005.040444).

had a chest CT scan on referral. They fail, however, to describe a role for chest CT, but do imply that it may be indicated for patients undergoing video-assisted thoracoscopic drainage (VATS). There is no evidence in the current literature supporting the use of CT scans before VATS. The British Thoracic Society guidelines do not recommend routine CT scans in children with empyema.[2]

In our centre all patients with empyema requiring intervention undergo VATS (approximately 40/year). We would suggest that chest CT scanning is not indicated before VATS in nearly all cases. We have found chest CT scans to be helpful, however, in situations where the patient has not responded to appropriate treatment with antibiotics and VATS. In this situation the possibilities are reaccumulation of pleural fluid, abscess formation or more extensive parenchymal involvement, differential diagnoses that are distinguished by CT scanning and information that is critical to the decision to reoperate (or not).

In addition, Jaffe *et al* do not take the opportunity to critically examine the role of chest ultrasound scans in patients with empyema. In our experience, clinical examination and chest radiography can determine the presence of pleural fluid. If the purpose of the ultrasound scan is to determine whether the fluid is simple (a parapneumonic effusion) or organised (empyema), this can be achieved more simply with a lateral decubitus or erect chest radiograph. The decision to undertake definitive management with urokinase or VATS is determined by the presence of unremitting infection and/or fluid volume in the pleural space. It is an outdated paradigm that the distinction between simple and organised pleural fluid makes any difference to subsequent treatment or outcome. The main use for ultrasound scanning should be for those children who are found to have a unilateral whiteout on the chest radiograph at presentation and for whom the distinction between pleural space and parenchymal disease is difficult to make.

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Author's response

We thank Massie *et al* for correctly questioning the clinical need for routine chest CT scanning before performing video-assisted thoracoscopic surgery (VATS). Our study was pragmatically designed to reflect clinical practice in our institute, where thoracic surgeons routinely request a pre-operative CT scan for use as a "road map" when performing minimally invasive endoscopic surgery where direct visual access is limited. This helps to plan and assist in placement of the ports and instruments in order to decrease risk and avoid potential complications such as bronchopleural fistula which would result as a consequence of puncturing the lung parenchyma in close proximity to the pleura. We agree with them that there is no evidence base to support this practice in terms of risk, and our study was not designed to answer this question.

The principle of providing surgical "road maps" (which cross-sectional imaging now provides) is prevalent in many areas of cardiothoracic imaging where CT and MRI are added as an adjunct to echocardiography and ultrasound scans in order to enhance anatomical (and, indeed, sometimes functional) information to enhance quality and provide a safer more informed patient journey.

We are surprised that Massie *et al* advocate the use of a lateral decubitus chest radiograph in place of an ultrasound scan which is not, in fact, a recommendation of the BTS guidelines. Indeed, this would be a retrograde step in terms of the quality of information and the radiation burden, and should only be advocated where there is no access to ultrasound.

As discussed in our paper, ultrasound is an invaluable tool as it is cheap, mobile, easy to use, can differentiate transonic from purulent fluid, solid lung from fluid and enables the radiologist to mark the spot for chest drain insertion. Although it has been used to stage the disease, we agree that it is not useful in predicting the clinical outcome as was evident in our study. Importantly, ultrasound does not carry a radiation burden.

One of the key messages we had hoped to emphasise in our study is the critical need to reduce exposure of children to unnecessary radiation. With this in mind, we disagree with Massie *et al* and continue to advocate the use of ultrasound as the most important imaging modality in managing children with empyema. The BTS guidelines also support this view.

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CORRECTIONS

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A U Wells, N Hirani, and on behalf of the British Thoracic Society Interstitial Lung Disease Guideline Group, a subgroup of the British Thoracic Society Standards of Care Committee, in collaboration with the Thoracic Society of Australia and New Zealand and the Irish Thoracic Soc. Interstitial lung disease guideline: the British Thoracic Society in collaboration with the Thoracic Society of Australia and New Zealand and the Irish Thoracic Society. *Thorax* 2008;**63**(Suppl V):v1–v58.

The correct list of authors for these guidelines is: B Bradley, H M Branley, J J Egan (Irish Thoracic Society), M S Greaves, D M Hansell, N K Harrison, N Hirani, R Hubbard, F Lake (TSANZ), A B Millar, W A H Wallace, A U Wells, M K Whyte, M L Wilsher (TSANZ), The British Thoracic Society Standards of Care Committee, in collaboration with the Thoracic Society of Australia and New Zealand, and the Irish Thoracic Society.

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