

From the Otopathological Laboratory, University ENT Department
(head: H. K. Kristensen, M.D.) and
the Medical Out-patients' Clinic, Division for Allergic Diseases,
(head: Egon Bruun, M.D.), Rigshospitalet, Copenhagen, Denmark.

BECLOMETHASONE DIPROPIONATE AEROSOL EFFECT ON THE ADRENALS IN NORMAL PERSONS

By

NIELS MYGIND & IB HANSEN

In the treatment of bronchial asthma with corticosteroids it is well known that a suppression of the hypothalamo-pituitary-adrenal (H.P.A.) function may be a serious side-effect, which to a certain degree limits the use of these drugs. To avoid the systemic effects it has for several years been tried to apply different corticosteroids locally in the lungs by means of an aerosol (7, 9). Neither with hydrocortisone, prednisolone (7) nor dexamethasone (9) has it been possible to demonstrate, that the local treatment gives a more optimal ratio between clinical effect on bronchial asthma and systemic side-effects. However, this seems to be the case with the new corticosteroid aerosol, beclomethasone dipropionate, as several investigations show increased plasma-cortisol values in patients, who from treatment with prednisone by mouth are transferred to beclomethasone dipropionate aerosol (b.d.a.) (1, 2, 3, 4,).

It is maintained that only doses of b.d.a., which are 5 times the recommended therapeutic dose of 400 μ g daily, has a suppressive effect on the H.P.A. axis (6). As information on this point is relatively scarce we have examined the suppressive effect in normal, non-allergic persons of daily doses of 400 μ g, 800 μ g and 1.600 μ g b.d.a.

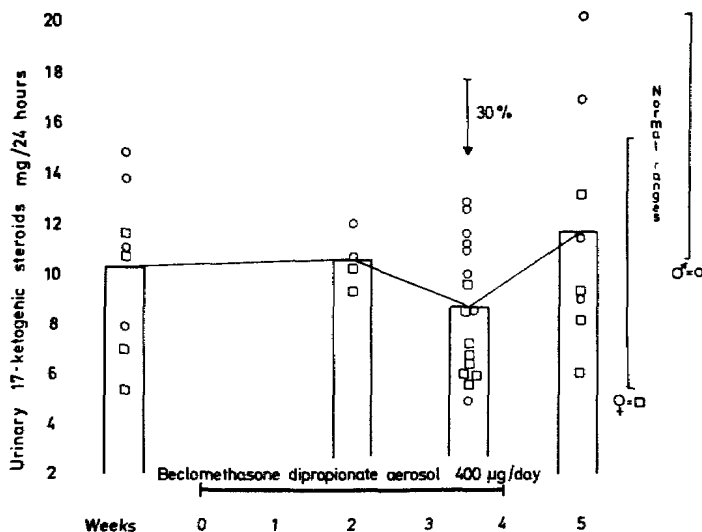


Fig. 1.

Urinary 17-ketogenic steroids before, under and after treatment of normal persons with 400 µg beclomethasone dipropionate aerosol daily for 4 weeks.

MATERIAL AND METHODS

Members of the medical staff at Rigshospitalet and personnel from "Glaxo" (the Danish distributor of b.d.a.) volunteered for the trial. 3 women and 9 men of the age of 25–35 years participated. All were in good health and had never taken corticosteroids before. In all cases the commercial Becotide® aerosol was used, which according to the directions for use gives 50 µg b.d. per inhalation. 4 persons had 400 µg (2 inhalations 4 times a day), 4 had 800 µg (4 inhalation 4 times a day) and 4 had 1.600 µg (4 inhalations 8 times a day) daily for 4 weeks. All were given a form in which every use of the aerosol was to be stated to make sure that each participant took the daily stipulated amount of b.d. The first day of inhalation was marked "day 1" and the last "day 28", and the hormone analyses were carried out as described below. For the estimation of 17-ketogenic steroids samples of urine were collected between 8 AM and 8 AM on day -4, -3, 14, 23, 24, 25, 26, 35 and 36. The analyses were carried out as double-estimations according to the method described by Few (5). Between 9.30 AM and 10.00 AM on day -3 and day 24 samples of blood were taken for the estimation of 11-hydroxy corticosteroids. The analyses were carried out

