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Oral versus intravenous corticosteroids in adults hospitalised with acute asthma

D. Cunnington[a,*], N. Smith[a], K. Steed[a], P. Rosengarten[b], A.M. Kelly[b], H. Teichtahl[a]

[a]*Department of Respiratory and Sleep Disorders Medicine, Western Hospital, Gordon Street, Footscray, Vic. 3011, Australia*
[b]*Department of Emergency Medicine, Western Hospital, Footscray, Vic., Australia*

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Abstract

Background: Systemic corticosteroids are routinely used in the management of acute asthma, however the optimum route of administration for patients requiring hospitalisation is unclear. Intravenous (IV) corticosteroids are used in practice, but they may not offer any advantage over oral corticosteroids.
Aim: To compare the efficacy of oral and IV administration of corticosteroids in the treatment of adults hospitalised with acute asthma.
Method: Adults admitted to hospital for treatment of acute asthma were randomised to receive oral prednisolone 100 mg once daily or hydrocortisone 100 mg IV 6 hourly for 72 h following admission. All patients concurrently received inhaled corticosteroids and bronchodilators. Improvements in peak expiratory flow rate (PEF) from baseline were compared for 72 h.
Results: Forty-seven patients were randomized, 30 females, 17 males. Twenty-four received oral prednisolone and 23 received IV hydrocortisone. At baseline the oral and IV groups were similar (mean, SD) in age (38.3, 12.8 vs 37.3, 12.9, $P=0.80$) and initial percent predicted (PP) PEF (61, 16.7 vs 69, 13.0, $P=0.11$). After 72 h both groups had similar improvements in PEF (27%, 26 vs 27%, 19, $P=0.96$).
Conclusion: Corticosteroids administered orally and IV had similar efficacy in the treatment of adults hospitalised with acute asthma.

Keywords: Asthma; Prednisolone; Hydrocortisone; Drug administration route; Randomized controlled trial

1. Introduction

Corticosteroids are used routinely in the management of acute asthma. They have been shown in clinical trials and meta-analyses to significantly improve lung function following episodes of acute asthma [1–4]. They have also been demonstrated to reduce the need for admission from the emergency department and reduce the rate of readmission to the emergency department [1,5,6]. Despite their demonstrated role, the route of administration used in the management of acute asthma remains controversial.

Oral corticosteroids are convenient to administer and potentially safer than high dose intravenous (IV) corticosteroids [7–10]. Although oral corticosteroids take longer to reach therapeutic blood levels than IV corticosteroids this does not appear to be clinically significant, with the current literature suggesting that oral administration of corticosteroids in acute asthma may be equivalent to IV administration [11–16]. There have been three randomised controlled studies in adults comparing oral and IV administration of corticosteroids for acute asthma, however each study was relatively small and underpowered to detect significant differences between the two routes of administration [14–16]. Another study examined the use of IV hydrocortisone in addition to prednisolone, but did not directly compare these two medications [13]. In total these studies enrolled 157 patients, and because of differing design, corticosteroid dose, and concomitant asthma medications used the results cannot be pooled. In addition, most of these studies used doses of corticosteroids much larger than is usual in clinical practice, making it difficult to generalize the results to everyday practice.

Current consensus guidelines for the management of asthma recognize that it is appropriate to use oral

* Corresponding author. Tel.: +61 3 8345 6853; fax: +61 3 9318 6342.
E-mail address: david.cunnington@wh.org.au (D. Cunnington).

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corticosteroids in acute asthma, however these recommendations reference the above studies or systematic reviews of the above studies which highlight the lack of good evidence [17–19]. Therefore in this study we aimed to directly compare oral and IV administration of corticosteroids in acute asthma in doses similar to that used in clinical practice to provide evidence to support current consensus recommendations.

2. Materials and methods

2.1. Study design

This study was a randomised, double dummy, double blind, parallel trial of oral prednisolone versus intravenous hydrocortisone for 72 h in the treatment of adults admitted to hospital with acute asthma. The study was conducted in a community based, university teaching hospital in Melbourne, Australia. Institutional ethics committee approval was given, and patients provided written informed consent prior to study entry. Patients were enrolled if they were deemed to require admission to hospital for acute asthma and met the eligibility criteria. Patients were randomly assigned to receive IV hydrocortisone 100 mg 6 hourly or prednisolone 100 mg orally daily for the first 72 h after admission to hospital.

