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Methylprednisolone pulse therapy in acute severe asthma

A randomized, double-blind study

T. Engel, A. Dirksen, L. Frølund, J. H. Heinig, U. Gerner Svendsen, B. Klarlund Pedersen & B. Weeke

Allergy Department 7511, State University Hospital, Copenhagen, Denmark

Methylprednisolone pulse therapy (MPPT) has been shown to possess a long-lasting effect in other immune-inflammatory diseases without the well-known side effects caused by long-term treatment with glucocorticosteroids. In an attempt to reduce the long-term use of oral steroids in asthmatics, we conducted this double-blind, double-dummy study to compare the use of MPPT (1 g of methylprednisolone intravenously) (8 patients) with a short course of oral prednisolone (10 patients) in asthmatics presenting with acute severe asthma. Both treatments were effective in relieving the acute attack of asthma. The MPPT-treated patients did not show a faster resolution than did the orally treated group. No patients needed assisted ventilation, and no deaths occurred. One week after the treatment FEV_1 tended to decrease in the methylprednisolone group compared with the oral prednisolone group ($P = 0.06$). The patients initially receiving MPPT needed supplementary prednisolone earlier and in higher doses than did the patients receiving oral prednisolone as initial treatment. At the end of the 12 weeks' study period, the groups reached identical FEV_1. In conclusion, we did not find intravenous methylprednisolone superior to oral prednisolone in the treatment of acute attacks of severe asthma, but methylprednisolone pulse therapy had a shorter duration as regards protection against future asthma attacks.

Key words: acute severe asthma; follow-up; methylprednisolone; pulse therapy; ventilatory capacity.

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Therapy with glucocorticosteroids (GCS) in acute severe asthma is still a subject of debate (6, 14) although well-conducted studies have shown an effect of GCS in acute severe asthma in adults (5) and children (12, 22). Other investigations have, however, failed to show any dose-response relationship of GCS when evaluated within the first 24 h (19, 20, 23). Within the last 25 years, no follow-up investigations of more than 2 weeks' duration have been published.

In controlled studies of methylprednisolone pulse therapy (MPPT), intravenous methylprednisolone (MP) 1g has proved effective for months in the treatment of immune-inflammatory disorders such as rheumatoid arthritis (25), lupus nephritis (3), acute allograft rejection after kidney transplantation (16), and idiopathic pulmonary fibrosis (7). Furthermore, an effect has been suggested in systemic lupus erythematosus (10) and ankylosing spondylitis (21).

The aim of the following study was to compare the effect of MPPT with a course of oral prednisolone in patients with acute severe asthma, evaluated as the immediate effect

(within 24 h) and the protective effect against new exacerbations during a 12 weeks' follow-up period.

MATERIAL AND METHODS

Design

The study was conducted as a randomized, double-blind, double-dummy study. One group received MPPT, 1 g of freeze-dried MP dissolved in 500 ml of isotonic sodium-chloride and infused intravenously over 30 min (the MP group). The MPPT was given only once, since an earlier study showed no cardiac side effects with this treatment regimen (24). The control group was treated with a course of oral prednisolone starting with 50 mg daily and tapered until zero (the OP group) within 18 days. Further to the intravenous MPPT, the MP group was also treated with identically appearing placebo tablets, and the OP group was treated with a placebo infusion indistinguishable from the MP. All patients took 10 tablets (placebo or prednisolone) on admission, reduced this by 1 tablet daily until a daily dose of 2 tablets, upon which the dose was reduced by 1/2 tablet every third day until no medication. If the patient received systemic GCS prior to admission, this therapy was withheld during the entire study period.

During the first 24 h PEF was measured hourly in the study subjects while awake. Prior to therapy a 12-lead electrocardiogram was obtained in all patients; no arrhythmias were detected. Prior to therapy and on Days 2, 7, 14, 28, 56, and 84, blood was drawn for analysis of sodium, potassium, creatinine, ESR, haptoglobin, IgG, IgA, IgM, IgE, haemoglobin, neutrophils, lymphocytes, eosinophils, and blood glucose, and clinical examinations incl. measurement of FEV_1, FVC and PEF were made.

