

Case report

Do inhaled steroids have similar efficacy? A case of bronchial asthma suggesting different efficacy of inhaled glucocorticosteroids

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We report a 35-year-old woman who had had bronchial asthma for 17 years. Her asthma worsened and became unstable on treatment with beclomethasone dipropionate (BDP), budesonide (BUD), and oral glucocorticosteroids (GC). At the age of 31, she had participated in a clinical trial with fluticasone propionate (FP), and after 2 weeks' treatment her asthma was well controlled. Because of pregnancy, her participation was terminated and treatment continued with available inhaled GC; however, the disease deteriorated and treatment with FP was resumed 2 years ago. Lung function normalized after 3 weeks and she has remained clinically stable since.

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Chronic inflammation is a dominant feature in bronchial asthma. Anti-inflammatory treatment with glucocorticosteroids (GC) has been used for many years and is considered effective and well tolerated in all degrees of severity of the disease. The potency of different topical GCs differs although this has no influence on efficacy in the lung. This has placed the focus primarily on the development of inhaled steroids with a higher therapeutic ratio, e.g., ratio between wanted and unwanted effects. Still, differences in efficacy may exist among inhaled steroids.

Case history

The patient was a 35-year-old woman. As a child, she had no atopic manifestations. At the age of 18, she started working on a farm, but soon experienced symptoms of rhinitis and cough, when she was in the stables. At the same time, she started smoking about 10 cigarettes daily.

Three years later, now 21, she gave up farming due to persistent cough as well as wheeze and rhinitis. Allergologic investigations showed increased s-IgE

(260 kU/l), and a normal count of blood eosinophils. Skin prick tests gave a positive reaction for dog, but the radioallergosorbent test (RAST) was negative for dog, horse, cow, pig, and storage mites. Histamine challenge showed a PC₂₀ of 8 mg/ml (normal > 8 mg/ml), and FEV₁ was 4.2 l (predicted normal 4.0 l). After having stopped farming, she trained as a nursery-school teacher and obtained a job in a boarding school. Unfortunately, there were stables with horses at the school.

Two years later, now 27, she was again referred to our clinic because of worsening asthma. Her treatment consisted of beclomethasone dipropionate (BDP) 200 µg daily, and salbutamol spray 0.1 mg prn. The BDP dose was increased to 400 µg daily and theophylline 250 mg twice daily was added, and the patient stopped smoking.

She responded well with symptom control. After a pregnancy in 1986, her asthma worsened. FEV₁ was 1.4 l. Treatment was increased to BDP 500 µg three times daily and terbutaline slow-release tablets 7.5 mg twice daily, but she still used rescue salbutamol 0.2 mg 6–8 times daily. Diary peak expiratory

flow (PEF) showed considerable variation; morning values were around 350 l/min, and evening values 500 l/min.

She improved somewhat and FEV₁ was 3.9 l. For the next 2 years, her condition was acceptable, and her medication needed only small adjustments.

In 1989, when the patient was aged 30, symptoms worsened and were present both day and night. The treatment was stepped up to BDP 2000 µg/day and salbutamol 0.2 mg prn. FEV₁ was 2.9 l. Skin prick test was positive and RAST was negative for *Der-matophagoides pteronyssinus*, *D. farinae*, and *Acarus siro*. Blood eosinophil count was normal ($0.36 \times 10^9/l$) and s-IgE still elevated (208 kU/l). She met the criteria for inclusion in an open study with fluticasone propionate (FP) 2000 µg/daily and agreed to participate. After a 2-week run-in period on her usual medication, FEV₁ was 2.7 l, and PEF was 350 l/min.

The treatment with FP was highly effective. After 2 weeks' treatment, FEV₁ was 4.0 l and PEF was 470 l/min. After a further 2 weeks, her symptoms had disappeared, FEV₁ was 4.5 l, and PEF 510 l/min. After 9 weeks, FEV₁ was 4.6 l and PEF 520 l/min. FP was reduced to 1500 µg/day, and 4 weeks later again reduced to 1000 µg/day. FEV₁ was 4.6 l and PEF 510 l/min.

After 15 weeks of treatment with FP, she informed us that she was pregnant, and she had to be withdrawn from the study. The medications and FEV₁ values from this period are shown in Fig. 1.

The FP treatment was terminated and treatment continued with budesonide (BUD) 1600 µg/day. Ten weeks later, her asthma worsened. FEV₁ was 1.5 l, and prednisolone (PRD) 25 mg/day was added. After 3 weeks, FEV₁ was 4.5 l, and PRD treatment was stopped. Two weeks later, FEV₁ was 3.7 l and PEF about 350 l/min. During the remainder of the pregnancy, her asthma stabilized. In May 1990, she gave birth to a healthy boy.

