

Inhaled versus Oral Steroids In Adults with Chronic Asthma: A Systematic Review of Therapeutic Equivalence

Mash, RJ

MB, ChB, MRCP, DRCOG, DCH

Department of Family Medicine and Primary Care, University of Stellenbosch and Community Health Services Organisation, Provincial Administration, Western Cape, South Africa.

Bheekie, A

BSc, MPharm

Medical Research Council, Health Systems Division, Parow and University of the Western Cape, School of Pharmacy, Bellville, South Africa.

Jones, P

BSc, MB, BS, PhD, FRCP

Division of Physiological Medicine, St. George's Hospital Medical School, London, United Kingdom.

Address for correspondence:

Dr Bob Mash

Department of Family Medicine and Primary Care

University of Stellenbosch

PO Box 19063

Tygerberg, 7505

SOUTH AFRICA

Tel: 021 938 9170

Fax: 021 938 9153

E-mail: rm@gerga.sun.ac.za

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Abstract

Objectives: To determine the therapeutically equivalent doses of inhaled versus oral steroids in the treatment of adults with chronic asthma.

Search strategy: The Cochrane Collaboration Airways Group conducted a search in MEDLINE (1966-1999), EMBASE (1980-1999) and CINAHL (1982-1999). The search included CENTRAL a database containing potential Randomised Controlled Trials (RCT) obtained by hand searching of journals within the Cochrane Collaboration.

Selection criteria: Randomised controlled trials of at least 4 weeks duration were selected and included persons over the age of 15 years with chronic asthma. Trials which compared inhaled steroids and oral prednisolone or prednisone were considered; the maximum daily dose for inhaled steroids was 2000 mcg and for oral steroids was 60 mg.

Data collection & analysis: Two independent reviewers screened 1285 titles and abstracts from the electronic search. From the results

of the screened electronic search, bibliography searches and other contacts, the reviewers independently selected 15 trials of which 10 met previously defined inclusion criteria. The two reviewers independently abstracted study characteristics, and outcome measures.

Main results: All trials were small and no data could be pooled. Data from six trials produced the same pattern, in which prednisolone 7.5-12 mg/day appeared to be as effective as inhaled steroid 300-2000 mcg/day. In two trials, inhaled steroid 300-400 mcg/day was more effective than prednisolone 5 mg/day. All doses of inhaled steroid appeared to be more effective than alternate day doses of prednisolone up to 60 mg on alternate days.

Reviewers' conclusions: A daily dose of prednisolone 10 mg/day appears to be equivalent to moderate-high dose inhaled corticosteroids. Alternate-day doses of oral steroids and doses < 5 mg/day appear to be less effective than low-moderate dose inhaled steroids.

Background

Asthma is one of the commonest chronic diseases in both developed and developing countries. Guidelines for the management of chronic asthma have been published in several countries and all emphasise inhaled corticosteroids in the control of symptoms and the underlying inflammation of airways^{1,2}. In developing countries however the use of inhaled steroids is often limited by cost constraints. In South Africa the Essential Drug List for Primary Care limits the dose of inhaled steroids to a maximum of 400mcg a day and in the Western Cape doses of 800mcg a day are limited at the primary care level to asthma clinics supported by specialists³. Although specialists are allowed to prescribe higher doses, access to this for a large number of patients with asthma is not possible. The implication of this is that patients with chronic asthma remain poorly controlled on low doses of inhaled steroids or they

must be controlled by the addition of oral steroids⁴.

The Health Department advocates the use of oral steroids in preference to inhaled for mild to moderate asthma³:

“Many adults patients needing more therapy for their asthma than only bronchodilator therapy, may be maintained on a low dose oral prednisone (5 to 7.5mg per day or 10 to 15mg alternative days) without any systemic side effects, even if used for years (including bone density deterioration). Because of the considerably higher costs of inhaled corticosteroids, low dose prednisone should be considered in mild to moderately severe asthma in adults.”

This systematic review aims to assess the evidence for this position, which is clearly in contradiction to most

published guidelines. If low dose oral steroids can be justified then developing countries may be able to make considerable financial savings and if this is not the case then it provides a basis from which to motivate for the availability of inhaled steroids without restrictions. In order to answer this question the review will first determine the dosage of oral steroids required to give a therapeutically equivalent effect to inhaled steroids. Further reviews will be necessary to fully answer the question regarding the relative safety of therapeutically equivalent dosages of inhaled and oral steroids.