Table 1

Descriptive data on admission for 18 patients treated for acute severe asthma with MP or OP

	MP-group	OP-group	*P*
Sex (M/F)	2/6	2/8	1.00*
Age (years)	47.9±11.0	46.0±13.4	0.76
Height (cm)	165.1±10.0	171.9±7.5	0.27
On oral steroids	4	3	0.63*
FEV_1 (% pred.)	32.8±10.6	43.1±14.3	0.14
PEF (% pred.)	43.3±22.3	47.2±12.5	0.91

P indicates levels of significance (Mann-Whitney test, *: Fisher's exact test).

Patients

All patients presenting at the clinic with an attack of acute severe asthma were given an inhalation of nebulized salbutamol 2.5 mg followed by a standardized treatment programme including $\beta_2$agonists and intravenous theophylline. If, 1 h after the beginning of the treatment, FEV_1 was still less than 60% predicted (4) and treatment with GCS was indicated, the patient was hospitalized, and participation in the study was offered. The standardized symptomatic treatment regimen was continued in all patients for at least the initial 24 h.

Eighteen treatments were given to 15 asthmatics (Table 1). Three patients were included twice with the reverse kind of treatment at the second inclusion, which took place at least 12 weeks after the initial treatment. Eight treatment courses were given with MPPT (MP group) and 10 with oral prednisolone (OP group). On admission, four patients in the MP group and three in the OP group received long-term prednisolone therapy in a dose not exceeding 10 mg daily (Table 1). Patients using prednisolone in a daily dose exceeding 10 mg daily were not included.

During the 12 weeks' follow-up study period all patients used a maintenance therapy comprising inhaled β_2-agonist on an as required basis, inhaled budesonide 800 µg b.i.d. through a 750 ml spacer (Nebuhaler®), sustained release theophylline tablets (Theo-Dur®) 200 mg or 300 mg b.i.d. according to the patient's weight, and possibly sustained release β_2-agonist tablets (Bricanyl® Retard) 5 or 7.5 mg b.i.d. Patients recorded their daily morning and evening PEF in a diary adding daily use of inhaled β_2-agonist and use of medication other than prescribed. In

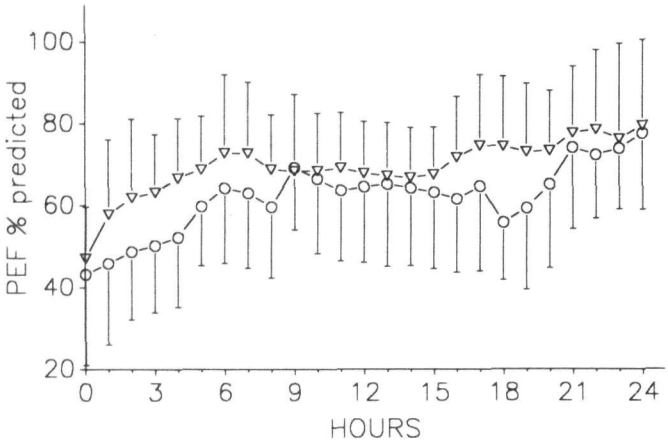

Fig. 1. PEF % predicted during the initial 24 h in 18 patients treated for acute severe asthma with MP (○) or OP (▽).

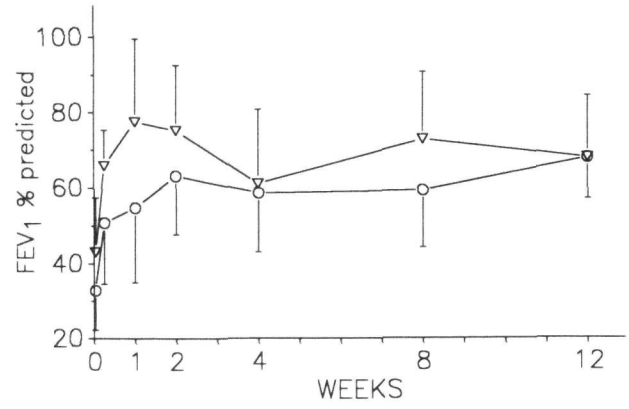

Fig. 2. FEV_1 % predicted on admission (O weeks) and during a 12 weeks' follow-up period in 18 patients treated for acute severe asthma with MP (○) or OP (▽).

the event of deterioration concomitant prednisolone was prescribed exclusively by one of the authors.