After birth, her asthma symptoms worsened, and FEV₁ was 1.9 l. She had almost no improvement in lung function after administration of an inhaled

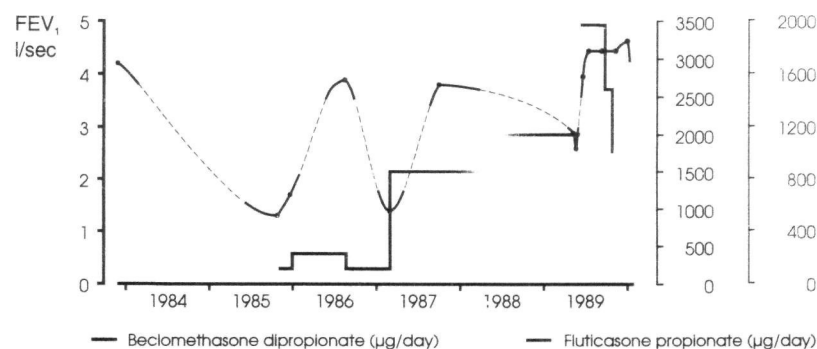


Fig. 1. FEV₁ and daily dose of inhaled glucocorticosteroids: — beclomethasone dipropionate (µg/day); fluticasone propionate (µg/day); ● FEV₁ (l/s) (bullet = observed values, dotted lines = expected course).

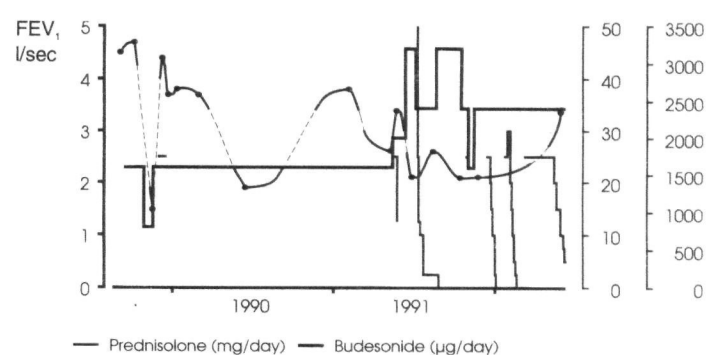


Fig. 2. FEV₁ and daily dose of glucocorticosteroids: — prednisolone (mg/day); budesonide (µg/day); fluticasone propionate (µg/day); ● FEV₁ (l/s) (bullet = observed values, dotted lines = expected course).

beta-2 agonist. PRD 40 mg/day was added with good results, and after some weeks the treatment could be stopped. The next year, her asthma was acceptably controlled, but in May 1991 she caught a cold; consequently, her asthma deteriorated. FEV₁ was 2.6 l, and a short course of PRD was started with 25 mg/day. The daily dose of BUD was increased to 2000 µg/day. After 2 weeks, FEV₁ was 3.4 l, but she still had asthma symptoms, especially in the morning and at night. She tried salbutamol slow-release tablets with no effect. BUD was increased to 3200 µg/day, but after a few weeks it was necessary to start PRD 50 µg daily due to decreasing FEV₁ (2.1 l).

In October 1991, now 32 years of age, she tried treatment with salmeterol without improvement, and the treatment was stopped.

In December 1991, she started PRD, but became discouraged when, despite continued oral PRD and a high dose of inhaled GC, she still had disabling asthma. She asked for FP, which earlier had resulted in a good response. At the time, FP was not available in Denmark as a commercial drug, but the producer agreed to supply her with FP on a specified basis.

The medications and FEV₁ values in the period between FP treatments are shown in Fig. 2.

On 29 May 1992, when the patient was 33, inhaled GC was changed to FP 2000 µg daily. FEV₁ was 3.4 l. Plasma cortisol before and 30 min after stimulation with tetracosactide (ACTH, Synacthen®) 0.25 mg i.m. was assessed 3 weeks after initiation of FP and every third month thereafter. The first baseline plasma cortisol was 3 nmol/l before and 76 nmol/l 30 min after stimulation with synthetic ACTH.

During the first week of treatment, an increase in PEF and a decrease in symptom score were observed, and PRD was stopped after 6 days. After 3 weeks of treatment, FEV₁ was 4.7 l and PEF morning and evening was around 500 l/min. The total daily symptom score was 0.