This systematic review was prepared with the support of the Cochrane Collaboration and is published as part of *The Cochrane Library*. It will be updated as more trials are either published or identified⁵.

Objectives

To determine the therapeutically equivalent doses of inhaled versus oral steroids in the treatment of adults with chronic asthma.

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) of at least 4 weeks duration.

Types of participants

Only RCTs with participants over the age of 15 years and with chronic asthma were included. Chronic asthma was defined as hyper-responsiveness of the airways, which narrow easily to a wide range of stimuli. This may result in coughing, wheezing, chest-tightness and shortness of breath.

Types of interventions

RCTs, which compared inhaled steroids and oral prednisolone or prednisone for the treatment of chronic asthma, were reviewed. The maximum daily dose considered for inhaled steroids was 2000 mcg and for oral steroids was 60 mg. Only studies with adequately controlled prospective comparisons of the two regimens in the same subjects were chosen. Therefore those studies which evaluated the steroid sparing effect of adding inhaled to oral were not included.

Types of outcome measures

Measures of nocturnal and daytime symptom frequency, peak expiratory flow (PEF) (ℓ/min), forced expiratory volume at one second (FEV1) (ℓ), vital capacity (VC) (ℓ), slow vital capacity (SVC) (ℓ), number of acute attacks requiring medical attention and quality of life assessments were used to compare therapeutically equivalent doses of inhaled and oral steroids.

Search strategy for identification of studies

The Cochrane Collaboration Airways Group conducted a search using the terms: (drug delivery systems OR [(nebuli* OR inhal* OR MDI) AND

oral*]) AND (steroid* OR corticosteroid* OR glucocorticoid* OR beclomethasone OR betamethasone OR fluticasone OR cortisone OR dexamethasone OR hydrocortisone OR prednisolone OR prednisone OR triamcinolone). This search was conducted in MEDLINE (1966-1999),

EMBASE (1980-1999) and CINAHL (1982-1999). The search included CENTRAL a database containing potential RCTs obtained by hand searching of journals within the

Cochrane Collaboration. All articles were considered regardless of language.

Appropriate references from the articles obtained, using the above

search, were reviewed and the authors of published asthma management guidelines as well as recognised experts approached for additional studies.

Methods of the review

Two independent reviewers (BM, AB) screened the titles and abstracts of the electronic search. From the results of the screened electronic search, bibliography searches and other contacts, the reviewers independently selected trials, which met previously defined inclusion criteria, and abstracted study characteristics and outcome measures.

The following parameters of methodological quality were assessed:

Studies were assessed as having a low risk of bias (A), a moderate risk of bias (B) or high risk of bias (C) using the following criteria as shown in Table I:

1. Were all patients who entered trial accounted for and attributed at conclusion?
2. Were patients analysed in the groups to which they were randomised (intention to treat)?
3. Was the assessment of outcomes blinded to type of treatment?

4. Were the groups similar at the start of the trial?
5. Aside from the intervention were the groups treated equally?

Sub-group Analyses:

Study setting, study duration, disease severity, type and doses of inhaled and oral steroids, delivery system of inhaled steroid, frequency of drug delivery, prior and concomitant treatment were all noted.

Description of studies

The search strategy yielded 1285 trials from which 15 studies were requested

and of these 5 were discarded leaving a total of 10 studies in the review. The

included studies are summarised in Table I and the excluded in Table II.

Table I: Characteristics of included studies

Study	Methods	Participants	Interventions	Outcomes	Notes
Bosman et al. ¹³	Double blind cross over. Risk of bias:A. Superiority trial.	17 (12M, 5F). Mild to moderate asthmatics. Prior treatment 800mcg of inhaled steroids.	Beclomethasone 2000mcg vs. Prednisone 10mg. Washout period between treatments. Delivered by aerosol x2/day. Treatment period 4 weeks. Concomitant treatment: Bronchodilators.	Diary Card: PEF am & pm; symptom score. Clinic visit: FEV1, SVC.	
Eriksson et al. ¹⁵	Double blind cross over. Risk of bias:A. Superiority trial.	22 (4M, 18F). Moderate-severe asthmatics. Prior treatment: Oral steroids.	Beclomethasone 300mcg vs. Prednisolone 5mg. No washout period between treatments. Delivered by aerosol x3/day. Treatment period 3 weeks. Concomitant treatment: Bronchodilators.	Diary Card: PEF am & pm, symptoms. Clinic visit: FEV1/VC/PEF	3 patients excluded from analysis. Data reported using SEM and in graphical form
Jenkins et al. ¹⁴	Single blind cross over. Risk of bias:B. Superiority trial.	18 (9M, 9F) Moderate to severe asthmatics. Prior treatment: Beclomethasone 400mcg, Prednisone up to 5mg/day in 4 patients.	Beclomethasone 1200mcg vs. Prednisone 12.5mg. Washout period given between treatments. Delivered by aerosol 6 puffs x4 a day. Treatment period 3 weeks. Concomitant treatment: Intervention added to prior treatment.	Diary Card: Airflometer am & pm, diurnal variability. Clinic visit: FEV1	

