EUROPEAN RESPIRATORY journal

FLAGSHIP SCIENTIFIC JOURNAL OF ERS

Early View

Original article

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Please cite this article as: Maijers I, Kearns N, Harper J, *et al*. Oral steroid sparing effect of high dose inhaled corticosteroids in asthma. *Eur Respir J* 2019; in press (https://doi.org/10.1183/13993003.01147-2019).

ORAL STEROID SPARING EFFECT OF HIGH DOSE INHALED CORTICOSTEROIDS IN ASTHMA

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Take home message:

In oral corticosteroid-dependent asthma, the majority of the oral corticosteroid-sparing effects of high dose inhaled corticosteroid (ICS) are due to their systemic effects. Clinicians should be aware of this bioequivalence when prescribing high dose ICS.

Funding: The MRINZ is supported by Independent Research Organisation funding by the Health Research Council of New Zealand.

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ABSTRACT 250 words

Background: The proportion of the efficacy of high dose inhaled corticosteroids (ICS) in oral corticosteroid-dependent asthma that is due to systemic effects is uncertain. This study aimed to estimate the ICS dose-response relationship for oral corticosteroid sparing effects in oral corticosteroid-dependent asthma, and to determine the proportion of oral corticosteroid sparing effect due to their systemic effects, based on the comparative dose-response relationship of ICS versus oral corticosteroids on adrenal suppression.

Methods: Systematic review and meta-analysis of randomised controlled trials reporting oral corticosteroid sparing effects of high dose ICS in oral corticosteroid-dependent asthma. Reports of oral corticosteroid to ICS dose-equivalence in terms of adrenal suppression were additionally retrieved. The primary outcome was the proportion of the oral corticosteroid sparing effect of ICS that could be attributed to systemic absorption, per 1000µg increase of ICS, expressed as a ratio. This ratio estimates the oral corticosteroid sparing effect of ICS due to systemic effects.

Results: Eleven studies including 1283 participants reporting oral corticosteroid sparing effects of ICS were identified. The prednisone dose decrease per 1000µg increase in ICS varied from 2.1mg to 4.9mg, depending on the type of ICS. The ratio of the prednisone sparing effect due to the systemic effects per 1000µg of fluticasone propionate was 1.02 (95% CI 0.68-2.08) and for budesonide was 0.93 (95% CI 0.63-1.89).

Conclusion: In patients with oral corticosteroid-dependent asthma, the limited available evidence suggests that the majority of the oral corticosteroid sparing effect of high dose ICS is likely to be due to systemic effects.

INTRODUCTION

Inhaled corticosteroids (ICS) are the cornerstone of the pharmacological treatment for asthma.[1] ICS treatment increases lung function, improves quality of life and reduces asthma symptoms, and lowers the risk of exacerbations, asthma-related hospitalisations, and death.[1] The therapeutic dose-response relationship of ICS in adults is well established, with 80 to 90% of the maximum achievable benefit being obtained with 'low doses', around 100 to 200µg/day of fluticasone propionate (FP), or equivalent, for major clinical outcome variables including lung function, symptoms, and risk of severe exacerbations.[2] The maximum therapeutic effect is achieved with 'medium doses', around 500µg/day of FP or equivalent, in patients with moderate to severe asthma.[2] At this dose level patients are at increasing risk of systemic adverse effects, such as adrenal suppression, cataracts, fractures and diabetes.[3–6]

However, ICS are commonly prescribed at inappropriately high doses. In one report from Australia, over two thirds of the defined daily dose of ICS was supplied in the highest dose preparations of budesonide and FP,[7] and in another report from Scotland over half of patients prescribed an ICS/LABA for the first time, were prescribed 'high-dose' combination therapy.[8] Key issues with 'high dose' ICS therapy are the extent to which there is any additional therapeutic benefit in patients with the most severe forms of asthma such as oral corticosteroid-dependent asthma, and whether this additional efficacy is actually attributable to systemic absorption. Systemic effects of corticosteroids may, for example, be necessary in certain patients to inhibit cytokine-related recruitment pathways that contribute to eosinophilic airway inflammation.[9]

The aim of this study was to estimate the ICS dose-response relationship for oral corticosteroid sparing effect in oral corticosteroid-dependent asthma in adults, and to then determine the component due to systemic absorption. This was based on published data of the comparative dose-response relationship of ICS versus oral corticosteroid (OCS) to

cause adrenal suppression. If the oral corticosteroid dose-sparing effect of high dose ICS is similar to the estimated systemic corticosteroid effect, it may be inferred that the therapeutic effect of high-dose ICS is primarily due to systemic effects rather than local airway action. If the evidence is consistent with this hypothesis then the important clinical implications are that increasing the dose of ICS to high or very high doses requires similar considerations as starting maintenance low dose OCS therapy, and that an alternative to increasing the dose of ICS to high or very high doses might be to start maintenance low dose OCS therapy. Thus this study does not attempt to address whether high dose ICS or low dose prednisone is more harmful, but rather what is the ICS dose which results in equivalent systemic effects as oral prednisone, and what proportion of the oral corticosteroid sparing effect of high does ICS is due to its systemic absorption.

