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ARTICLES

Relative efficacy of hydrocortisone and methylprednisolone in acute severe asthma

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The relative clinical efficacy of different types of intravenous glucocorticosteroids in acute severe asthma is not clear in published studies. We conducted a randomised prospective study of asthma unit admissions over a 3-month period. Therapy consisted of 4-hourly nebulised salbutamol, intravenous aminophylline and either intravenous hydrocortisone 200 mg 4-hourly or intravenous methylprednisolone 125 mg 12-hourly. Three hundred and eighty-six patients were admitted to the asthma unit. After exclusions, 191 patients were included in the analysis (hydrocortisone — 91, methylprednisolone — 100). The groups were comparable in respect of baseline data. The median time to maximum peak expiratory flow rate was 19 hours for hydrocortisone and 23 hours for methylprednisolone (median test, $P = 0,21$). Median duration of asthma unit stay was 30 hours for hydrocortisone and 36 hours for methylprednisolone (median test, $P = 0,01$). A similar difference was evident on comparison of the trial medications in patients who had previously been on oral maintenance steroids. We conclude that, at the dosages selected, hydrocortisone is more effective than methylprednisolone in acute severe asthma.

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Since the MRC trial in 1956[1] and many subsequent studies,[2-4] the use of glucocorticosteroids in the management of acute severe asthma (ASA) has become standard practice. Steroids have been shown to decrease morbidity, hospitalisation and the need for repeat emergency room care.[5,6] The choice of steroid has, however, largely been determined empirically.

Hydrocortisone (HC) and methylprednisolone (MP) are both commonly used in the treatment of ASA. To date no large study has examined their relative clinical efficacy. Sue *et al.*[7] found no significant difference in the short-term airway response of 14 subjects treated with equivalent low doses of intravenous HC, MP and dexamethasone (equivalent to HC 400 mg/24 hours in divided doses 6-hourly). Despite a large margin for type II error in this study, the authors felt that a clinically significant difference was unlikely to become evident with larger numbers. The optimal dose intervals of longer-acting steroids remain undetermined. In view of the longer plasma and biological half-life of MP (and dexamethasone), Sue *et al.* raised the question of possible cost-saving (assuming equivalent efficacy) by less frequent dosing. MP has several theoretical advantages over HC, including greater anti-inflammatory potency, longer duration of action, less sodium-retaining properties and lower cost than an equivalent biopotent dose of HC.[8,9]

In this study we examined the clinical efficacy of MP compared with HC in the management of ASA using equivalent anti-inflammatory doses. The study was prompted by a wide disparity in the cost of the two drugs. In view of the lack of certainty regarding their relative clinical efficacy and considering the hospital's budgetary constraints, the need to determine the most cost-effective therapy had become a priority for the adoption of a rational treatment schedule in our hospital's asthma service.

Patients and methods

Over a 3-month period we prospectively studied all admissions to the asthma unit. The unit forms part of the emergency service of Groote Schuur Hospital.

At the time of the study, all patients with ASA who failed to show a satisfactory clinical response to nebulised β_2-stimulants and intravenous aminophylline within 2 hours were routinely admitted to the asthma unit. All patients received 4-hourly nebulised salbutamol and intravenous aminophylline (dose calculation based on estimated lean body mass and adjusted when serum theophylline levels became available).

Except in the mildest cases, intravenous steroids were routinely administered. The first dose of steroid (administered in the emergency unit) was almost always given within an hour of presentation to hospital. The trial required that either HC (200 mg 4-hourly intravenously) or the equivalent dose of MP (125 mg 12-hourly intravenously) be used. The criteria for the initiation of steroid therapy are listed in Table I. Failure to respond to this therapy served as an indication for a salbutamol infusion.

Table I. Criteria for initiation of steroid therapy

1. All patients who have received corticosteroids in the preceding 3 months as part of their maintenance asthma treatment.
2. All patients admitted to the asthma unit during the preceding 4 weeks.
3. Failure to show a satisfactory response* to nebulised salbutamol and intravenous aminophylline within 1 hour.
4. All patients who on a previous admission to the asthma unit showed a slow recovery curve and/or required intravenous steroids.