All patients fulfilled the criteria for asthma stipulated by the American Thoracic Society (1). None suffered from diabetes mellitus, cardiac failure, hypertension, or was pregnant. The Helsinki II declaration was fully observed.

Measurement of ventilatory capacity

Peak expiratory flow (PEF) was measured on a mini-Wright peak flow meter (Airmed, Clement Clarke International Ltd., London, U.K.), and 1st s forced expiratory volume (FEV_1) and forced vital capacity (FVC) were measured on a calibrated dry wedge spirometer (Vitalograph Ltd., Buckingham, England). Three measurements were performed, and the highest values obtained were used for the subsequent analysis. All data on ventilatory capacity are reported as % predicted (4).

Statistics

Data are given as mean ± SD unless otherwise stated. The Wilcoxon rank sum test (paired data), the Mann-Whitney rank sum test (unpaired data), and Fisher's exact test were used as appropriate. Concomitant oral prednisolone consumption was compared by area under the curve (AUC) using the Mann-Whitney test. AUC was calculated by adding the week-by-week mean daily dose of prednisolone for each patient.

RESULTS

On admission, FEV_1 % predicted tended to be higher in the OP group than in the MP group (Table 1). The trend did not, however, reach statistical significance ($P = 0.14$). PEF % predicted was identical in the two study groups (Table 1).

Hourly measurements of PEF during the initial 24 h after admission showed no significant difference between the two treatments (Fig. 1). The mean time taken to reach a PEF > 70% predicted was the same in the two groups ($P = 1.00$, Mann-Whitney). One patient in the OP group and three in the MPPT group did not reach a PEF > 70% predicted within the first 24 h after start of treatment ($P = 0.11$, Fischer's exact test).

Twenty-four hours after start of treatment, FEV_1 % in the OP group (65.8% ± 9.5%) tended to be higher than that of the MP group (50.8% ± 16.2%) ($P = 0.06$, Mann-Whitney). The mean increase in FEV_1 in both groups was, however, comparable, the MP group increasing their FEV_1 by 54.9% (from 32.8% to 50.8% predicted), the OP group by 52.7% (from 43.1% to 65.8% predicted).

One week after the initial treatment, the OP-treated patients still had a trend towards higher

FEV_1 % predicted ($P = 0.06$, Mann-Whitney) (Fig. 2). During the remaining study period, the trend of increased FEV_1 in the OP group disappeared, and no difference in FEV_1 % predicted between the two groups could be demonstrated. To a minor degree PEF % predicted showed the same pattern as FEV_1. On admission, two patients in the MP group and one in the OP group showed pulsus paradoxus of more than 15 mmHg, which was, however, present in only one patient in the MP group 3 h later. Pulsus paradoxus no longer occurred in the remaining study period.

Due to deterioration, additional oral prednisolone was prescribed within 12 weeks to six patients (75%) in the MP group and five (50%) in the OP group. In none of the treatment groups was additional prednisolone required during the first 2 weeks. A rapidly increasing prednisolone prescription pattern was seen in the MP group during weeks 3 through 6, the maximal dose being reached 6 weeks after the initial treatment (Fig. 3). The OP treated patients reached the maximal dose of concurrent prednisolone by week 10. There was a trend towards increased prednisolone usage in the MPPT group, expressed as the AUC ($P = 0.07$, Mann-Whitney test). In the OP group one patient was admitted to a local hospital for exacerbation of asthma and had been given very large doses of hydrocortisone; this patient was therefore omitted from the analysis of concomitant prednisolone usage.