METHODS

This review is registered with PROSPERO (registration number: CRD42019119674).

Search strategy

PubMed, EMBASE and The Cochrane Library were searched for randomised controlled trials published from 1960 to present, assessing the oral corticosteroid sparing effect of lower versus high dose ICS in corticosteroid-dependent adolescent or adult asthma patients.

The following search terms were used to identify papers:
asthma AND (steroid or corticosteroid or corticosteroid or fluticasone or flovent or flixotide or beclomethasone or beclometasone or becloforte or becotide or QVAR or budesonide or pulmicort or flunisolide or aerobid or bronalide or triamcinolone or kenalog or beclovent or azmacort or vanceril or aerobec or ciclesonide or Alvesco or prednisone or prednisolone) AND (inhaled or aerosol) AND oral.

In all databases, the search was limited to clinical trials published in the English language. The references of included papers were searched for additional potentially relevant trials. The date of the search of the databases was 10 December 2018.

In order to estimate ICS to oral corticosteroid (OCS) dose equivalence in terms of systemic effects, studies using an ACTH stimulation test to assess adrenal suppression were identified.[10,11] Studies using other measures of adrenal suppression, such as plasma cortisol or serial urinary cortisol were excluded. Search terms for this search can be found in the online study protocol.

Eligibility criteria

We included studies in adolescent or adult patients with oral corticosteroid-dependent asthma. Only randomised controlled trials comparing the change in oral corticosteroid dose following administration of high dose (as defined by GINA asthma guidelines [1]) versus a lower dose ICS were included. Studies in children, those involving nebulised corticosteroids, and studies conducted in acute asthma were excluded.

Study selection

All search results relating to oral corticosteroid sparing effects were imported into Covidence,[12] an online software tool for management of systematic reviews. Titles of studies retrieved using the search strategy were filtered for duplicates then screened by two independent reviewers to identify potentially eligible studies. Abstracts for these titles were then screened further to identify potential studies. The full text of these studies were retrieved and independently assessed for eligibility by two reviewers. If there was uncertainty about eligibility of studies for the review this was resolved through discussion with a third reviewer.

Outcomes

For the assessment of oral corticosteroid dose reduction in relation to increasing ICS dose, the outcome was oral corticosteroid dose at the end of the study assessment period, for each of the doses of ICS used in a particular study.

The relationship between oral corticosteroid dose and ICS dose to cause adrenal suppression was quantified as prednisone mg per 1000µg increase in ICS dose.

The primary inferential outcome was the ratio of the oral corticosteroid dose causing equivalent adrenal suppression per unit dose of ICS, to the oral corticosteroid sparing per unit dose of ICS. For example, if dose-response studies of ICS ‘X’ showed that a daily dose increase of 1000ug caused the same degree of adrenal suppression as 5mg oral

prednisone, and studies in oral corticosteroid-dependent asthma showed that ICS 'X' achieved 5mg greater oral prednisone sparing effect than placebo, then the ratio would be 1.0 i.e the proportion of the oral corticosteroid dose sparing effect due to the systemic absorption of ICS is estimated to be 100%.

A secondary outcome was the odds ratio for the proportions of research participants with total oral corticosteroid elimination (0mg prednisone) per unit dose of ICS.

Data extraction

Data extraction from eligible studies included study setting, study sample characteristics, demographic descriptors, recruitment details, details on the intervention and controls, outcomes and information for assessment of the risk of bias. The data were extracted independently by two reviewers and reviewed in combination to confirm data values.

Risk of bias assessment

Two reviewers assessed the risk of bias in each study, using the Cochrane Risk of Bias Tool. The characteristics considered were random sequence generation, allocation concealment, blinding, completeness of outcome data, selective outcome reporting and any other source of bias.

Data synthesis and statistical methods

To estimate the regression coefficient relating oral corticosteroid dose and ICS dose inverse variance weighted regression was used, with a random intercept term for study, based on the mean and standard deviation of oral corticosteroid dose at each dose of ICS. This gives a regression coefficient with 95% CI for dose response. In the event as the identified studies only had two doses of ICS, only a linear relationship could be fitted. Logistic regression was used to estimate the odds ratio for oral corticosteroid elimination per 1000µg unit dose increase in ICS dose. Where only one study was available ordinary logistic regression was used. Where more than one study was available a mixed

generalised linear model, using logistic regression, was used, treating study as a random effect.

Bubble plots were used to show the estimated regression line and 95% confidence limits for the mean corticosteroid dose reduction, based on the mixed linear model regression. For budesonide and beclomethasone dipropionate (BDP) the prednisone slope estimates were based on end-point prednisone dose. For FP and mometasone, these plots were based on the change from baseline, as data on covariance for end-point prednisone was not extractable.

SAS version 9.4 was used.