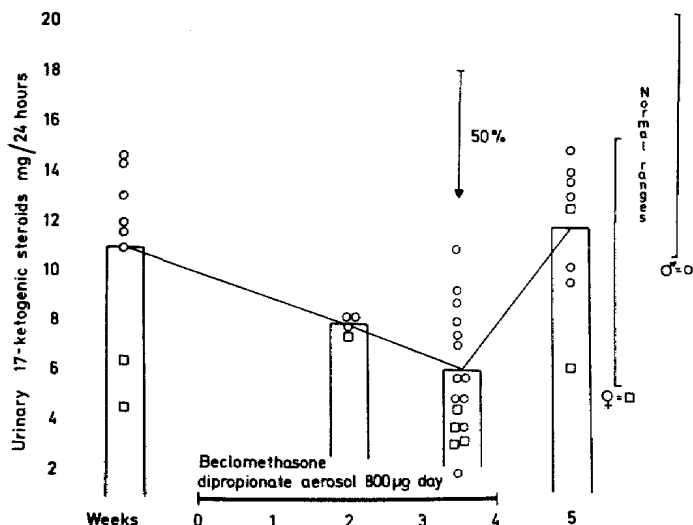


Fig. 2.

Urinary 17-ketogenic steroids before, under and after treatment of normal persons with 800 μ g beclomethasone dipropionate aerosol daily for 4 weeks.

as described by Mattingly (10). Weight and blood-pressure were continuously controlled and all urine samples were tested for glucose and protein.

RESULTS

One person was removed from the trial and replaced by another as she after 14 days of treatment had an acute infection around a tooth (parulis). It is, however, not possible to decide whether this had any connection with the use of the aerosol, as the person in question several times previously had had similar infections. 5 complained of a feeling of dryness in the throat and sometimes a dry cough, specially in connection with common colds. During the treatment a slight fonasthenia in one person was so aggravated that it undoubtedly would have prevented a continued use of the aerosol.

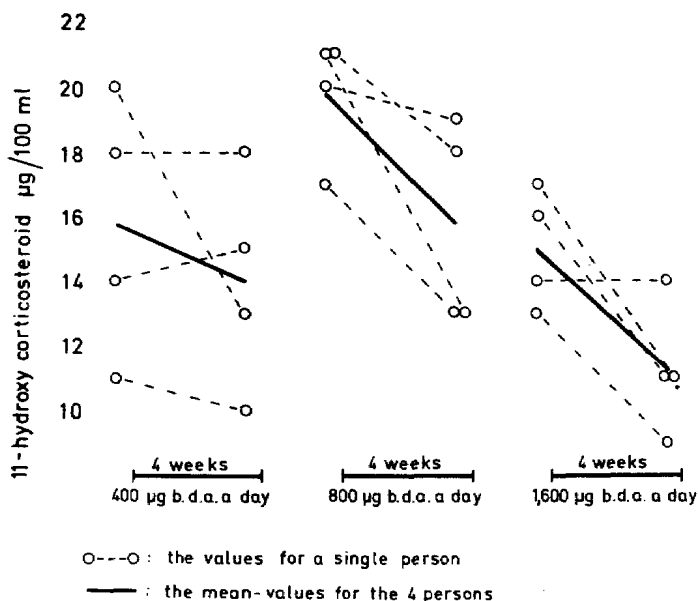


Fig. 3.

11-hydroxy corticosteroids before and under treatment of normal persons with beclomethasone dipropionate aerosol (b.d.a.) for 4 weeks.