Table 1: (continued)

Study	Methods	Participants	Interventions	Outcomes	Notes
Lahdensuo et al. ¹⁶	Double blind cross over. Risk of bias: A. Superiority trial.	18 (13M, 5F) Moderate - severe asthmatics. Prior treatment: Prednisolone 5mg (7 patients), disodium chromoclycate (2 patients).	Beclomethasone 800mcg vs. Prednisolone 10mg. No washout period given between treatments. Delivered by aerosol 4 puffs x4 a day. Treatment period 2 weeks. Concomitant therapy: Intervention added to prior treatment. Bronchodilators.	Diary Card - PEF am & pm; symptom score, bronchodilator use.	Data was reported with SEM not SD.
Lal et al. ¹⁷	Double blind cross over. Risk of bias: B. Superiority trial.	40 (9M, 31F) Severe asthmatics. Prior treatment: Prednisolone 7.5mg; disodium chromoclycate (31 patients).	Beclomethasone 300mcg vs. Prednisolone 7mg. No washout period between treatments. Delivery system aerosol (micronised powder) x3 a day. Treatment period 4 weeks. Concomitant therapy: Bronchodilators. Use of chromoclycate was unclear.	Diary Card - PEF am & pm; bronchodilator usage. Clinic visit: FEV1 and VC.	Data reported with range not SD.
BTTA. ¹⁸	Double blind non-cross over. Risk of bias: A. Equivalence trial.	75 (37M, 38F) Mild to moderate asthmatics. Prior treatment: sodium chromoclycate (28 patients).	1) Placebo aerosol + Prednisone 5mg. 2) Beclomethasone 100mcg + Placebo tablets. 3) Betamethasone valerate 100mcg + Placebo tablets. Patients were started on 4 double puffs of aerosol + 4 tablets per day and then reduced by 1 double puff + 1 tablet weekly until not adequately controlled when the dosage was increased by 1 double puff + 1 tablet to give the maintenance dose. This dose was then evaluated for 24 weeks. Concomitant treatment: Sodium chromoclycate and bronchodilators.	Number of "failure days"; % patients given prednisone short course; % patients whose maintenance dose was increased. Mean monthly PEF.	Data reported without SD.
Namsirikul et al. ¹²	Double blind cross over. Risk of bias: A. Superiority trial.	28 (12M, 16F) Moderate asthmatics. Prior treatment: No oral steroids.	1) Budesonide 400mcg vs. Prednisolone 5mg. 2) Budesonide 800mcg vs. Prednisolone 10mg. Washout period given between treatments. Delivery system tube spacer x2 a day. Treatment period 3 weeks. Concomitant treatment: Bronchodilators.	Diary Card - PEF am & pm; symptom score, bronchodilator usage. Clinic visit: PEF, FEV1 and FVC.	
Rosenhall et al. ¹⁹	Randomised Blinding unclear. Non-cross over. Risk of bias: C. Superiority trial.	17 (13M, 4F) Severe asthma. Prior treatment: oral steroids, mean 5mg/day.	Budesonide 400mcg or 800mcg or Prednisolone 10mg or 20mg. No washout period recorded between treatments. Delivery system not stated. Treatment period 2 weeks. Concomitant treatment: Bronchodilators.	Diary Card - PEF am & pm; symptom scores, bronchodilator use. Clinic visit: FEV1 and VC.	Data presented graphically.