RESULTS

Study selection

A total of 1088 studies on oral corticosteroid-sparing were screened for eligibility, of which ten studies [13–22] were included in the analyses. During background literature review one additional study [23] was identified from a previous Cochrane review [24] and was included in the analyses, for a total of 11 studies. The PRISMA flow diagram of the search strategy is depicted in Figure 1.

Study characteristics

The 11 studies included a total of 1283 participants. The participants in all the studies had oral corticosteroid-dependent asthma. The majority of studies used a run-in period to establish the lowest maintenance dose of prednisone while maintaining asthma control, or collected information on the participant's lowest tolerable prednisone dose from their medical records. Pre-specified protocols for the reduction of prednisone dose were used in seven studies; in three studies the prednisone dose was reduced at the investigators discretion; in one study how decisions on prednisone reduction were made was not specified. The duration of ICS treatment varied from 12 to 26 weeks. Five different types of ICS were used in the 11 included studies. Three studies used budesonide, three FP, two BDP, two mometasone, and one study ciclesonide. An overview of the study characteristics is shown in Table 1.

Risk of bias

The risk of bias assessment is shown in Figure 2. The majority of the studies did not provide information on sequence generation or allocation concealment. All studies had a double-blind study design.

Proportion of oral corticosteroid effect due to systemic effects

For the assessment of the relationship between ICS dose and adrenal suppression two publications were identified, one a meta-analysis of studies of FP [10] and the other a study of budesonide.[11] As a result this assessment was only available for FP and budesonide. In both the identified studies the ICS dose which resulted in the same magnitude of adrenal suppression as 10mg of prednisone was estimated.

The meta-analysis by Masoli and colleagues [10] identified two placebo-controlled studies [25,26] in which adrenal function was assessed following 4 weeks treatment with different doses of FP and 10mg prednisone daily by measurement of mean peak plasma cortisol concentration with 6 hour, 0.25mg cosyntropin stimulation, or the 8-hour area under the concentration – time course curve for plasma cortisol. By linear regression it was estimated that 10mg prednisone once daily was equivalent to 2000ug inhaled FP, suggesting that FP 1000µg/day was equivalent to 5mg/day of oral prednisone.

In a placebo-controlled study, Aaronson and colleagues [11] assessed the effect on adrenal function of 6 weeks treatment with different doses of budesonide and prednisone 10mg daily, by measurement of mean plasma cortisol concentration at the end of a 6 hour 0.25mg cosyntropin infusion. By linear regression, it was estimated that 10mg prednisone daily was equivalent to 5,000ug/day inhaled budesonide. This suggests that budesonide 1000ug/day is equivalent to 2mg prednisone/day. These analyses assume a linear relationship between ICS dose and adrenal suppression, as has previously been demonstrated. [10]

Oral corticosteroid dose reduction

Nine studies were included in the analysis for oral corticosteroid dose reduction in relation to different doses of ICS. There was one study of budesonide [19] that did not report

sufficient data from which variance could be extracted and could therefore not be included in the analyses. Only one study for ciclesonide [13] was identified so no meta-regression for this ICS-type could be performed. The extracted summary data for prednisone dose at study end point and change from baseline by ICS type and dose are summarised in Table 2.

Three placebo-controlled studies had extractable data for prednisone reduction in relation to FP dose. The difference between the highest and lowest (placebo) dose was 2000µg/day in all studies. The estimated prednisone difference in change from baseline between the highest and lowest dose was 15.3mg (95% CI 8.5 to 22.1),[23] 7.8mg (95% CI 3.9 to 11.7),[20] and 10.9mg (95% CI 7.8 to 14.0).[21] The meta-regression estimates were for a prednisone decrease of 4.9mg (95% CI 2.4 to 7.4) per 1000µg increase in FP dose. A plot of the change from baseline in prednisone dose versus FP dose is shown in figure 3A.

Two studies had extractable data for prednisone reduction for budesonide, one study was placebo-controlled and the other study no placebo-controlled, with the highest dose of 1600ug/day. The estimated prednisone difference at end point between the highest and lowest dose of ICS was 3.9mg (95% CI 1.5 to 6.2) [18] and 2.0mg (95% CI-0.7 to 4.7) [17] for the two studies with a difference of 1600µg/day and 1200µg/day ICS dose, respectively. The meta-regression estimates were for a prednisone decrease of 2.14 mg (95% CI 1.1 to 3.2) per 1000µg increase in budesonide. Figure 3B shows the prednisone dose at study end-point versus budesonide dose.

Two studies (non placebo-controlled) had extractable data for BDP, with the highest dose 1500 and 2000ug/day respectively. The estimated prednisone difference at end point between the highest and lowest dose was 1.6mg (95% CI -1.8 to 5.0) [15] and 4.3mg (95% CI -0.6 to 9.2).[22] The meta-regression estimates were for a prednisone decrease

of 3.0mg (95% CI -10.4 to 16.4) per 1000µg increase in BDP. Figure 3C shows the prednisone dose at study end-point versus BDP dose.

