

Short communication

Plasmapheresis in the treatment of steroid-dependent bronchial asthma

Background: Can plasmapheresis improve disease severity and lung function and reduce steroid doses in severe asthma patients dependent on oral corticosteroids?

Methods: A pilot study with four asthma patients was undertaken using PEF (peak expiratory flow) symptom score, number of puffs of β_2 -agonist, and dose of systemic steroids as disease variables. After at least an 8-week run-in, the patients were randomized to a crossover treatment regimen consisting of either 10 days of plasmapheresis or placebo treatment. Each treatment was succeeded by an 8–26-week follow-up period.

Results: No patients achieved a significant effect of plasmapheresis treatment according to the established criteria, nor did anyone experience deterioration.

Conclusions: Removing humoral factors extensively over a 10-day period did not significantly influence the clinical condition of the four steroid-dependent asthma patients studied. Circulating humoral factors seem to be of little importance for the maintenance of the established chronic allergic inflammation in these patients. Plasmapheresis does not seem to be a treatment option for this patient category.

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Key words: plasmapheresis; steroid-dependent asthma.

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Accepted for publication 7 August 2001

Patients with severe chronic bronchial asthma need therapy, including systemic corticosteroids, either regularly or in frequently repeated courses at the considerable risk of severe side-effects. At present, the use of low-dose cytostatic (i.e., methotrexate) or immunosuppressive (cyclosporin A) drugs have been advocated as corticosteroid-sparing treatments (1–6). However, studies on methotrexate disagree on the effect on disease variables and side-effects (2–4, 7–11) and side-effects of cyclosporine are of considerable concern (12, 13).

Present knowledge of the pathogenesis of severe chronic asthma includes the concept of chronic allergic/eosinophil inflammation in the bronchial mucosal wall (14). Several humoral factors (complement, antibodies, cytokines, chemokines, etc.) are thought to contribute to the local inflammatory processes. Hypothetically, removing such factors from the circulation for a sufficient period of time would improve the clinical condition and consequently reduce the need for anti-inflammatory medication. The side-effects and risks of plasmapheresis are thought to be less serious than those of the alternative steroid-sparing therapies.

Based on a few reports of the efficacy of plasmapheresis in the treatment of severe bronchial asthma (1, 15, 16), this study aimed to validate a double-blind, crossover treatment protocol, including extensive plasmapheresis in a pilot population with steroid-dependent bronchial asthma.

Material and methods

Patients

Four patients suffering from bronchial asthma, as defined by the National Heart, Lung, and Blood Institute (17), and dependent on systemic steroids were included in the study. The criteria of systemic steroid dependence were met if the patient during the last year prior to the study had:

- 1) six or more periods using systemic steroids for 14 days or more starting at a dose equal to or above 30 mg per day of prednisolone, or
- 2) had been using systemic steroids constantly.

During the year prior to the study, all the patients had a documented variation in PEF or FEV₁ of 20% or more related to their best performance. They did not suffer from other chronic diseases, none of the women were pregnant, and the patients were all nonsmokers. A short patient presentation follows.

Patient no. 1. Male, born 1946. Asthma since 1982. At inclusion, using betamethasone 2 mg/day. Total IgE 429 kU/l. During run-in, FVC 2.45 l (52%), FEV₁ 1.77 l (47%).

Patient no. 2. Female, born 1975. Asthma since 1980. At inclusion, using prednisolone 10 mg/day. Total IgE 1930 kU/l. During run-in, FVC 3.30 l (75%), FEV₁ 2.60 l (67%).

Patient no. 3. Female, born 1954. Asthma since 1974. At inclusion, had for a short time stopped taking systemic steroids. Total IgE 101 kU/l. During run-in, FVC 2.89 l (84%), FEV₁ 2.00 l (67%).

Patient no. 4. Female, born 1959. Asthma since 1961. At inclusion, using prednisolone 60 mg/day. Total IgE 925 kU/l. During run-in, FVC 1.78 l (55%), FEV₁ 1.68 l (60%).

During the run-in period, chest radiographs and bronchoscopy were normal in all patients.

Study design

After inclusion, each patient was studied for five consecutive periods:

- 1) run-in period of at least 8 weeks to achieve basic values of disease variables
- 2) a period of 2 weeks to administer plasmapheresis treatment
- 3) effect evaluation period for 8–26 weeks after the treatment period
- 4) a 2-week placebo period
- 5) effect evaluation period for 8–26 weeks after the placebo period.

The order of periods 2) and 4) was randomized and blinded to the patients and the monitoring physician.