Table I: (continued)

Study	Methods	Participants	Interventions	Outcomes	Notes
Toogood (1) et al. ²⁰	Double blind cross over. Risk of bias:A. Equivalence trial.	17 non oral steroid dependent (NON DEP) and 17 oral steroid dependent (DEP). (20M, 14F) Moderate and severe asthmatics Prior treatment: Beclomethasone.	In DEP group: Budesonide 800mcg vs Prednisone 10mg; Budesonide 1600mcg vs Prednisone 20mg; Budesonide 3200mcg vs Prednisone 40mg. Washout period given between treatments. In NON DEP group: Budesonide 400mcg vs Prednisone 7.5mg; Budesonide 800mcg vs Prednisone 15mg; Budesonide 1600mcg vs Prednisone 30mg. Delivered by nebulizer x4/day. Treatment period: 2 weeks. Concomitant treatment: Bronchodilators.	Diary Card: lower am and pm PEFR; symptom frequency; mean severity of asthma using visual analog scale; during week 2 of each treatment period. Clinic visit: FEV1.	Data presented graphically.
Toogood (2). ¹¹	Double blind cross over. Risk of bias:C. Equivalence trial.	Number of participants and disease severity unclear. Prior treatment: 15mg alternate day Prednisone and 800mcg Beclomethasone.	Prednisone given on alternate days. Budesonide 800mcg vs Prednisone 15mg; Budesonide 1600mcg vs Prednisone 30mg; Budesonide 3200mcg vs Prednisone 60mg. No washout period recorded between treatments. Delivered by cone spacer x4/day. Treatment period: 2 weeks. Concomitant treatment: unclear.	Diary Card: Asthma frequency (attacks per week) Mean severity of asthma (average score per week using visual analog scale). Clinic Visit: FEV1.	Data presented graphically.

Table II: Characteristics of excluded studies.

Study	Reason for exclusion
Cooper et al. ⁶	Not a RCT and does not test therapeutic equivalence.
Prakash et al. ⁷	Outcome measures inadequately reported.
Takashashi et al. ⁸	Not a RCT
Wempe et al. ⁹	Comparison of steroids not primary purpose of study. Main focus on effectiveness of bronchodilators.
Wilmsmeyer et al. ¹⁰	Does not test therapeutic equivalence.

Methodological quality of included studies

Six of the studies were rated as having a low risk of bias (A), two of the studies as a moderate risk (B) and two of the studies as a high risk of bias (C). In the 2 studies rated as "B" one was only single blind and the other had 2 patients

unaccounted for at the end of the trial. In the two studies rated as "C", Toogood (2) did not clarify the number of participants or the severity of asthma and Rosenhall did not clarify the process of blinding. Both studies did not present

their basic data. Although the Lahdensuo study was rated an "A" according to our criteria, his study design failed to prevent considerable carry-over effects between the two treatments and this limits the usefulness of his conclusions.

Results

Six of the 10 studies compared daily oral steroids with inhaled beclomethasone and three with budesonide. In the Toogood (2) study alternate day prednisone was compared with inhaled budesonide¹¹. Only the studies by Namsirikul, Bosman and Jenkins presented data that could be entered into a metanalysis and the data from these studies is summarised in Table III. Namsirikul's study concluded that inhaled budesonide 400mcg was more potent than prednisolone 5mg, but that budesonide 800mcg was therapeutically equivalent to prednisolone 10mg¹². Bosman's study concluded that 2000mcg of inhaled beclomethasone was therapeutically equivalent to 10mg of oral prednisone, apart from superiority of beclomethasone for the morning PEF¹³. Jenkin's study concluded that inhaled beclomethasone 1200mcg was therapeutically equivalent to 12.5mg of oral prednisone¹⁴.