The MP group tended to use β_2-agonists more extensively (Fig. 4); however, this difference never reached significance by a week-by-week comparison (all $P > 0.05$, Mann-Whitney); neither was any difference shown when expressed as the AUC ($P = 0.29$, Mann-Whitney).

No serious side effects occurred. Reported were euphoria, tiredness, flushing, sleep disturbances, headache, and diarrhoea, stated equally often by both groups. No cardiac side effects occurred in any of the treatment groups.

Measurements of plasma immunoglobulins G, A, M, and E on admission revealed no difference between the groups, and no change could be demonstrated on Days 1, 7, and 14 in any of the groups. On admission, no difference in blood eosinophils between the groups was found. Blood eosinophil values were significantly decreased in both groups on Day 2 compared with the values on admission, but no significant differences were found from Day 7 and during the remaining study period. No changes were found in sodium, potassium, creatinine, ESR, haptoglobin, haemoglobin, neutrophils, lymphocytes, or blood glucose.

DISCUSSION

For some years MPPT has been used as an alternative treatment in immunoreactive diseases (3, 7, 10, 16, 21, 25), in which the clinical effects have been shown to last several weeks. Apart from decreased natural killer cell activity

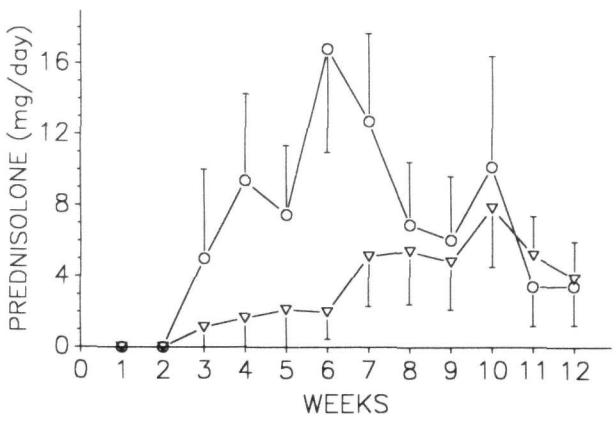

Fig. 3. Concomitant use of prednisolone apart from the study medication in 18 patients treated for acute severe asthma with MP (○) or OP (▽).

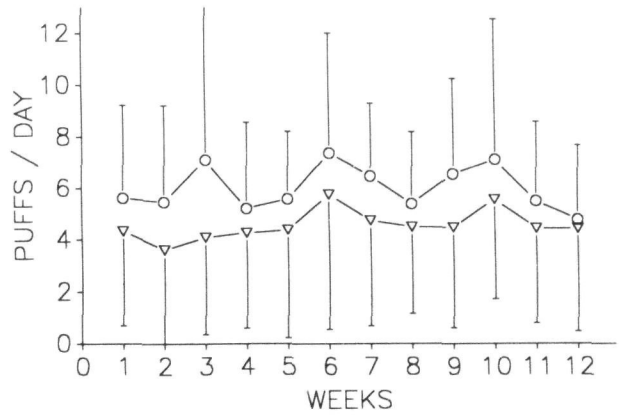

Fig. 4. Use of inhaled $\beta_2$agonist aerosol - recorded as the number of puffs of salbutamol or terbutaline per day - used on an as required basis in 18 patients treated for acute severe asthma with MP (○) or OP (▽).

(17), the exact modes of action of MPPT are still speculative, and the rationale for such megadoses has been questioned (2).

Therapy with glucocorticosteroids (GCS) in acute severe asthma is still up for debate (6, 14). Some investigators have found a significant increase in ventilatory capacity measurements (FEV_1 or FVC) within the first 24 h after the start of GCS therapy compared with placebo (5, 12, 22), even though other studies have failed to show such significant differences in ventilatory capacity between GCS and placebo in the treatment of acute severe asthma (11, 18). Some studies have found a significant difference in parameters other than ventilatory capacity, such as blood gasses (18) or frequency of hospital admissions (11).