During the run-in and the effect evaluation periods, the patients had clinical appointments every 2 weeks. At the last appointment before and the first after each treatment period, blood tests were taken for hematology, C-reactive protein (CRP), electrolytes, renal and liver function, total immunoglobulin E (IgE, [Pharmacia CAP-FEIA, Pharmacia Diagnostics, Uppsala, Sweden]) and the ratio CD4/CD8. Spirometry for FVC and FEV₁ was done (SMI III Spirometer, Spirometrics, Inc., Auburn, ME, USA). Every morning and evening during the whole period, the patients registered three PEF measurements (mini-Wright Peak Flow Meter, Clement Clarke International Ltd, London, UK), symptom score, number of doses of β_2 -agonist since last registration, and dose of systemic steroids. The morning symptom score was registered according to a stepwise scale of numbers from 0 to 4, 0 meaning "No symptoms" and 4 meaning "Symptoms preventing sleep". Similarly, the evening symptom score was registered according to a number scale from 0 to 5, 5 meaning "Symptoms severe enough to make you stay at home from work and avoid usual activities".

At each appointment, the highest values of the recorded morning and evening PEF were extracted, and their mean values for the period since last visit were calculated. The mean values of the symptom score and number of puffs of β_2 -agonist in the morning and evening were similarly calculated, as was the mean daily dose of systemic steroids.

We regarded a treatment effect to be achieved if the following criteria were met during the last 2 weeks: mean values for PEF were increased by at least 20%, the number of β_2 -agonist doses was reduced by at least 20%, the symptom score was reduced by at least 1 score point, and the dose of systemic steroids was reduced by at least 20%. All calculations were compared to the respective mean values of the run-in data. If the treatment effect was achieved, the effect evaluation was continued either until the treatment effect disappeared or for a maximum of 26 weeks.

Plasmapheresis and placebo

During the 2-week treatment period, the patients received plasmapheresis through a double lumen catheter in the femoral vein once every day except Saturday and Sunday. Each plasmapheresis withdrew 4 l of plasma through a single filter (Fresenius P2S, Fresenius Medical Care, Bad Homburg, Germany) and was replaced by 4 l of albumin solution 40 g/l (Octapharma PP GmbH, Vienna, Austria). During the placebo plasmapheresis, the same procedure was followed except that plasma was not withdrawn and replacement was not given. The plasmapheresis apparatus (ADM 08, ABM

Fresenius, Fresenius Medical Care, Bad Homburg, Germany) was completely covered so that the patient could not observe whether active or placebo plasmapheresis was taking place.

Statistics

For the measurements (PEF morning, PEF evening, PEF_E-PEF_M, symptoms morning, symptoms evening, and number of doses of β_2 -agonists), individual means with 95% confidence intervals were calculated for each of the three periods of observation. In addition, individual means with confidence intervals were calculated for the percentage of predicted FEV₁ during the same periods. The statistical analyses were done by SPSS 9.0 for Windows (ISBN 0-13-020401-3, SPSS Base 9.0 Application Guide).

Ethics

The study protocol was approved by the regional ethics research committee. Written informed consent was obtained from each patient before admission to the study.

Results

Effects

Fig. 1 shows the mean values for PEF, symptom score, number of puffs of β_2 -agonist, and the mean daily dose of systemic steroids recorded by the patients during the run-in and the observation periods. None of the patients achieved a treatment effect after active treatment; however, patient 3 showed a treatment effect after placebo plasmapheresis. Regarding the use of systemic steroids, patients 1 and 2 had unchanged doses during all periods, while patient 4 had a dose reduction of approximately 50% after the active plasmapheresis and patient 3 reduced the dose by more than 80% after the placebo plasmapheresis.

None of the patients deteriorated significantly during any of the observation periods. The blood test values, including the CD4/CD8-ratio and IgE, showed no significant change during the study period or before and after plasmapheresis in any of the subjects. FEV₁ did not change significantly in any of the patients.

Side-effects

One patient experienced an infection at the site of the catheter on one occasion. This was treated effectively by local antibiotics and did not cause any delay in the treatment program.

Discussion

This was a pilot study with a design made to look for marked effects of plasmapheresis in steroid-dependent asthmatic patients, and patients were their own control. The number of patients participating in the study was small.

The cost of plasmapheresis is approximately \$1000 a day, and it immobilizes the patient during the treatment period. If plasmapheresis were to be of use in steroid