Two placebo-controlled studies had extractable data for mometasone, with the highest dose of 1600ug/day. The estimated prednisone difference in change from baseline between the highest and lowest dose was 15.0mg (95% CI 0 to 30) [14] and 14.1mg (95% CI 3.5 to 26.7).[16] As both studies did not provide data on level of covariance, these confidence intervals are based on pooled standard deviations.

Primary inferential outcome

For FP the proportion of the prednisone sparing effect due to the systemic effects per 1000µg was ICS was 1.02 (95% CI 0.68 to 2.08). For budesonide the proportion of the prednisone sparing effect due to the systemic effects per 1000µg was 0.93 (95% CI 0.63 to 1.89) (Table 3 and Figure 4).

Total elimination of oral corticosteroid

Extractable data on total elimination of oral corticosteroid in relation to ICS dose was available in eight studies, shown in Table 2. The odds ratio for oral corticosteroid elimination and ICS dose increase by 1000µg was: for budesonide; OR (95% CI) 4.50 (2.44 to 8.30), P<0.001; fluticasone 8.05 (4.99 to 12.99), P<0.001; mometasone OR 3.01 (1.37 to 6.64), P=0.006, and ciclesonide OR 2.48 (1.13 to 5.43), P=0.023. For BDP no statistically significant association between was found, OR 1.88 (0.25 to 14.2), P=0.54.

DISCUSSION

Key findings

This systemic review and meta-analysis of randomised controlled trials of the oral corticosteroid sparing effect of ICS in oral steroid dependent asthma has shown that high dose ICS results in a dose-associated decrease in prednisone dose. The point estimates suggest that the majority of the oral corticosteroid dose sparing effect can be attributed to their systemic absorption, rather than local airways effects. However, this finding should be interpreted with caution due to the small number of studies describing the dose-equivalence for prednisone to ICS in terms of systemic effects and the imprecision of the dose-response estimates with wide confidence intervals. With these limitations in mind, the lower confidence bounds of the estimates suggest that at least 60% of the oral corticosteroid dose reduction can be attributed to the effects from systemic absorption of high dose ICS. The clinical relevance of this finding is that increasing the ICS dose to high or very high doses may require similar consideration as starting maintenance low dose OCS.

Limitations of the study

When interpreting the results of this meta-analysis, there are a number of methodological considerations. As in all systemic reviews, this review was restricted by the quality of existing research and the way in which data was reported. The number of papers that met our eligibility criteria was limited, consequently the analyses per ICS type were performed by pooling a relatively small number of studies. Because of the limited number of studies investigating oral corticosteroid sparing effects, we have pooled studies that used DPI with studies that used MDI. Several studies have demonstrated no significant difference in potency between the two inhaler types.[27] Although most studies used pre-specified protocols for reduction of prednisone, their methods differed across the studies. Furthermore, the standard deviation of prednisone dose reduction was wide in the majority of studies. In some studies a large proportion of participants completely

eliminated their prednisone use. Particularly for the studies that were pooled based on mean prednisone at the final outcome, the data may be highly skewed and normal distribution based methods may not be appropriate. Although the majority of the studies did not provide information on sequence generation or allocation concealment, all had a double-blind study design.

There is little published literature comparing the systemic effects of OCS and ICS. We based our assessment on the measurement of adrenal suppression as it is a sensitive marker of adverse systemic ICS effects and provides the most appropriate surrogate marker for clinically relevant systemic effects of ICS.[28] We chose to only include studies utilising the ACTH-stimulation test, and excluded measures of adrenal function such as serial plasma and urinary cortisol level measurement. Whilst these other methods may be sensitive for the detection of systemically bioavailable ICS, they are poor predictors of clinically significant effects including adrenal suppression. [29–33] It should also be noted that both Aaronson et al.[11] and Masoli et al.[10] evaluated the level of adrenal suppression using the high-dose ACTH test (250 micrograms). Whilst this test remains popular as a quick and safe method for diagnosing adrenal insufficiency, there are concerns regarding the diagnostic accuracy of using high dose ACTH. In patients with secondary adrenal insufficiency, the supra-physiological dose of ACTH may mask adrenal insufficiency resulting in false negatives[34–36]. The lower and more physiological 1 microgram ACTH test has been recommended by some as an alternative to the high-dose ACTH test. The low dose test has proven to be more sensitive and more discriminating than the high-dose test in diagnosing adrenal insufficiency[35–39]. Conversely, some studies have shown that the results in diagnosing secondary adrenal failure using both high and low dose ACTH stimulation tests did not differ [40,41]. Regardless, as this testing was undertaken in all randomised comparator groups, it will not bias the assessment of comparative effects between randomised treatments.