* Satisfactory response was defined as a reduction in general state of distress, reduction of tachycardia and pulsus paradoxus, and improvement of PEFR by 50% or more.

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Randomisation was achieved by alternation of the steroid available for use in the asthma unit on a weekly basis throughout the study period.

Management protocol. During the trial period the criteria for admission to the asthma unit, therapy with bronchodilators and/or steroids, referral to the intensive care unit and discharge from hospital were not different from those in place for the preceding 7 years. Decisions to intensify therapy, e.g. by adding a salbutamol infusion, to discharge patients (according to discharge criteria outlined in Table II) or to admit a patient to an intensive care unit or medical ward were taken by emergency unit staff independently of research personnel.

Table II. Discharge criteria

1. No features of distress; able to walk to the toilet.
2. PEFR showing an upward trend and/or having reached a plateau at more than 70% of the patient's best PEFR in the past year (or, if not available, 70% of predicted normal PEFR)
   and
   morning dipping not below 50% of the patient's best PEFR in the past year (or predicted normal PEFR).
3. Patient feels that he/she would be able to cope at home.

NB: All 3 criteria to be fulfilled.

Patients were monitored, as usual, by charting of 4-hourly peak expiratory flow rate (PEFR) measurements and daily theophylline levels. The same Wright's mini peak-flow meter was used on all patients and was checked daily on a non-asthmatic control. Serum electrolyte, urea and creatinine and arterial blood measurements, chest radiograph and sputum bacteriology were performed when indicated on clinical grounds.

The *endpoints* of the study were the time taken to achieve maximum PEFR (in hours) and the duration of asthma unit stay. The hospital notes of all patients admitted to the asthma unit were reviewed upon their discharge (by C.M.H.). The time taken to achieve maximum PEFR (in hours) was calculated from the time of arrival in the emergency unit to the maximum PEFR recorded on the peak flow chart. As the exact time of discharge is more dependent on the unit's routine than on the patient's response, each day was divided into 6-hour time units (00h00 - 06h00, 06h00 - 12h00, 12h00 - 18h00, 18h00 - 24h00). The duration of stay was then calculated in time units from that of arrival in the emergency unit to that of discharge. A note was made of the need for salbutamol infusion and the need for intensive care unit or medical ward admission. The prior use, if any, of oral maintenance steroids was recorded.

Inclusions. Strict criteria for the *reversibility* of airflow obstruction and *severity* of asthma were used: (*i*) an initial increase in PEFR > 20% (over the value on presentation) after the first salbutamol nebulisation, or an increase in PEFR > 100% at any time during the admission; and (*ii*) an initial PEFR < 50% of predicted. Predicted PEFR was calculated according to Coates' formula.[10]

Exclusions. Patients with evidence of other significant cardiorespiratory disease were excluded from further analysis. Patients whose therapy deviated from the basic protocol were analysed separately, as were those who were transferred to a medical ward or intensive care unit.

Ethics. Verbal consent to participate in the study was obtained. The study was approved by the University of Cape Town Medical School Ethics and Research Committee.

Statistics. The chi-square, Student's *t*, Mann-Whitney *U*- and median tests were used to determine the significance of differences between the HC and MP groups, as well as the 4 subgroups: HC and maintenance steroid, HC without maintenance steroid, MP and maintenance steroid, and MP without maintenance steroid.

Results

Three hundred and eighty-six patients were admitted to the asthma unit, of whom the following were excluded: non-asthmatics (38), those who did not meet criteria for severity (58), those not given intravenous steroids (47), those who received additional therapy (salbutamol infusion) (33), and those who had ward transfers (19). There was no significant difference between the numbers treated with HC v. MP in those who required a salbutamol infusion (HC = 8,7%, MP = 13,3%; $P = 0,20$, chi-square), or in those transferred to the medical wards (HC = 7,3%, MP = 5,3%; $P = 0,47$, chi-square). The indications for ward transfer were: associated medical illnesses (4), asthma unit full (1), and persistent bronchospasm or judged to be unstable (14). No patients required transfer to an intensive care unit.