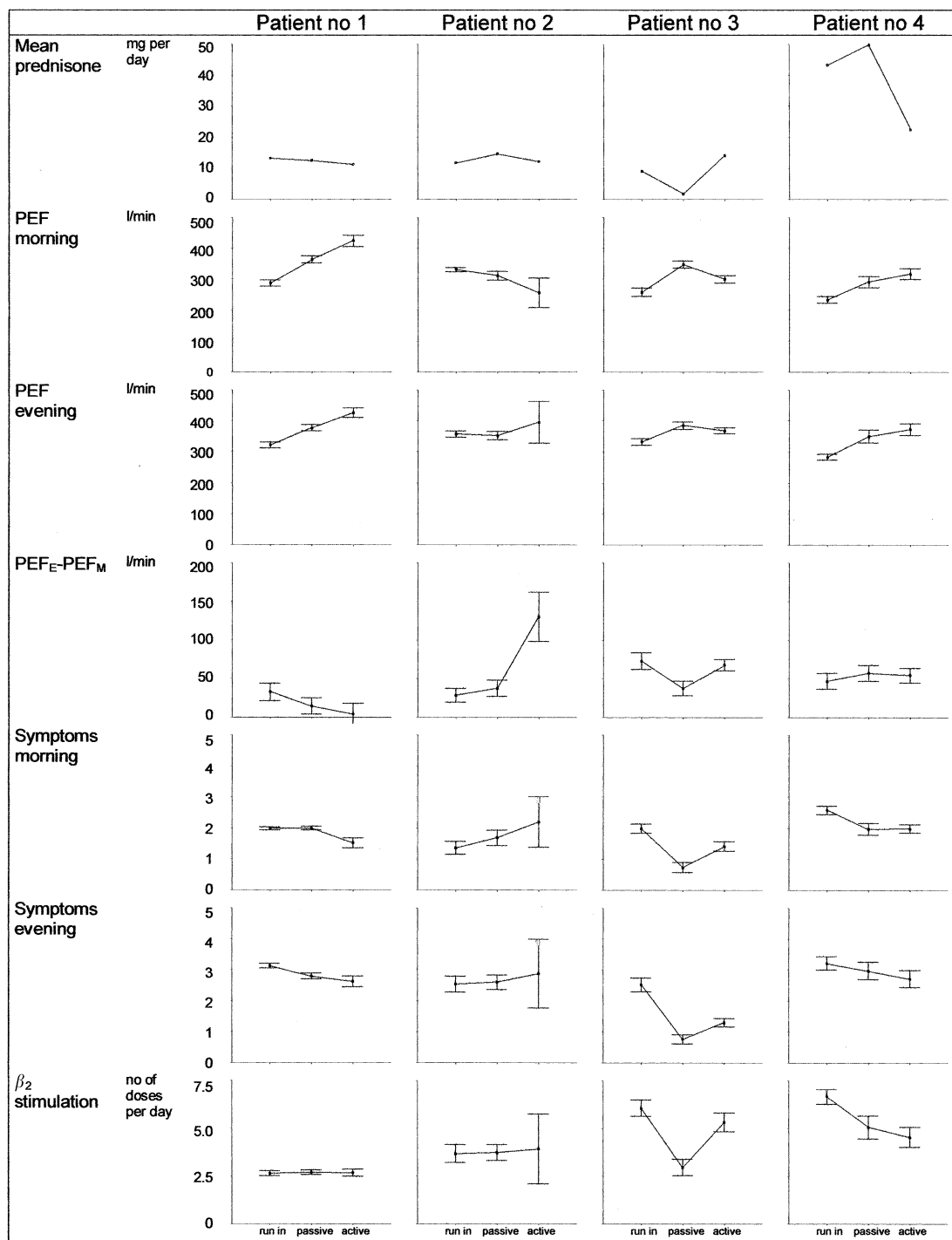


Figure 1. For each subject, mean values with 95% confidence intervals during run-in and observation periods after placebo and active treatment are shown for daily doses of systemic steroids, PEF morning (PEF_M), PEF evening (PEF_E), difference PEF_E-PEF_M, symptom score in morning, symptom score in evening, and number of puffs of β_2 -agonist during day. As patient 1 used Celeston (betamethasone), dose of prednisone was estimated by assuming Celeston 0.75 mg to be equal to prednisone 5 mg.

dependent asthma, the effect should be marked, and therefore the criteria of effects were put on a high level. No such effects were found in this pilot study.

According to clinical data from previous years, patient 4 would most probably improve during the summer season. However, the reduction in dose of

steroids seen during the study was somewhat greater than expected, and we cannot exclude that she had a partial treatment effect.

Plasmapheresis takes away humoral factors in the blood, while cells and factors attached to cells remain in the circulation. Our results indicate that plasmapheresis

has no marked influence on the inflammatory activity of the airways mucosa. The interpretation may be either that circulating inflammatory factors are unimportant and that the inflammation is pacing itself, or that it is paced by cells or/and factors attached to the formed corpuscles of the blood. The former alternative, locally produced and locally working inflammatory factors including IgE, has recently been suggested as a pathogenetic mechanism of the inflammation affecting patients suffering from intrinsic asthma (18).

In conclusion, this pilot study shows that extensive plasmapheresis with a total plasma exchange of 40 l during 10 consecutive days seemed to have no significant clinical effect on patients with steroid-dependent bronchial asthma. Thus, circulating humoral factors seem to be of little importance for the maintenance of

the established chronic inflammation in these patients. In view of the lack of benefit and the cost of treatment, plasmapheresis does not seem to be a potential alternative treatment in patients with steroid-dependent bronchial asthma.

Acknowledgments

This study was made possible by financial support from AstraZeneca Norway AS, Glaxo Wellcome AS, and the Norwegian Heart and Lung Association. The albumin solutions were supplied by Kabi Pharmacia. We thank Dr C. M. Lockwood for advice on the method of plasmapheresis, and the staff of the Dialysis Unit, Medical Department of Haukeland University Hospital, for skillful performance of active and placebo plasmapheresis.

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