No change of weight or blood-pressure could be shown during the treatment nor any glucosuria or proteinuria. The results of the hormone analyses can be seen from Table 1 and Fig. 1-3. In all persons who had 800 μg and 1,600 μg b.d. there is a decrease in 17-ketogenic steroids of 50 per cent on an average. This is seen when one compares the 4 estimations in the last week of treatment with the two estimations before and the two estimations after treatment (Fig. 2). The single analysis after 14 days does not, however, disclose this decrease in all persons. The estimations of 11-hydroxy corticosteroids in serum are too few to allow an independent statistic calculation, but the tendency is in accordance with what has been found by the urine analyses (Fig. 3).

TABLE 1

The Urine 17-Ketogenic Steroid Values in Normal Persons Before, Under and After Treatment with Beclomethasone Dipropionate Aerosol (b.d.a.) for 4 Weeks.

day	-4	-3	14	23	24	25	26	35	36
400 µg b.d.a. daily									
♀	11,6	10,7	10,1	7,1	6,6	6,4	9,5	6,0	9,2
♀	5,4	7,0	9,2	5,6	8,4	6,0	5,9	13,1	8,1
♂	13,8	7,9	10,6	12,7	11,5	11,1	10,9	19,8	15,9
♂	14,8	11,0	11,9	8,5	12,5	9,9	4,9	11,4	9,0
mean	11,4	9,2	10,5	8,5	9,8	8,4	7,8	12,6	10,6
800 µg b.d.a. daily									
♀	6,4	4,5	7,3	3,0	3,7	4,4	3,1	6,0	12,5
♂	14,3	11,6	8,1	8,7	7,9	9,1	10,8	13,9	12,9
♂	11,9	13,0	7,7	1,8	4,8	3,7	5,7	9,5	10,1
♂	14,5	10,9	8,2	7,4	7,0	5,7	4,8	13,6	14,8
mean	11,8	10,0	7,8	5,2	5,9	5,7	6,1	10,8	15,1
1.600 µg b.d.a. daily									
♂	14,7	11,8	12,5	5,8	7,4	8,8	5,0	12,6	9,7
♂	16,6	12,9	13,4	10,4	7,6	6,6	7,7	10,8	12,8
♂	8,4	8,5	6,7	4,6	6,0	5,6	7,3	8,6	11,4
♂	8,4	11,3	4,8	5,2	6,3	5,8	4,0	13,2	14,1
mean	12,0	11,1	9,4	6,5	6,8	6,7	6,0	11,3	12,0

If one compares the 4 17-ketogenic steroid values in the last week of treatment with the two values before and the two values after treatment, also in patients who inhaled 400 µg daily, a slight decrease of about 30 per cent is seen. Statistical calculations (Wilcoxon's sign-rank test) show that the decrease is significant ($0.05 > p > 0.02$), but it is hardly permissible to draw too definite conclusions based on examination of only 4 persons, when there is no clear, common tendency as the case is with 800 µg and 1.600 µg. In all persons the hormone analyses were normal one week after the treatment was discontinued. It must be emphasized that there was

full agreement between the results from members of the medical staff at Rigshospitalet and the personnel from "Glaxo".

DISCUSSION

The slight local irritation in the throat occurring in some normal persons who inhaled b.d. especially in larger doses, is undoubtedly due to the aerosol propellant. It was, however, characteristic that the inconveniences in form of irritation and dry cough became more pronounced in connection with common colds. This may cause some asthmatic patients to discontinue the aerosol or reduce the doses in connection with an respiratory tract infection. It is therefore important to inform the patients regarding this matter and to instruct them to take corticosteroids by mouth, if they are not able to use the aerosol.

Examining healthy volunteers Harris et al. (6) found that inhalation of 1.000 μg b.d. a day for periods of up to 28 days caused no change in the plasma cortisol values, and they concluded that with doses below 1.000 μg daily a suppression of the H.P.A. axis is unlikely to occur. This is not in accordance with the results of our investigations. These show that 800 μg have a quite clear suppressive effect, and they also indicate a slight suppressive effect even at the therapeutically recommended dose of 400 μg a day. A possible explanation of this discrepancy is that Harris et al. used plasma cortisol estimations, and we mainly 17-ketogenic steroids in urine. Harris et al. also mention that inhaled doses between 600 and 2.000 μg a day for two-day period lead to some reduction in the urinary 17-ketogenic steroid rate.