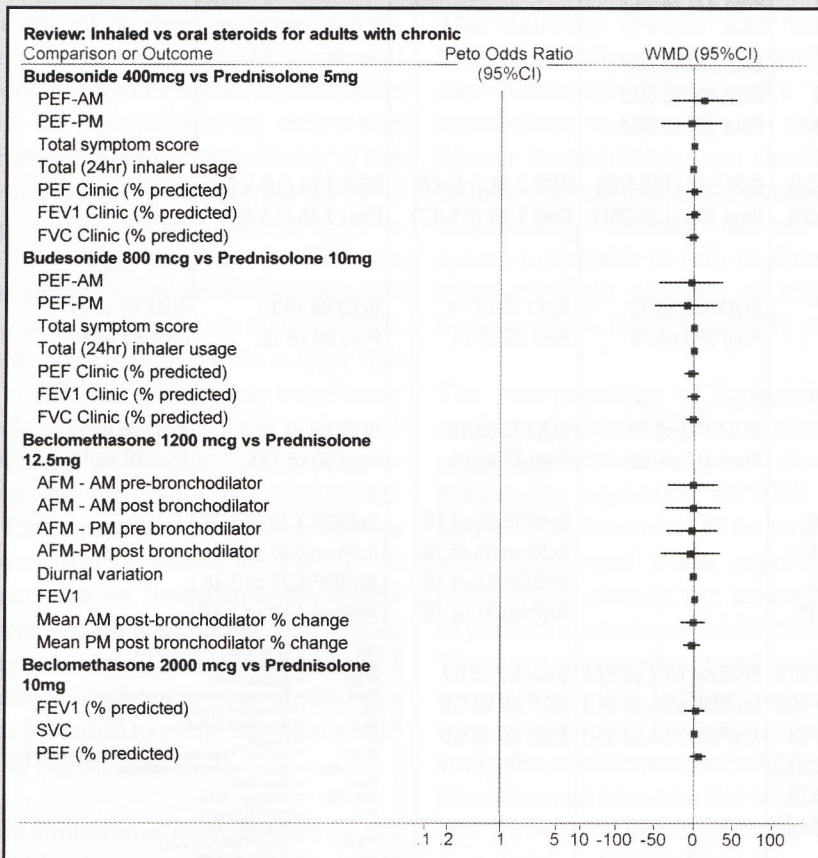
Data from Eriksson, Lahdensuo, Lal, Namsirikul, Bosman and Jenkins is presented in Table IV (*overleaf*). In Eriksson's study¹⁵ it was concluded that 300mcg of inhaled beclomethasone gives a better therapeutic effect than 5mg of oral prednisolone. Lahdensuo's study reported his data according to two groups¹⁶. Group A had beclomethasone 800mcg and then prednisolone 10mg and group B received the same drugs in reverse order. The effect on the morning PEF values was not significantly different between the drugs, but the effect on the evening PEF values was significantly better with prednisolone. The study concluded that 800mcg of inhaled beclomethasone was therapeutically equivalent to 10mg of oral prednisolone. Lal's study compared beclomethasone 300mcg and prednisolone 7mg¹⁷. This study concluded that 300mcg of inhaled beclomethasone is therapeutically equivalent to 7mg of oral prednisone.

In the BTTA Study data for 67 patients were analysed; the remaining 8 patients were withdrawn because of side effects and poor control of asthma¹⁸. In the BTTA study, data from diary cards (frequency of use of inhaled and oral steroids, asthma severity and additional use of corticosteroids) and clinic visits (monthly PEF) were analysed. Failure day was defined as days on which > 4 puffs of bronchodilator were used; or days on which oral and inhaled steroid therapies were increased to obtain a new stable dose. On average there was less than 1 'failure day' per month per patient in each of the three test groups. There was no significant difference between treatment groups whose maintenance dose was increased (between 14% and 26% of patients) and for those prescribed short course prednisone (between 4% and 10% of patients). The mean monthly PEF was much the same in each group: 302 for patients who received prednisone, 300 for those who used beclomethasone dipropionate and 270 who were treated with betamethasone valerate. On average, 400mcg of inhaled corticosteroid provided control of asthma similar to that provided by 7.5mg of prednisone. The different study design precluded presentation of the data in Table III.

In Rosenhall's study data for 16 patients were analysed¹⁹. Basic data on his results were not provided. When compared to baseline, the morning PEF had significantly improved with the two high dose treatments (budesonide 800mcg and prednisolone 20mg) but not with the low dose (budesonide 400mcg and prednisolone 10mg) treatments. Overall budesonide 400mg was found to be equipotent to prednisolone 10mg (as well as baseline) and budesonide 800mg gave the same additional effect as prednisolone 20mg.

In the Toogood(1) study data from two groups of 17 patients were analysed²⁰. The DEP group was defined as the patients previously dependent on regular

Table III: Metanalysis of Selected Studies



dose of prednisone and the NON DEP group as patients not previously dependent on prednisone. Both DEP and NON DEP groups demonstrated dose-dependent improvement in the mean frequency and severity of asthma symptoms, FEV1 and lower morning and evening PEFs. Basic data was not provided and results were given in graphical form. The study conclusions were based on the potency ratio of the number of milligrams of prednisone that were equivalent to budesonide 1000 mcg per day. In the DEP group the following potency ratios for different outcomes were given: Lower PEF am and pm 136mg, FEV1 85mg, symptom frequency

35mg, mean severity of asthma symptoms 27mg. For the NON DEP: Lower PEF am and pm 53mg, FEV1 91mg, symptom frequency 58mg, mean severity of asthma symptoms 42mg. When combining both DEP and NON DEP for all outcome measure an equivalent potency of 57.5mg of prednisone was obtained for 1000mcg of budesonide.