After 2 months of treatment with FP, she complained of pharyngeal irritation, but after a few days'

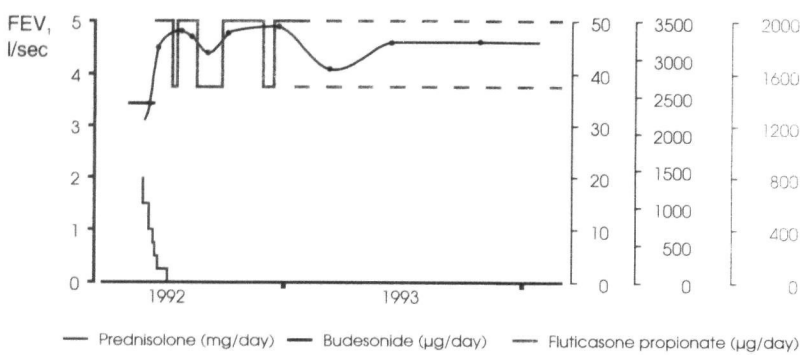


Fig. 3. FEV₁ and daily dose of glucocorticosteroids: — prednisolone (mg/day); — fluticasone propionate (µg/day); — FEV₁ (l/s) (bullet = observed values, lines = expected course).

antifungal therapy, these symptoms disappeared. The daily dose for the optimal efficacy was adjusted to 1500 and 2000 µg on alternate days.

The medications and FEV₁ values after FP was reintroduced are shown in Fig. 3.

After 3 months' treatment, plasma cortisol was increased. Serum cortisol before and after ACTH stimulation during 2 years' treatment with FP is shown in Table 1.

The patient is now aged 35. Her condition has been stable for 2 years, and she has no local side-effects. Before treatment was started, she worked only part time and considered early retirement because of asthma. Now she is employed full time without any problems. She also participates in various sports; this was impossible before. During the first year of treatment with FP, antibiotic treatment was necessary once, for acute bronchitis with expectoration and fever. During this episode, her asthma was unaffected.

Discussion

Since the early 1970s, inhaled GC has represented a significant therapeutic advance in the treatment of asthma. Severe asthma requires high doses of GC to control the inflammatory process. It should be mentioned that for all inhaled drugs a large proportion (70–90%) of the delivered dose is swallowed. The two most commonly used inhaled GCs, BDP and BUD, are recommended in doses up to 2000 µg/day. For patients with severe asthma, this dose is often too low to control the inflammatory response, and it is necessary to add oral steroids. Daily doses of

inhaled GC above 2000 µg/day increase the number of local side-effects and the cost considerably, although the therapeutic ratio always favors inhaled therapy. Consequently, it is necessary to develop new GCs with a more favorable ratio between therapeutic effects and systemic side-effects.

We do not know whether this extraordinarily good clinical response was patient specific and limited to this case. The extremely good response in this case could not be explained either fully or partially by the placebo effect. On two separate occasions, salmeterol had been tried without either any subjective or measurable effect, in spite of the fact that the expectations of the drug were great.

It is well known that asthmatic patients experience great variability in their symptoms. Our patient felt that the condition was chronically unstable with some worsening connected with infections. Her job as teacher involved great exposure to infectious agents. This exposure had seasonal variation, but no seasonal influence on her asthma could be observed during the last year on BUD (1991–2). There was no worsening during the winter when the incidence of infections is greatest.

It seems unlikely that her GC receptors should be unique, and FP may be of value in other cases of asthma difficult to control with available therapy. Tissue retention of FP seems high, and the affinity of FP for the human GC receptor is about 18 times that of dexamethasone and three times that of BUD (3). FP has twice the anti-inflammatory activity of BDP in the McKenzie skin vasoconstriction assay in man (1). Such factors may have been of importance for the favorable response.

Our patient always complied with treatment regimens. Her inhalation technique was optimal, and record cards and use of prescriptions show her compliance with drug regimens to be unquestioned.

Our case demonstrates that FP was effective in the treatment of severe unstable asthma, as compared to other steroids. This was first observed when the patient participated in a large multicenter study testing high-dose FP. The individual response to different corticosteroid molecules may vary (2). It is necessary in larger populations of patients with severe asthma to find out whether a proportion of patients might have an extremely good response to FP. Large studies in "difficult-to-manage patients" are very difficult to organize and perform partly be-

Table 1. Plasma cortisol levels (ng/l) before and 30 min after stimulation with ACTH

	Jun 1992	Aug 1992	Oct 1992	Feb 1993	Jun 1993	Oct 1993	Feb 1994	Jun 1994
Baseline	3	135	29	157	110	35	117	34
After ACTH	76	316	164	510	360	166	285	172

cause of the heterogeneity of this population. Multi-center studies on severe and oral-steroid-dependent patients are in progress, but the results are still not public.

The side-effects observed (hoarseness and a single episode of oral candidiasis) have been negligible. The considerable suppression of the hypothalamo-pituitary adrenal (HPA) axis before treatment was started was due to the long-term treatment with an oral steroid. After 9 months of treatment, the HPA function had normalized, but has lately shown signs of slight suppression.

Our patient can now live an active life like people without asthma. She is employed full time in the

same kindergarten. Last year, she even made her first parachute jump.

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