Randomisation was performed according to a randomisation table developed before the study commenced. Patients, investigators and ward staff were blinded to patients' treatment allocation. Patients randomised to receive IV hydrocortisone received four placebo tablets identical in appearance to prednisolone, once daily, while those who received oral prednisolone received IV placebo identical in appearance to hydrocortisone every 6 h. After 72 h patients in both groups were changed to oral prednisolone 50 mg daily for 2 days. The dose of prednisolone was then reduced to zero in 5 mg decrements every second day.

All patients received bronchodilator therapy with nebulised salbutamol 5 mg/2.5 ml (Ventolin, Glaxo Smith Kline, Research Triangle Park, NC, USA) and ipratropium bromide 0.5 mg/2 ml (Atrovent, Boehringer Ingelheim, Ridgefield, CT, USA) four times daily and as required. All patients also received inhaled corticosteroids throughout the study. If patients were taking inhaled corticosteroids prior to randomisation they were continued on these, otherwise patients were commenced on budesonide 1200 mcg twice daily (Pulmicort Turbuhaler 400 mcg per dose, Astra Zeneca, Westborough, MA, USA). All asthma treatment apart from route of administration of corticosteroids was kept the same to reduce the confounding effect of other treatments. Antibiotics were only administered if patients were considered to have lower respiratory tract infection, and patients considered to have pneumonia were excluded from the study.

Treatment failures were defined as deterioration in the first 48 h requiring endotracheal intubation, transfer to the intensive care unit (ICU) or administration of a higher dose of corticosteroids than given in the trial protocol. Adverse events were defined as major: death, myopathy, sepsis, hyperglycaemia or peptic ulceration, and minor: nausea or tremor.

2.2. Patients

Patients admitted to hospital with acute asthma were eligible to be enrolled in the study, however not all patients hospitalised with acute asthma during the study period were enrolled as many did not meet inclusion criteria. To be included in the study, patients had to have significant short-term reversibility in FEV1 $>20\%$ or peak expiratory flow $>30\%$, or have a documented history of asthma without significant chronic obstructive pulmonary disease (COPD), and be between 18 and 65 years of age. The reversibility in lung function could have been demonstrated at visits prior to the current asthma admission. Patients who had received more than a total of 70 mg prednisolone in the 7 days prior to admission were excluded from the study. Patients were also excluded if they had clinically significant disease other than asthma such as unstable diabetes, ischaemic heart disease, malignancy, or hepatic or renal failure. If patients had changes on a chest radiograph consistent with pneumonia they were excluded. Patients with severe asthma, defined as acute respiratory failure (PaO_2 <60 mmHg on 8 l/min of supplemental O_2, or $PaCO_2$ >45 mmHg), or those requiring endotracheal intubation, salbutamol or adrenaline infusions were also excluded from the study.

2.3. Measurements

All patients had PEF measured using hand-held Mini-Wright PEF meters (Clement Clarke, Harlow, United Kingdom) before and after salbutamol in the emergency department. Once admitted to the respiratory ward all patients had peak expiratory flow (PEF) measured 6 hourly before and 10 min after nebulised salbutamol for the first 72 h and then twice daily and as required until discharged from hospital. Predicted values for PEF were calculated using reference equations from the European Community for Steel and Coal for PEF [20]. Hospital length of stay (LOS) was recorded for all patients.

2.4. Power calculation

We defined a clinically significant difference in lung function after 72 h of study treatment to be a difference in the mean improvement in PEF of 50 l/min between the two groups. This size of difference was determined as one that is both clinically significant, but also allows for the variability of repeated measures of PEF within subjects in the early

phase of acute asthma [21]. To detect this difference between the two treatment groups after 72 h of treatment with a power of 80% and an α of 0.05, a total of 68 patients (34 per group) would be needed.

2.5. Analysis

The primary endpoints were PEF measurements at the end of the study period (after 72 h) and improvement in PEF (actual measurement and percent improvement) over the study period. All PEF measurements used in analysis were post-bronchodilator measurements. Improvement in PEF was calculated for each patient as the difference between the first and final measurements performed during the study period. The percent improvement was calculated as the improvement in PEF divided by the initial measurement. This summary method for comparing groups with repeated measures over time is valid, and where there is missing data, is preferable to more complex methods such as repeated measures analysis of variance [22–24]. Differences between the two treatment groups were compared with Wilcoxon rank-sum tests as most data was not normally distributed. Chi-squared tests were used for comparison of proportions. Significance was set at alpha less than or equal to 0.05. Data was analysed using STATA 6.0 (Stata Corporation, College Station, TX, USA). Analysis was performed as intention-to-treat, with all patients meeting inclusion criteria and randomized being included in the analysis. Four patients were randomized but did not meet inclusion criteria and were withdrawn from the study and their data was not included in the analysis.