The dose-equivalence of ICS to OCS in terms of adrenal suppression by measurement of ACTH-stimulation tests could be estimated for budesonide and FP. The estimate for FP was based on a meta-analysis of three studies,[25,26,42] whereas the estimate for budesonide was based on a single study,[11] both resulting in wide confidence intervals. This has resulted in uncertainty regarding the precision of the estimates of equivalence between the systemic effects of ICS and oral corticosteroids, on which the primary outcome was derived. Furthermore, different patient populations were included in the studies relating to OCS dose sparing and those studies relating to ICS and systemic effects. Relating the results of these studies to one another should therefore be interpreted with caution, particularly in view of the report of a non-significant two fold greater systemic potency between ICS relative to oral prednisone with non-oral steroid-dependent compared with oral steroid-dependent adult asthma.[43]. Possible non-linear effects were not able to be assessed in these data sets. However, several studies have shown a linear relationship between increasing ICS dose and the risk of adrenal suppression,[10] fractures,[5] cataracts [4] and diabetes.[6]

Implications of the findings

This analysis confirms that the subset of patients with severe, OCS-dependent asthma benefit from high or very high doses of ICS. [44,45] This is illustrated by the 2.5 to 8 fold increase in the probability of OCS elimination with ICS dose increase per 1000µg observed for budesonide, fluticasone, mometasone and ciclesonide. However, it is likely that the major component of the steroid sparing effects of high doses of ICS in this severe subgroup is due to their systemic effects. These may relate to their inhibitory role in the recruitment and survival of inflammatory cells in the airways and are also involved in switching on genes that have anti-inflammatory effects.[46]

The dose equivalence between OCS and ICS for effects on adrenal function provides a useful guide for prescribers in clinical practice. Despite the uncertainty in the estimates, available data suggests that 1000ug FP has similar systemic effects as 5mg

prednisone,[10] and that 2500ug budesonide has similar systemic effects as 5mg prednisone.[11] It would be reasonable to suggest that prescribers should advise patients of this bioequivalence to enable the patient to put the risk in perspective.

The clinical relevance of these findings have been acknowledged in the most recent 2019 update of the GINA guidelines [47] in which ICS/LABA therapy with an ICS dose of >500µg of FP or equivalent is now recommended at Step 5, the same level as low dose maintenance OCS. This represents a change from the previous versions in which such high doses in combination ICS/LABA therapy were recommended at Step 4. While recognising the limited available data and the substantive limitations of the analyses undertaken in the review, we cautiously suggest that the clinical implication is that increasing the dose of ICS to high or very high doses requires similar considerations as starting maintenance low dose OCS therapy. Furthermore, it suggests that an alternative to increasing the dose of ICS to high or very high doses may be to start maintenance low dose OCS therapy.

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Table 1: Characteristics of included studies

Study	N	ICS type	Inhaler type (propellant)	Placebo Y/N	Low dose (µg/day)	High dose (µg/day)	Treatment period	OCS dose reduction	Total elimination of OCS
Bateman 2006	141	Ciclesonide	MDI (HFA)	Y	640	1280	12 weeks	Y	Y
Fish 2000	132	Mometasone fuorate	DPI	Y	800	1600	3 months	Y	Y
FLTA3022 2005	165	Fluticasone propionate	MDI (HFA and CFC)	Y	1000*	2000*	16 weeks	Y	Y
Hummel 1992	143	Beclomethasone dipropionate	MDI + spacer (not specified)	N	300	1500	6 months	Y	Y
Karpel 2007	123	Mometasone fuorate	MDI (HFA)	Y	800	1600	3 months	Y	NE
Laursen 1986	60	Budesonide	MDI + spacer	N	400	1600	15 weeks	Y	N
Miyamoto 2000	113	Budesonide	DPI	Y	800	1600	26 weeks	Y	Y
Nelson 1998	159	Budesonide	DPI	Y	800	1600	20 weeks	NE	Y
Nelson 1999	111	Fluticasone propionate	DPI	Y	1000	2000	16 weeks	Y	Y
Noonan 1995	96	Fluticasone propionate	MDI (not specified)	Y	1500	2000	16 weeks	Y	Y
Tarlo 1988	40	Beclomethasone Dipropionate	Not specified	N	800	2000	6 months	Y	N

Y = yes; N = no data; NE = not extractable

* Doses are converted to metered dose, delivered dose was 440µg BID and 880µg BID

Table 2: Oral corticosteroid dose reduction and elimination per dose of inhaled corticosteroid