In the Toogood(2) study data from 14 patients were analysed¹¹. Basic data was not provided and results were given in graphical form. From baseline the inhaled budesonide 800mcg produced a significant and sustained increase in FEV1, but there was no accompanying

reduction in asthma frequency or severity. When patients were prescribed alternate day prednisone, FEV1, asthma frequency and severity deteriorated despite increasing doses. The differences between the budesonide and prednisone were statistically significant at most of the individual dose levels (p<0.05). Patients on inhaled budesonide showed statistically less asthmatic disability than with oral alternate-day prednisone (p=0.05). Budesonide 800mcg or 1600mcg/day proved more effective than any of the three doses used in terms of the effects on FEV1 (p=0.06), frequency of asthma attacks (p=0.02) and mean severity of asthma (p=0.008).

Table IV: Data from included studies (not presented in metaview).

Study	Intervention	Diary-am PEF	Diary-pm PEF	Clinic-FEV1	Clinic-VC	Clinic-PEF
Eriksson	BDP 300mcg vs Pred 5mg	BDP 266 Pred 243#	BDP 326 Pred 306#	PreBDP 1.97 se 0.18 PrePred 1.79 se 0.18 PostBDP 2.30 se 0.22 PostPred 2.07 se 0.27	PreBDP 2.73 se 0.22 PrePred 2.52 se 0.21# PostBDP 3.15 se 0.18 PostPred 2.95 se 0.19	PreBDP 326 se 26 PrePred 268 se 27 PostBDP 382 se 36 PostPred 338 se 41
Lahdensuo: Group A	BDP 800mcg vs Pred 10mg	Base 220 se 30.9 BDP 272 se 22.1 Pred 315 se 26.1	Base 336 se 44.8 BDP 373 se 30.3 Pred 421 se 25.3			
Lahdensuo: Group B	BDP 800mcg vs Pred 10mg	Base 250 se 19 BDP 353 se 28.2 Pred 302 se 24.4	Base 362 se 26.7 BDP 440 se 30.9 Pred 395 se 37.6			
Lal	BDP 300mcg vs Pred 7mg	BDP 288 (125-532) Pred 281 (124-509)	BDP 310 (150-538) Pred 293 (139-501)	BDP 2.38 (1.0-4.8) Pred 2.34 (0.9-4.7)	BDP 3.54 (2.0-5.7) Pred 3.48 (1.5-5.9)	
Namsirikul	BUD 400mcg vs Pred 5mg	BUD 375 sd 75 Pred 361 sd 82	BUD 388 sd 72 Pred 390 sd 74	BUD 73 sd 14 Pred 73 sd 14	BUD 88 sd 13 Pred 89 sd 12	BUD 84 sd 17 Pred 83 sd 16
Namsirikul	BUD 800mcg vs Pred 10mg	BUD 397 sd 82 Pred 399 sd 71	BUD 408 sd 79 Pred 417 sd 68	BUD 75 sd 15 Pred 74 sd 14	BUD 89 sd 12 Pred 90 sd 13\$	BUD 86 sd 17 Pred 88 sd 16
Bosman	Pred 10mg BDP 2000mcg vs Pred 10mg	BefBDP 81 sd 18 BefPred 82 sd 15 AftBDP 92 sd 15 AftPred 86 sd 11*		BefBDP 85 sd 18 BefPred 86 sd 16 AftBDP 93 sd 18 AftPred 91 sd 15*	BefBDP 4.74 sd 1.29 BefPred 4.67 sd 1.41 AftBDP 4.77 sd 1.36 AftPred 4.77 sd 1.37	
Jenkins	BDP 2000mcg vs Pred 12.5mg	PreBase 44.3 sd 40.8 PreBDP 60.1 sd 46.9 PrePred 60.9 sd 48 PostBase 67.2 sd 53.2 PostBDP 77.2 sd 52.1 PostPred 78.6 sd 54.3@	PreBase 63.2 sd 52.5 PreBDP 69.6 sd 54.4 PrePred 71.5 sd 44.3	Base 1.9 sd 0.7 BDP 2.2 sd 0.8 Pred 2.0 sd 0.8		