Analysis of the remaining patients showed 91 in the HC and 100 in the MP groups respectively (Table III). Analysis of

Table III. Baseline comparisons and outcome

	Hydrocortisone (*N* = 91)	Methylprednisolone (*N* = 100)	*P*-value
Baseline data			
Mean age (yrs) (±SD)	41,1 ± 16,6	42,6 ± 17,1	0,53 *t*-test
Mean predicted PEFR (l/min)	486 (368/456)	415 (376/533)	0,72 Median test
Median admission PEFR (% of predicted)	24 (17,2/33,6)	24,9 (18,8/30,8)	0,89 Mann-Whitney *U*
Male (%)	18,7	31	0,05 Chi-square
Prior maintenance steroids (%)	48,4	48,5	0,99 Chi-square
Outcome			
Median hours to maximum PEFR	19 (12/31)	23 (14/33,8)	0,21 Mann-Whitney *U*
Maximum PEFR (% of predicted) (±SD)	81,5 ± 20,3	81 ± 21,6	0,87 *t*-test
Median hospital stay (h)	30 (18/42)	36 (18/48)	0,01 Median test

Bracketed figures denote values of 25th and 75th centiles.

Table IV. Subgroup comparisons — prior maintenance steroids

	Hydrocortisone		Methylprednisolone	
Maintenance steroid*	Yes (N = 44)	No (N = 47)	Yes (N = 48)	No (N = 51)
Age (yrs)	45,5† (35/56,8)	33†‡ (23/45)	44‡ (29,3/56,8)	41 (27/49)
Predicted PEFR (l/min)	400 (348/469)	418 (379/456)	423 (368/552)	406 (381/486)
Admission PEFR (% predicted)	22.2 (16,9/30)	25,4 (18,3/35)	27,4 (18,8/35)	23,2 (17,7/28,6)
Maximum PEFR (% predicted)	78,8 (61,5/97)	84,5 (71,3/95,1)	81,1 (67,0/96,7)	76,4 (67,6/90,6)
Hours to maximum PEFR	18 (10/28,5)	23 (12/33)	22,5 (16/30,5)	24 (12/35)
Hospital stay (h)	30† (18/30,5)	30 (18/42)	36† (24/48)	36 (18/42)

Median values quoted throughout with 25th and 75th percentiles in brackets below. Mann-Whitney U test employed in all cases except 'hospital stay' where median test was used.
* Data missing in one case.
† P = 0,01.
‡ P = 0,02.
All other comparisons not significant.

baseline data showed no significant difference between the two groups in age, predicted PEFR or 'PEFR as a percentage of predicted' after the first nebulisation was administered. There were significantly more males in the MP group. Almost equal percentages of both groups were on prior oral maintenance steroid therapy.

There was no significant difference in the time to maximum PEFR, nor did the maximum PEFR (% of predicted) differ in the two steroid groups. A significant difference emerged in the duration of asthma unit stay, with a median of 30 hours (5 6-hour time units) for HC compared with 36 hours for MP (P = 0,01, median test).

In the HC group, 58 patients remained in the asthma unit for 24 hours or longer. By 24 hours, 58 had achieved a median percentage of predicted PEFR of 70,7% (25th/75th percentiles 54,7 and 85,0). The corresponding MP group contained 72 patients with a median percentage of predicted PEFR of 68% (25th/75th percentiles 56,6 and 87). These values did not differ significantly (P = 0,99, Mann-Whitney U-test). A significant difference favouring HC was apparent 48 hours following admission in those with an admission duration $\geq$ 48 hours (HC: N = 19, median % predicted PEFR = 71,8 (25th/75th percentiles 57,4 and 81,9) v. MP: N = 24, median % predicted PEFR = 56,9 (25th/75th percentiles 51 and 61,0) (P = 0,01, Mann-Whitney U)). Table IV compares the duration of admission and time to maximum PEFR in the subgroups which were and were not on previous oral maintenance steroids. The HC patients not on maintenance steroids were significantly younger than those who had been on maintenance therapy in both the HC and MP groups. The HC subgroup on prior oral steroids had a significantly shorter hospital stay than the equivalent MP group.