Study	ICS Type	ICS Dose (µg/day)	N	Prednisone dose at study end point Mean (SD)	Prednisone change from baseline† Mean (SD)	Oral corticosteroid Elimination N/N (%)
Laursen 1986	Budesonide	400	25	8.5 (6.0)	5.4	No data
		1600	25	6.5 (3.0)	7.5	
Miyamoto 2000	Budesonide	Placebo	28	8.6 (4.0)	0.9	1/28 (3.6)
		800	33	6.8 (5.0)	4.2	5/33 (15.2)
		1600	29	4.7 (4.7)	7.1	7/29 (24.1)
Nelson 1998	Budesonide	Placebo	50	14.3	5.4	4/50 (8.0)
		800	50	3.3	16.2	34/50 (68.0)
		1600	44	3.6	15.1	28/44 (64.0)
Hummel 1992	Beclomethasone	300	64	15.1 (9.0)	5.2 (7.9)	1/64 (1.6)
		1500	61	13.5 (10.1)	5.0 (9.4)	2/61 (3.3)
Tarlo 1988	Beclomethasone	800	18	8.7 (8.0)	4.5	No data
		2000	13	4.4 (5.4)	5.8	
FLTA3022 2005	Fluticasone propionate	Placebo	32	18.1	-3.9 (17.0)	4/32 (12.5)
		1000	36	1.9	11.1 (9.6)	30/36 (83.3)
		2000	33	2.9	11.4 (10.9)	26/33 (78.8)
Nelson 1999	Fluticasone propionate	Placebo	34	7.8	5.2 (8.6)	3/34 (8.8)
		1000	41	3.4	12.0 (6.5)	31/41 (75.6)
		2000	36	0.6	13.0 (7.7)	32/36 (88.9)
Noonan 1995	Fluticasone propionate	Placebo	31	11.8	-1.6 (7.2)	1/31 (3.2)
		1500	32	2.9	6.6 (5.4)	22/32 (68.8)
		2000	32	0.9	9.3 (4.9)	28/32 (87.5)
Fish 2000	Mometasone	Placebo	20	23.4	-11.8	0/20 (0.0)
		800	42	5.6	6.3	18/42 (42.9)
		1600	38	8.8	3.2	16/38 (42.1)
Karpel 2007	Mometasone	Placebo	38*	19.0	-9.0	Data not extractable
		800	42*	9.7	2.7	
		1600	43*	8.0	5.0	
Bateman 2006	Ciclesonide	Placebo	45	13.6	-1.6	5/45 (11.1)
		640	47	8.6	5.0	14/47 (29.8)
		1280	48	4.7	6.8	15/47 (31.9)

† Prednisone dose at baseline minus prednisone dose at study end point

* These are baseline N’s, as study end point N’s were not extractable

Table 3: Proportion of oral corticosteroid sparing effect of ICS due to systemic absorption

ICS	OCS dose reduction in relation to 1000µg increase in ICS dose (95% CI)	OCS dose resulting in same adrenal suppression as 1000µg of ICS (95% CI)	Ratio (95% CI)
Fluticasone propionate	4.9mg (2.4 to 7.4)	5mg	1.02 (0.68 to 2.08)
Budesonide	2.1mg (1.1 to 3.2)	2mg	0.93 (0.63 to 1.89)