In investigations in which normal persons have to take a drug several hundred times, it is of paramount importance for the results that the persons are motivated for the trial and are under constant control. In our trial the test-persons participated out of interest for the trial, and there was daily contact between and control of the participants.

Patients with bronchial asthma and airways obstruction are

not always able to inhale an aerosol as normal persons and furthermore these patients on their bronchial mucosa may have a thick layer of mucus, which will impair the penetration of b.d. It is therefore possible that more b.d. is absorbed in normal persons than in patients with bronchial asthma. This is in agreement with the fact that some authors (1, 4, 8) could not show any biochemical evidence of adrenal suppression in patients who inhaled 400 μ g b.d. a day.

Based on previous investigations on the suppressive effect of different doses of prednisone by mouth (11, 12) and in comparison with our results, it must be concluded that the therapeutically recommended dose of 400 μ g b.d.a. a day corresponds to maximally 3-4 mg prednisone by mouth as regards suppressive effect. If the b.d.a. treatment is instituted as a supplement to treatment by mouth one must therefore demand a reduction of 5 mg prednisone or more. When only the 400 μ g b.d.a. is given the risk of systemic side-effects is negligible. The risk of increased frequency of infections especially with fungus in the throat and in the respiratory tract and the risk of degeneration of the elastic fibrils in the bronchial wall are still unknown in longterm treatment with an extremely potent corticosteroid preparations as b.d.a.

SUMMARY

The suppressive effect on the hypothalamo-pituitary-adrenal axis of different doses of beclomethasone dipropionate aerosol was examined in 12 normal persons. 4 persons inhaled 400 μ g (the recommended therapeutic dose), 4 inhaled 800 μ g and 4 inhaled 1.600 μ g daily. In all persons who had 800 and 1.600 μ g daily a partial suppression could be demonstrated and the 17-ketogenic steroids in the urine decreased at about 50 per cent during the treatment. Even with 400 μ g the results indicated a slight suppression on the adrenals. It is concluded that the risk of systemic side-effects is negligible when the only corticosteroid treatment is 400 μ g beclomethasone dipropionate aerosol a day. If this treatment is given together with

oral corticosteroid treatment the suppressive effect of the aerosol corresponds to maximal 3-4 mg prednisone by mouth.

REFERENCES

1. Brown, H. M., Storey, G. & George, W. H. S. (1972): *Brit. med. J.* *1*, 585-590.
2. Chatterjee, S. S., Ross, A. E., Carroll, K., Harris, D. M. & Butler, A. G. (1972): *Current Medical Research and Opinion* *1*, 173-181.
3. Choo-Kang, Y. F. J., Cooper, E. J., Tribe, A. E. & Grant, I. W. B. (1972): *Brit. J. Dis. Chest.* *66*, 101-106.
4. Clark, T. J. H. (1972): *Lancet* *1*, 1361-1364.
5. Few, J. D. (1961): *J. Endocrin.* *22*, 31-46.
6. Harris, D. M., Martin, L. E. & Tanner, R. J. (1973): *Brit. med. J.* *1*, 111.
7. Herxheimer, H. (1973): *Lancet* *1*, 374-375.
8. Lal, S., Harris, D. M., Bhalla, K. K., Singhal, S. N. & Butler, A. G. (1972): *Brit. med. J.* *3*, 314-317.
9. Makino, S., Miyamoto, T. & Oshima, Y. (1972): *Acta allergol.* *27*, 364-371.
10. Mattingly, D. (1962): *J. clin. Path.* *15*, 374.
11. Westerhof, L., van Ditmar, M. J., der Kinderen, P. J., Thijssen, J. H. H. & Schwarz, F. (1970): *Brit. med. J.* *4*, 534-537.
12. Wood, J. B., Frankland, A. W., James, V. H. T. & Landon, J. (1965): *Lancet* *1*, 243-245.

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