Discussion

There was a significantly shorter duration of hospital stay in the HC group as a whole, as well as in the subgroup which had been on previous maintenance oral steroids. In the subgroups not on maintenance steroids a similar trend in favour of HC was seen but did not reach statistical significance. In contrast, there was no difference in the HC and MP groups in respect of maximum peak flow rates achieved or in the time taken to achieve this level. However, the validity of the observed difference in the duration of hospital admission is supported by the additional observation that patients in the MP group who remained in the asthma unit for longer than 48 hours showed a smaller increase over baseline in PEFR compared with those in the HC group.

It is relevant to consider why MP proved less effective than HC in this study. The optimal dosage interval for the longer acting steroids is not known, and the commonly practised 12-hourly dose interval may be too long. It is possible that the more frequent corticosteroid peaks achieved with 4-hourly HC administration may have some added benefit in asthma. In an animal model, Nichols *et al.*[11] examined the effect of prednisone on the induction of hepatic tyrosine aminotransferase activity and free hepatic glucocorticoid receptors. They concluded that repeated small doses of prednisone are more effective than a single large dose.

Although the optimum steroid dose in ASA remains controversial, Britton *et al.*[12] suggested that there is no advantage to using very high-dose corticosteroid (equivalent to HC > 3 g/24 hours). Haskell *et al.*[13] found that a dose equivalent to 300 mg/24 hours was inadequate. Dwyer *et al.*[14] and later Collins *et al.*[15] proposed a dose of HC sufficient to maintain plasma cortisol levels at 100 - 150

µg/dl. These levels could be achieved with a dose of HC of between 1 000 and 1 750 mg/24 hours. The use in the present study of the equivalent of 1 200 mg HC per 24 hours (for both limbs of the trial) could therefore be regarded as appropriate.

The HC and MP groups were well-matched in terms of age, baseline status and previous oral maintenance steroid therapy. Although a difference in gender distribution was noted, this is unlikely to have influenced outcome. There was no difference between the two steroid groups in respect of the numbers excluded from primary analysis because of ward transfer or the need for salbutamol infusion. This study was performed in the working situation of an emergency unit with a staff of 18 full-time and 12 or so sessional doctors (the number of the latter varied over time). Individual doctor bias with regard to admission or discharge decisions is therefore unlikely to have affected the study results systematically.

Clinical studies and comparisons of treatments of ASA present several difficulties.[16,17] Major aspects are the varying degrees of severity, rates of deterioration, bronchospasm and inflammation as well as causes of the acute attack; each of these is expected to influence the rate of recovery. Because of this heterogeneity in the asthmatic population, the study was designed to ensure minimal interference with the usual practice of asthma unit staff in the application of discharge criteria. This ensured the recruitment of the maximum number of patients over the 3-month period. The results, therefore, highlight the relative efficacy of HC and MP in a commonly encountered clinical situation using a population sample which is representative of the uncomplicated hospital asthmatic population. We have attempted to answer the clinical question at a pragmatic level guided by the principles of epidemiological rather than pure experimental research.

The fact that a difference between the efficacy of two high-dose steroid regimens could be shown in the present study raises questions about the current tendency to introduce lower-dose and oral steroid regimens.[18,19] Clinicians should be aware that, unless these regimens can be shown under local conditions to be as effective as intravenous high-dose regimens, they may be doing their acute asthmatic patients a disservice.

An additional consideration in this study was the cost of treatment. In the absence of a clinically meaningful difference in efficacy, the cheaper drug would be the preferred agent. The assessment of relative drug costs must, however, also include the influence of treatments on the duration of hospitalisation. The 12-hourly administration of MP resulted in a two-thirds reduction in consumable expenditure and nursing time compared with 4-hourly HC. This advantage would only be clinically relevant if overall hospital stay was similar (or favoured MP). At the time of the study MP was considerably cheaper than HC at our institution. This, together with the lower staff costs, led to the use of MP as the standard intravenous steroid in the asthma unit.

We have shown decreased duration of hospital stay in patients with ASA treated with HC v. MP at the selected doses and dose intervals. The differences, although small, are statistically significant. However, practical considerations (i.e. cost and convenience) may weigh more heavily in the clinical choice of steroid.

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