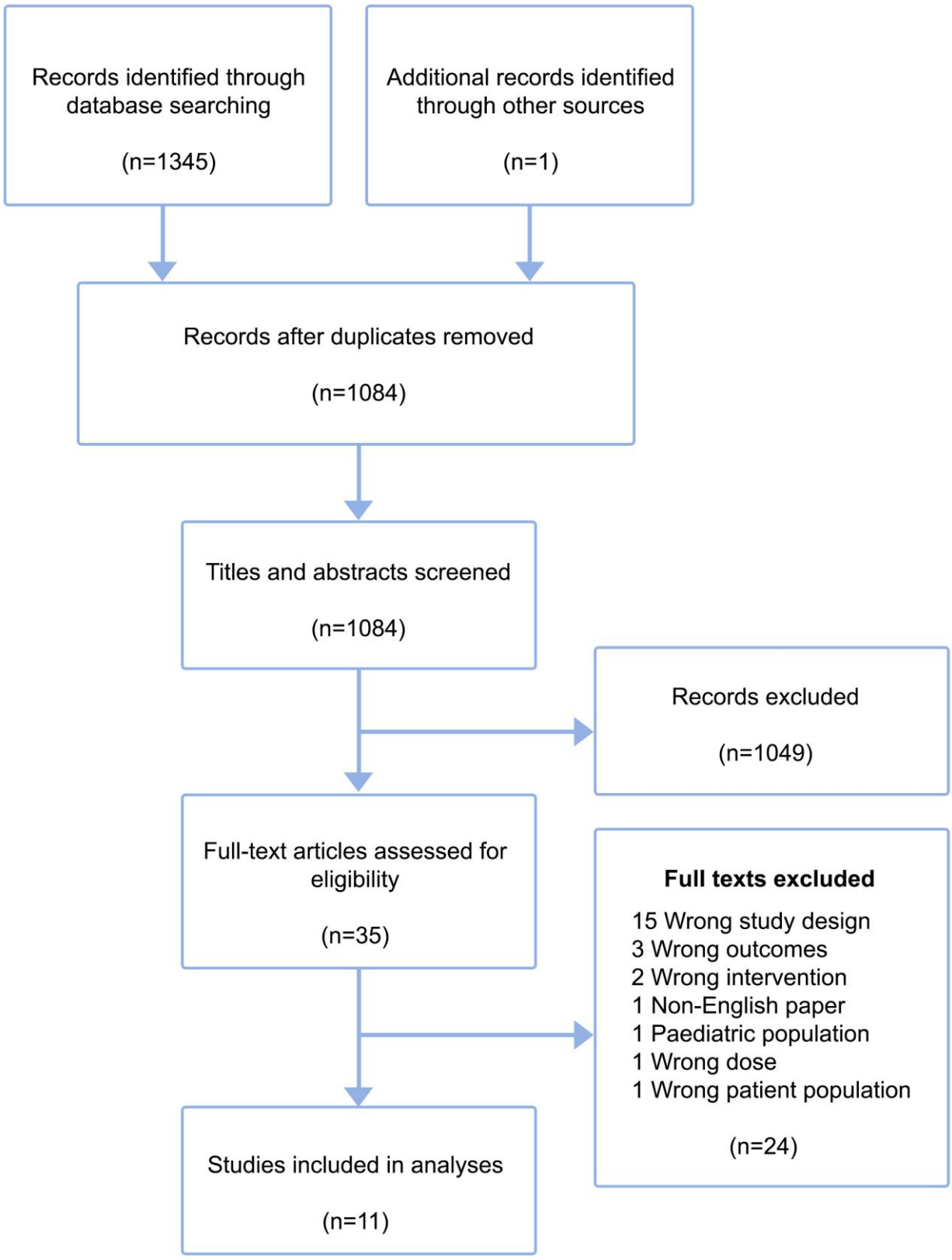
FIGURE LEGENDS

Figure 1: PRISMA flow diagram

Figure 2: Risk of bias summary

Figure 3: OCS dose reduction in relation to ICS dose

Figure 4: Proportion of oral corticosteroid sparing effect of ICS due to systemic absorption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Records excluded
(n=1049)
Full-text articles assessed for eligibility
(n=35)
Full texts excluded
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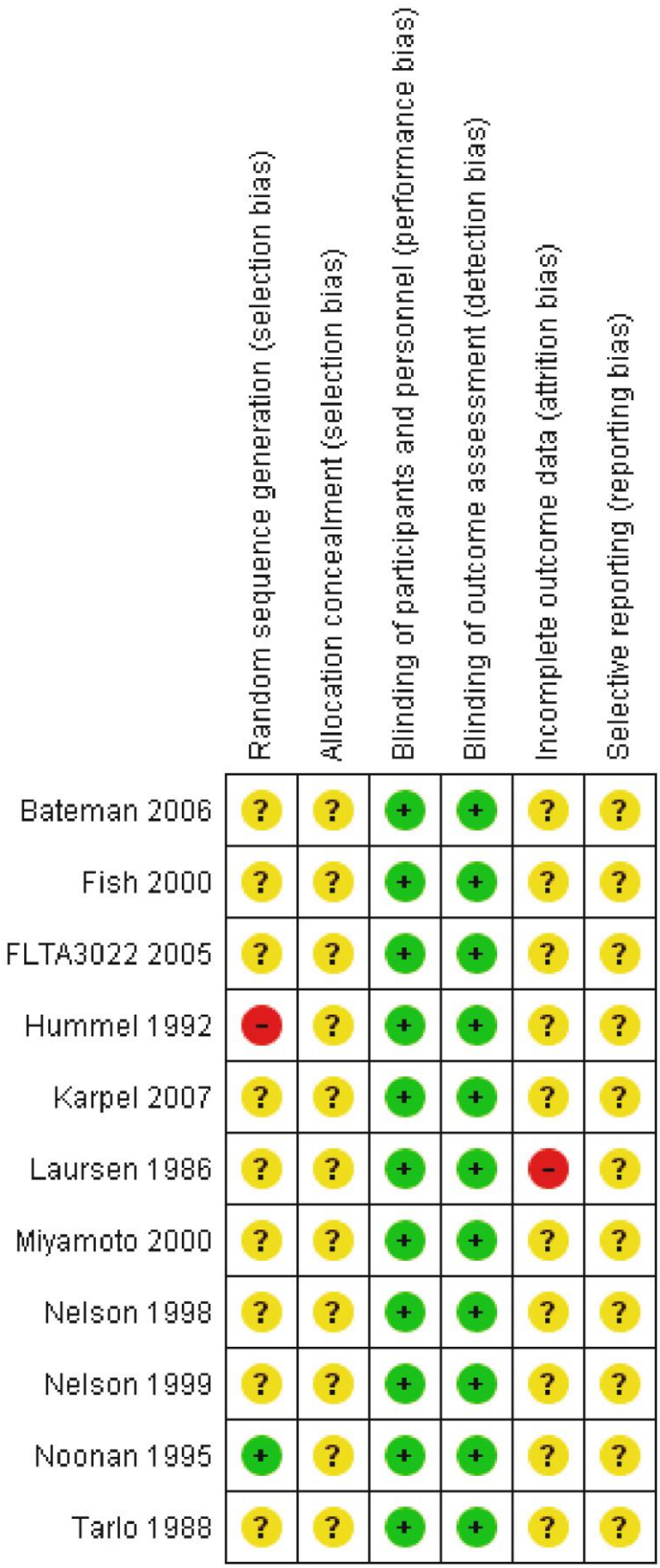
3 Wrong outcomes
2 Wrong intervention
1 Non-English paper
1 Paediatric population
1 Wrong dose
1 Wrong patient population
(n=24)
Studies included in analyses
(n=11)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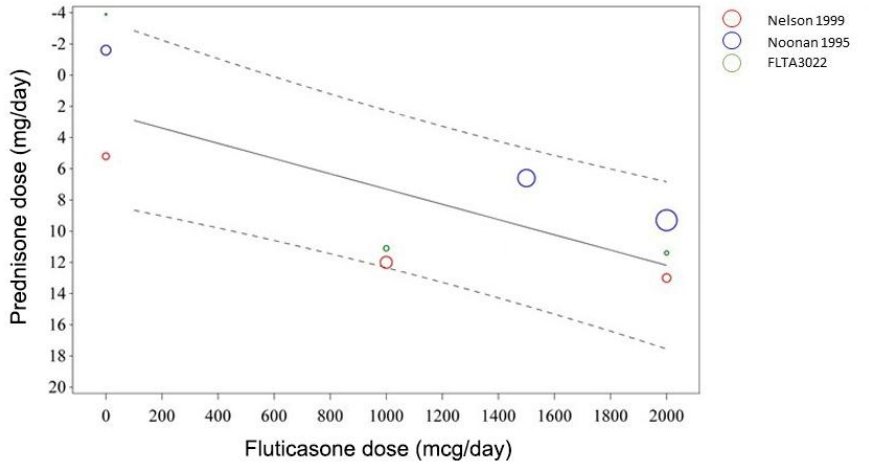
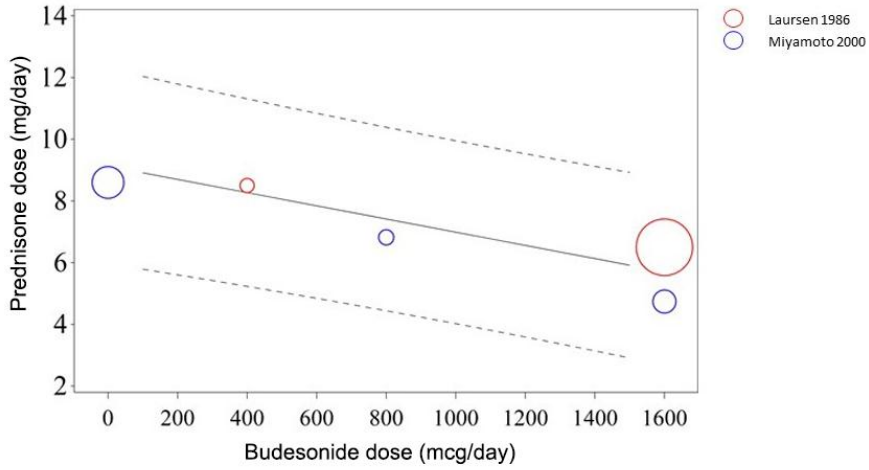
Allocation concealment (selection bias)
Blinding of participants and personnel (performance bias)
Blinding of outcome assessment (detection bias)
Incomplete outcome data (attrition bias)
Selective reporting (reporting bias)
Bateman 2006
Fish 2000
FLTA3022 2005
Hummel 1992
Karpel 2007
Laursen 1986
Miyamoto 2000
Nelson 1998
Nelson 1999
Noonan 1995
Tarlo 1988