PEF = Peak Expiry Flow Rate
 BDP = Beclomethasone
 BUD = Budesonide
 Pred = Prednisolone or prednisone
 Sd = Standard Deviation
 Se = Standard Error
 () = Range
 FEV1 = Forced Expiratory Volume in 1 second
 Post-/Pre- = Post-/Pre-bronchodilator
 Base = Baseline
 Bef./Aft. = Before / After
 VC = Vital Capacity
 * = % predicted
 **SVC = Slow Vital Capacity
 @ = Airflowmeter
 \$FVC = Forced VC

The design of trials to assess equivalence of treatments has a number of important methodological issues. One requirement of equivalence studies is the need for limits of equivalence to be set, a priori. Absolute equivalence, i.e. zero difference between treatments will not occur, so it is necessary to set limits above and below zero difference within which equivalence can be assumed. These limits are usually set at $\pm 50\%$ of the therapeutic effect of the treatment. Such limits have not yet been established for steroid therapy for asthma. In the absence of empirically derived limits, values of ± 0.15 litres for FEV1 or ± 15 l/min for PEFV might be reasonable conservative estimates²¹. A further consideration is the effect of floor and ceiling effects. In the former, inadequate doses of drug may be given, leading to a false assumption of equivalence, neither dose being effective. Ceiling effects occur when a drug is close to the top of its dose response curve. Very large increases in dose will produce small increases in effect that will be insufficient to move the difference between the efficacy of the two treatments outside the limits of equivalence. False equivalence is shown by equally ineffective treatment as demonstrated by the lower dosage schedule in Rosenhall's study, which also scored a high risk of bias. A ceiling effect may be relevant in Bosman's study where a dose of 2000mcg is used in a study population who were already well controlled. Unfortunately, very little is known about dose-response effects for steroids in chronic asthma. Thus 800mcg/day inhaled steroid may lie towards the top of a dose response curve for inhaled steroid and produce an effect indistinguishable from that produced by prednisolone in a dose of 40 mg/day.

This limitation is compounded by the need for larger sample sizes in trials

that assess equivalence and not difference²². In addition to the methodological quality a number of other factors must be considered in trying to explain the diversity of findings. The included studies all had small sample sizes and were unable to be combined in a meta-analysis due to significant heterogeneity with differences in pharmacokinetic properties of drugs, dosages, delivery systems and outcome measurements. In addition the review was limited by the poor reporting of basic data, failure to adequately report on allocation concealment and inability to access the basic data from the original authors²³. The patient populations included in the studies are described as mild, moderate or severe asthmatics, but the basis of this classification is unclear and open to interpretation. The dosing schedule of 4 times a day has been shown to be up to 8 times as potent as the same dose given twice a day and the studies varied considerably in this respect²⁴. The delivery system also varied between studies, with Toogood(1,2) and Namsirikul being the only researchers to use a spacer device. Spacer devices have been shown to double the anti-asthmatic potency of budesonide²⁵ however the use of a spacer is not able to fully explain the relatively high potency of inhaled budesonide in the Toogood(1) study.

The interpretation of Toogood(1)'s study is limited by the method of reporting the results - as the dose of prednisone equivalent to 1000 mcg budesonide. A number of factors may have influenced these results. As pointed out already, the assumption of perfect equivalence is not correct. There are measurement and sampling errors in all trials. In the presence of very small patient numbers, as in this study, the confidence intervals around the difference between the two drugs will be wide. Thus there is a high probability of one drug appearing

more effective than another. Dose-response effects may also have played a role. The prednisone doses in this study ranged 10-40 mg/day. It is quite possible that the dose-response curve for prednisone is rather flat above 20 mg/day, so budesonide 1000 mcg/day could appear equivalent to prednisone in doses of 20 mg/day and 40 mg/day. Thirdly, the results were expressed as a ratio. This permits an apparent inflation of effects if the denominator is small. As can be seen from the results from other studies in this review, the degree of scatter around the response to steroids may be large. Thus a chance 'under-estimate' of the numerator coupled with a chance 'over-estimate' of the denominator will give an apparently large ratio of effect in favour of the numerator. These factors and the absence of basic measured data mean the results of this trial are effectively uninterpretable.