3. Results

Fifty-one patients were enrolled in the study between August 1996 and June 1999. Five subjects were withdrawn from the study following randomisation, one due to an adverse event and four due to protocol violations. There were no treatment failures during the study. The one adverse event that occurred, was in a patient randomised to prednisolone who developed a rash following injection of IV placebo. The patient was removed from the study after 36 h. The four protocol violations occurred in patients randomised to hydrocortisone. Two of these patients were withdrawn from the study, as they had been randomised despite requiring adrenaline infusions for severe asthma in the emergency department. A third patient was withdrawn after one dose of hydrocortisone as they were felt to have radiographic changes consistent with pneumonia. The fourth patient was withdrawn after 24 h, as they had not given written informed consent to participate in the study. All patients withdrawn from the study were treated with oral prednisolone 50 mg daily upon withdrawal from study.

Forty-seven patients were included in the analysis. Of these, 24 patients received prednisolone and 23 patients received hydrocortisone. The two groups were well matched at baseline, with respect to age, and initial percent predicted (PP) PEF (Table 1). Even though there was no difference in PP PEF at enrollment the actual PEF was higher in the hydrocortisone group.

Table 1
Patient characteristics on admission

	Prednisolone ($n=24$)	Hydrocortisone ($n=23$)	P
Sex	M=6, F=18	M=11, F=12	0.10
Age	38 (12.8)	37 (12.9)	0.80
Pre-bronchodilator			
PEF (l/min)	226 (80)	224 (89)	0.93
PEF (percent predicted)	51 (18)	47 (15)	0.39
Post-bronchodilator			
PEF (l/min)	263 (86)	329 (74)	0.03
PEF (percent predicted)	61 (17)	69 (13)	0.11

Mean (SD).

PEF improved over the first 72 h, with the prednisolone group PP PEF (mean$\pm$SD) improving from 61$\pm$17% initially to 95$\pm$26% by day 3 ($P<0.0001$) and the hydrocortisone group PP PEF improving from 69$\pm$13 to 102$\pm$22% ($P<0.0001$). After 24, 48 or 72 h there was no significant difference in percent predicted PEF between the two groups (Fig. 1). Over the course of the study, the improvements seen between initial and final PEF for individual patients were also similar between the oral and IV groups (Fig. 2).

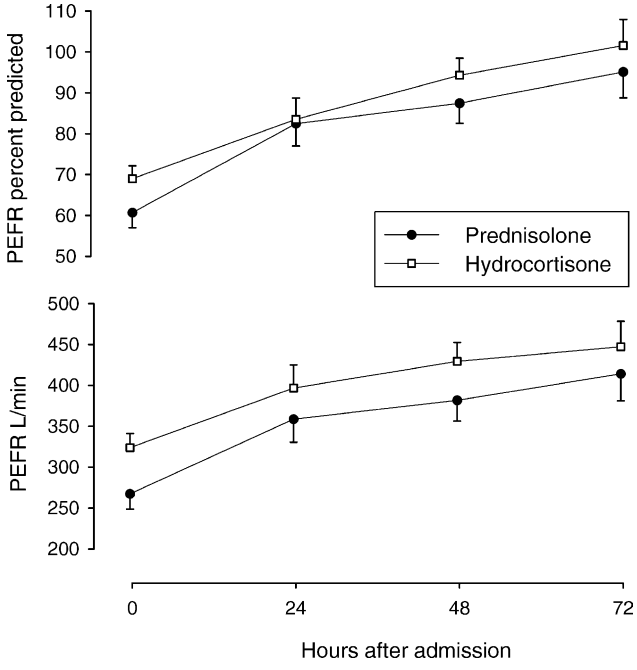

Fig. 1. Post-bronchodilator peak expiratory flow rate measurements over the first 72 h of admission. No significant differences between treatments at any point. Means with standard error bars.