Dose-response studies of GCS therapy in acute severe asthma have failed to show any such relation within the first 24 h of treatment (19, 20, 23) except one study including very low doses of MP (13).

In acute severe asthma, MPPT can be expected to be advantageous compared with conventional long-lasting GCS therapy owing to a single dosing schedule with increased patient compliance and a long-lasting effect. The well-known side effects from chronic GCS therapy including weight gain, moon face, decalcification, diabetogenic effect, peptic ulcers, capillary fragility, skin atrophy, and adrenal suppression are probably not seen with MPPT. The side effects of MPPT are of short duration and consist of bradycardia, psychological disorders, and seldom myopathia (13) and anaphylaxis.

The results of this study suggest, however, that no benefit is obtainable by increasing the dose of GCS, administered as MPPT, in the alleviation of acute severe asthma. The methylprednisolone (MP) group had a mean FEV_1 of 33% of predicted at entry and the oral prednisolone (OP) group had an FEV_1 of 43%. There were fewer differences in peak expiratory flow. Half the MP group and only one third of the OP group had been on long-term corticosteroids. All this suggests that the MP group had either more severe asthma in the long term or that the attacks studied were more severe.

At 24 h only one patient in the OP group failed to reach a peak flow of 70%, compared with three in the MP group. The FEV_1 had increased to 66% predicted, compared with 51% in the OP and MP groups, respectively. At 1 week the difference was large, the FEV_1 being 78% predicted in the OP group compared with 54% in the MP group.

That the FEV_1 in both groups reached identical levels at 12 weeks, without major differences in concomitant prednisolone therapy at that time, suggests that the groups had comparable severity of asthma in the long term. Since both groups had increases in FEV_1 % and PEF % during the initial 24 h of identical magnitude, we find the treatments equally effective in the initial phase of acute severe asthma.

Previously, administration of oral prednisolone has been shown to result in maximal serum levels within 15 min of administration (15), which could account for the prompt effect seen in the OP group. Harrison also found no effect of adding administration of intravenous hydrocortisone to oral prednisolone when studying adults with acute severe asthma (8).

A few studies of large doses of GCS in the treatment of acute severe asthma have been reported (19, 20). In a dose-dependent manner, Ratto treated 70 adults with a single bolus of intravenous MP in doses ranging from 160 mg to 1 g (20) and found no dose-response relationship. Raimondi (19) reported the results of a study administering intravenous hydrocortisone 6-hourly during the initial 24 h in a total dose of hydrocortisone 80 mg/kg/day corresponding to approximately methylprednisolone 1.12 g (70 kg person), and compared this with the effect of a lower dose (3). He found no significant differences in either FEV_1 or FEF_{25-75} between the two treatments.

Together with our results, the results of the above-mentioned studies therefore indicate that increasing the dose of GCS above "medium doses" in the treatment of acute severe asthma offers no additional effect when evaluated within the first 24 h.

During the 12 weeks' follow-up period five

patients in the OP-treated group required additional GCS with the maximum dose being reached at week 10. Six of eight patients in the MPPT group deteriorated during the study and required additional prednisolone, five of them within the first 4 weeks. The MPPT group did not reach its maximal ventilatory capacity until after the addition of this supplementary prednisolone. We therefore did not find MPPT superior to oral prednisolone in the long-term protection against exacerbations of asthma.

We felt that the side effects reported during repeated administration of MPPT (24) demand careful judgement. To reduce the risk of cardiovascular and other side effects, we decided to give only one bolus injection of MP instead of three consecutive injections. This does not affect the immediate effect (within 24 h) but might have some influence on the long-term effect.

In conclusion, we did not find MPPT superior to oral treatment with prednisolone in the acute resolution of asthma, or as a long-term protection against new exacerbations. Consequently, in acute severe asthma we cannot recommend the use of MPPT as a substitute for GCS therapy in conventional doses.

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Address:
Thim Engel
Allergy Department 7511
State University Hospital
Tagensvej 20
DK-2200 Copenhagen N
Denmark

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