Studies also differed in their use of concomitant therapy; in particular the Jenkins and Lahdensuo studies added the intervention to prior therapy with inhaled and oral steroids. Variation in the determination of equivalence may also depend on the inclusion of a washout period in the study design and type of outcome measure chosen. When designing the study, absence of a proper washout period minimises treatment effects because of carryover effect or slow response, which would favour equivalence. The evaluation of equivalence will also vary depending on the outcome measure used. In the Toogood(1) study this was well demonstrated with a five-fold difference between equivalence in different outcome measures. In all these studies which compare inhaled with oral therapy in the same subjects there may be wide variation in the actual inhaled drug delivered relative to the stated

dose given. The actual deposition may vary with the type of delivery device and particle characteristics, its use by the patient as well as the physical characteristics of the patient²⁶. It is difficult therefore to define the actual inhaled dose being compared to the oral regime.

Alternate day treatment due to its short duration of action is unable to induce remission in a person with active and uncontrolled inflammation and is best suited to maintaining remission once achieved by daily therapy²⁷. It cannot therefore be seen as an alternative to daily therapy but rather a desired endpoint once remission is obtained. The Toogood(2) study showed a consistent advantage to daily inhaled budesonide over alternate day prednisone even up to 60mg on alternate days.

Is it possible to draw any conclusions from these trials? A firm conclusion cannot be drawn, but a pattern emerges from these data. Three studies with a washout phase (Namsirikul, Bosman, Jenkins) suggest that prednisolone 10-12.5 mg/day is equivalent to beclomethasone 800-2000 mcg/day. In the studies without a washout (Lal and BTTA), prednisolone 7-10mg/day

was equivalent to 300-400 mcg/day of beclomethasone or budesonide. In the first part of the Group A of the Lahdensuo study, the change in PEF from baseline to beclomethasone 800 mcg/day was 52 l/min. In the first part of the Group B of the Lahdensuo study, the change in PEF from baseline to prednisolone 10 mg/day was 48 l/min. Thus similar efficacy was obtained in this trial. Overall, there appears to be equivalence between 7.5-12.5 mg/day prednisolone and 300-2000 mcg/day inhaled steroid. This conclusion should be set against the results from two studies (one with a washout (Namsirikul) and one without (Eriksson)) in which doses of inhaled steroid in the range 300-400 mcg/day were more effective than prednisolone 5mg/day. Finally, it should be noted that inhaled therapy appeared to be more effective than oral prednisone in doses up to 60mg on alternate days.

The strongest conclusions to be drawn from the study are that prednisolone in a dose of approximately 10 mg/day is equivalent to moderate-high doses of inhaled steroids. Lower doses of prednisolone and any alternate day dose appear to be less effective than

even moderate doses of inhaled steroids. If this review is correct in concluding that prednisolone 10 mg/day has equivalent efficacy to that from moderate dose inhaled steroids, the next question concerns side effects. Unfortunately the data from the trials reviewed here give no in depth information concerning this important issue. Few side effects would be expected at the doses used in most of these studies over the short time period studied, so even if these were reported, they would give little indication of the long term probability of side effects. To complement the efficacy data reviewed here, side effects of long term oral steroids in the doses used here can only be obtained from other studies, most probably in diseases other than asthma. There will, however, be problems when extrapolating from other diseases in which there may be an interaction between disease effects and side effects, for example in rheumatoid arthritis²⁹. Age will also be important since steroid side effects such as cataracts, diabetes and osteoporosis may be age dependent. In this context, it should be noted that inhaled steroids do have side effects themselves. A recent Cochrane review has shown that linear growth is reduced in children with asthma given beclomethasone 400 mcg/day²⁸.

Reviewer's Conclusions

Implications for practice

What practical advice can be given to the doctor practising in a developing country scenario? A daily dose of prednisolone 10 mg/day appears to be equivalent to moderate-high dose inhaled corticosteroids. Alternate-day doses of oral steroids and doses < 5 mg/day appear to be less effective than low-moderate dose inhaled steroids. At present there is no evidence about the long-term effects of oral steroids in adults with asthma. If there is no alternative to oral steroids, the lowest effective dose (which appears to be 7.5 mg/day) should be prescribed.

Implications for research

This review demonstrates that there is little evidence to accurately determine the therapeutically equivalent dosage of inhaled and oral steroids. Would it however be ethically justified in the year 2000 to recommend that further research be done to determine this equivalence? A systematic review of the side effects of inhaled and low dose oral steroids would help physicians to weigh the potential benefit and harm to their patient.

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Potential conflict of interest

None.

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