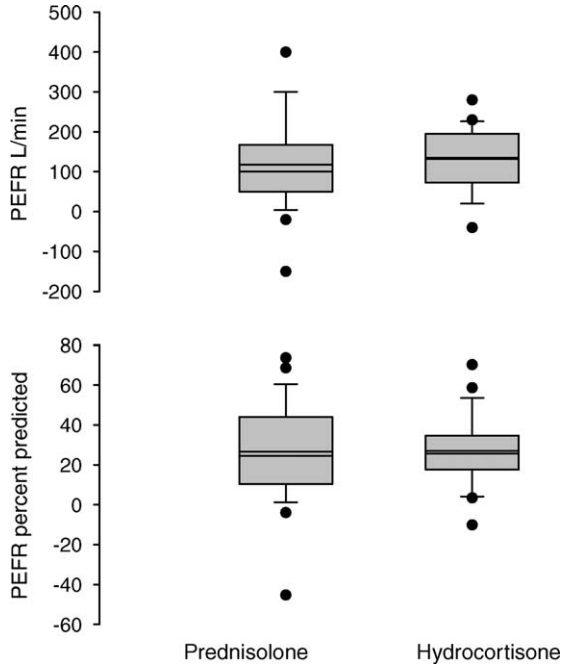

Fig. 2. Improvement in PEFR (final reading–initial reading) over the course of the study. Box plots show median, mean, 25th and 75th centiles (box), 10th and 90th centiles (whiskers) and all outliers.

The hospital LOS ranged from 2 to 6 days with 38 patients (83%) staying for 3 or 4 days, 3 (6%) staying for 2 days, and 5 (11%) staying for 5 to 6 days. The mean hospital LOS was similar in the two groups, being (mean $\pm$ SD) 3.7 ± 0.8 and 3.4 ± 0.9 days ($P = 0.41$) in the prednisolone and hydrocortisone groups, respectively.

4. Discussion

In this study of adults hospitalised with acute asthma, oral prednisolone appeared to be at least as effective as IV hydrocortisone in improving lung function in the first 72 h after admission to hospital. This is in keeping with the results of other published studies that have concluded that there is no significant clinical benefit in giving corticosteroids IV instead of orally in adults with acute asthma [13–16].

There have been four randomised controlled trials comparing oral and IV administration of corticosteroids in adults hospitalised with acute asthma [13–16]. Although each of these studies conclude that oral corticosteroids are as effective as IV corticosteroids, they differ in design, patient selection, dose of corticosteroids and concomitant medications used, which makes pooling of results in meta-analysis inappropriate. Within each of these studies, inconsistency in randomization procedures, doses of corticosteroids and patient selection introduce bias, and reduce the ability of each study to detect a difference in effectiveness of oral versus intravenous corticosteroids. Therefore, although there are four randomized controlled trials published in this area, the studies lack internal and external validity making it difficult to generalize the results to clinical practice.

Although current consensus guidelines for the management of asthma recognize that it is appropriate to use oral corticosteroids in acute asthma, these recommendations reference the above studies and subsequent systematic reviews. In the recent British Thoracic Society/Scottish Intercollegiate Guidelines Network guidelines for the management of asthma the reference given to justify the statement that 'Steroid tablets are as effective as injected steroids' is the systematic review by Rowe et al. [18,19]. However, in that systematic review there is no comparison of the effectiveness of IV versus oral corticosteroids, and it is noted that in adults only studies of IV steroids vs placebo were considered [18]. In the only systematic review looking at the evidence for oral versus IV corticosteroids in the treatment of acute adult asthma, Manser et al. pooled 2 randomised controlled studies and found a trend for greater FEV1 at 24 h in those treated with oral corticosteroids [14,16,17]. They note however, that the larger of the 2 studies, which contributed 70 of the 88 patients in the pooled data was only quasi-randomised with no blinding and the intravenous group received a corticosteroid dose equivalent to 625–1250 mg of prednisolone per day [16]. In the second study, the 8 patients randomized to IV treatment received a single dose of methyprednisolone 1 g, equivalent to 1250 mg prednisolone, and this was followed with oral corticosteroids. These doses are much higher than used in clinical practice and are well above what appears to be required according to the same systematic review [17]. In fact, the difference in doses between the oral and intravenous groups may account for the trend towards a benefit for oral steroids seen in the systematic review, rather than reflecting route of administration. This highlights the lack of data to answer this important clinical question using doses of corticosteroids similar to that used in clinical practice.