Predicted mean prednisone dose
95% Confidence Interval for mean prediction

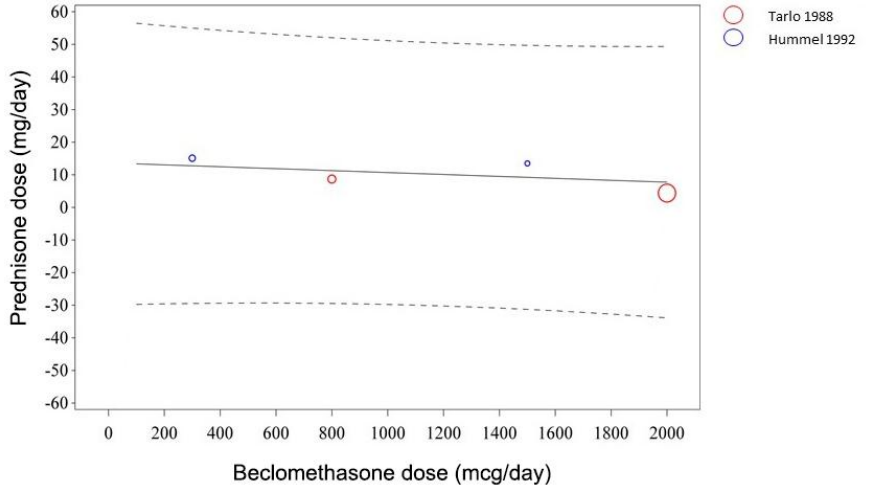
A: Change from baseline of prednisone vs fluticasone dose



B: Prednisone dose at study end point vs budesonide dose



C: Prednisone dose at study end point vs beclomethasone dose



Proportion of oral corticosteroid sparing effect of ICS due to systemic absorbtion