A strength of our study is the randomised, double-dummy, double-blinded, parallel design. This reduces the likelihood of bias in the results obtained and is a methodologically sound way of conducting a comparative study between the efficacy of different drugs. A further strength is the relatively low dose of corticosteroids used and the use of inhaled corticosteroids as concomitant asthma treatment, as these reflect current clinical practice making the results more relevant and generalisable to adults admitted to hospital with acute asthma. The dose of corticosteroids used in this study was based upon the commonly used IV dose of hydrocortisone 100 mg 6 hourly. Then oral dose was then set as prednisolone 100 mg daily, a dose with equivalent glucocorticoid and mineralocorticoid properties to 400 mg of hydrocortisone, or 80 mg methylprednisolone. Although the dose of prednisolone is higher than commonly used and recommended in clinical practice, we felt it was important to the dose of corticosteroids was

the same given IV and orally so that this study compares route of administration without the confounding effect of unequal dosing [19]. The dose of corticosteroids used in this study is low compared to other studies that used the equivalent of up to 19.2 g of hydrocortisone per day [17,25,26]. There are few studies to base dosage recommendations on, evidenced by differing conclusions in two recent reviews. In a meta-analysis, Rodrigo and Rodrigo reported a trend towards improvement in pulmonary function with doses above the equivalent of 13 mg/kg/day of hydrocortisone [25]. This is in contrast to the findings of a Cochrane Review which suggested there was no difference in lung function improvement between patients given less than 80 mg methylprednisolone per day compared to those given more than 80 mg per day [17]. This systematic review provides the strongest level of evidence that relatively low doses of corticosteroids are effective in acute asthma and makes us confident that the doses of corticosteroids in this study were adequate.

The dose of prednisolone was tapered after 5 days as that was the clinical practice at our institution at the time the study was designed. This is not in keeping with evidence that suggests tapering of steroids is unnecessary, and is reflected in national guidelines [19]. However, the choice to taper steroids does not affect the reported results of this study, as tapering did not begin until the 6th day after admission, and all results reported in this study were measured in the first 72 h after admission to hospital.

Theophyllines (aminophylline or theophylline) were used in all the other studies, but in Australia, aminophylline is not routinely used in adults with acute asthma making the results of these previous studies less generalisable to current practice [14–16,27–29]. In this study we used high doses of inhaled corticosteroids instead of theophyllines as a concomitant treatment for acute asthma. Inhaled corticosteroids have a potent effect in acute asthma and can themselves result in rapid improvements in lung function [25]. As patients in both treatment groups received the same dose this should not cause differential bias, but may reduce the magnitude of any difference in improvement in lung function seen between groups. This would make a negative result in this study more likely.

Despite using lower doses of systemic corticosteroids and different concomitant medications (inhaled corticosteroids instead of theophyllines) we showed similar changes in lung function to those seen in previous studies [13–16]. This occurred even though our inclusion criteria did not allow enrollment of patients with very severe asthma. The fact that patients with very severe asthma were excluded may also make it less likely for our study to detect a difference between the two routes of administration. The magnitude of improvement in PEF seen in our study population is likely to be less than that seen in very severe patients, as they start from a higher baseline at presentation than more severe patients.

The major weakness of our study is that we were unable to exclude a small difference in PEF improvement between groups due to the large variability in response seen between individuals and the relatively small number of patients studied. This is a common problem in asthma research with large variability of airway obstruction and response to treatment that has resulted in many published studies being unable to reliably exclude type II error [30]. We had problems recruiting patients, in part due to the perception of patients and physicians that the oral and IV routes of administration of corticosteroids are equivalent, despite the lack of evidence as discussed above. Even though this study did not achieve the planned recruitment, post-hoc power calculations indicate that this study had 80% power to detect a difference in PEF improvement of 86 l/min between groups at a significance level of 0.05. Therefore, although we cannot exclude a small difference between groups we can be reasonably confident that the magnitude of the true difference between the two groups is less than 86 l/min.

Another potential criticism of our paper is that the hydrocortisone group appeared to be less severe at enrollment than the prednisolone group. After allowing for possible differences in gender and height between the groups, the hydrocortisone group may have been less severe, as suggested by higher PEF measurements at enrollment. If patients were in fact more severe in the prednisolone group, it is reassuring that in all 23 patients treated with prednisolone, there were no treatment failures, and the overall magnitude of improvement seen in the prednisolone group was not different to that seen in less severe hydrocortisone group.

In this study oral corticosteroids were effective in the treatment of acute asthma in adults requiring hospitalisation, and appeared to be at least as effective as corticosteroids administered intravenously. This strengthens the case for administering oral corticosteroids in this patient group. Given that oral administration of corticosteroids has advantages over IV administration in terms of side effects, cost, ease of administration, and patient comfort, we recommend the use of oral corticosteroids where possible in the treatment of acute asthma in adults requiring hospitalisation [7–10]. However, we caution that although methodologically sound, this study did not achieve planned recruitment numbers, so we cannot exclude a small difference in effectiveness between oral and IV corticosteroids on lung function in adults 72 h after admission to hospital for acute asthma.

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