Br. J. clin. Pharmac. (1983), **15**, 419–422

ACUTE DOSE-RESPONSE STUDIES IN BRONCHIAL ASTHMA WITH A NEW CORTICOSTEROID, BUDESONIDE

R. ELLUL-MICALLEF[1] & S.A. JOHANSSON[2]

[1]Department of Pharmacology, University of Kuwait, Kuwait and [2]Medical Department, AB DRACO, Lund, Sweden

1 Budesonide is an epimeric mixture of a new synthetic non-halogenated glucocorticoid (16α, 17α,-(22R,S)-prophylmethylenedioxypregna-1,4-diene-11/3,21-diol-3,20-dione).

2 Acute dose response studies with three different inhaled doses of budesonide, have been carried out in a group of 12 chronic asthmatic patients.

3 The lowest dose (100 μg) of inhaled budesonide produced a more marked effect in relieving airflow obstruction, than a much larger (1600 μg) oral dose of the drug.

4 When the area under the curve for peak expiratory flow rate values was calculated, a dose-response relationship could be seen between the different inhaled doses.

5 It appears that budesonide has a predominantly local anti-asthmatic action in the lung.

Introduction

Budesonide (16α, 17α,-(22R,S)-prophylmethylenedioxypregna-1,4-diene-11β,21-diol-3,20-dione) is an epimeric mixture of a new synthetic non-halogenated glucocorticoid. Animal studies show it to have high local and low systemic activity (Thalén & Brattsand, 1979). In man it has recently been shown that budesonide has a higher topical anti-inflammatory and a lower systemic effect than beclomethasone dipropionate, both after oral and aerosol administration (Johansson *et al.*, 1982). This seems to be due to the fact that budesonide undergoes an extensive and rapid biotransformation in the liver (Andersson *et al.*, 1983). Unlike beclomethasone dipropionate, budesonide is not metabolised in the lung (Martin *et al.*, 1974; Hartiala *et al.*, 1979; Ryrfeldt *et al.*, 1983). Budesonide thus appears to be a promising drug in the treatment of bronchial asthma.

We investigated the time course of response to budesonide, administered both by aerosol inhalation and orally in a group of patients with chronic bronchial asthma (Ellul-Micallef *et al.*, 1980b). The drug has since been further studied and favourably reported on in asthma (Willey *et al.*, 1981), rhinitis (Balle *et al.*, 1980; Pipkorn *et al.*, 1980; Malm *et al.*, 1981) and in psoriasis (Agrup *et al.*, 1981).

The present study was undertaken to establish whether acute dose-response studies with inhaled corticosteroids could be carried out in a group of very carefully selected patients with chronic bronchial asthma. At the same time an attempt has also been made to monitor the effect on airflow obstruction of much lower doses of inhaled budesonide than those used in our previous study in an attempt to determine a therapeutic dose range.

Methods

Twelve patients, six males and six females, suffering from chronic bronchial asthma participated in the study. Five suffered from intrinsic asthma, the rest being extrinsic asthmatics. The duration of asthmatic symptoms ranged from 1 to 25 years. Individual patient data are summarized in Table 1. For the purpose of this study, chronic bronchial asthma is defined as a condition in which widespread reversible airflow obstruction is present for a prolonged period of time with or without brief spontaneous remissions. Informed consent was obtained from all patients. Only patients with an $FEV_1 < 80\%$ of predicted normal value were admitted to the study. They were not adequately controlled by existing treatment and all showed a fair degree of stability in their condition. The patients showed a mean increase in FEV_1 of 23% (range 13–56%) 15 min after two inhalations from a pressurized salbutamol inhaler. Patients who had used corticosteroids during the 4 weeks preceding the study or suffered from any disease likely to interfere

0306–5251/83/0400–4190 $02.00

Table 1 Data on twelve asthmatic patients

Patient	Age (years)	Sex	Duration (years)	Type	FEV_1 (ml) (predicted)	FEV_1 (ml) (initial)	FEV_1 (ml) (post-salbutamol)
1	30	M	12	Ext.	3600	2550	2950
2	18	F	5	Ext.	3000	2250	2725
3	17	F	8	Ext.	2800	2200	2585
4	35	F	1	Int.	2750	1850	2250
5	46	M	3	Int.	3150	2150	2550
6	33	M	3	Int.	3800	2800	3300
7	37	F	25	Ext.	2650	1825	2250
8	35	M	11	Ext.	3700	2650	3000
9	38	F	4	Int.	2500	1750	2100
10	50	F	2	Int.	2350	1700	2650
11	41	M	22	Ext.	3350	2175	2700
12	22	M	10	Ext.	4000	2850	3550

Ext – extrinsic, int – intrinsic.

with the objective of the study such as other respiratory or hepatic diseases, or thyroid dysfunction as well as females who were pregnant, lactating or actively sought pregnancy were not admitted into the study.

In the first part of the study the patients received under single-blind conditions a single oral dose of 40 mg (0.11 mM) prednisolone phosphate on the first day and a placebo tablet on the second day. This was done to ensure that the patients were corticosteroid responders. Only patients who had an increase in their peak expiratory flow rate (PEFR) of at least 25% above the pretreatment value were admitted into the second half of the study.

The second part of the study was carried out under double-blind, cross-over conditions and performed during 4 consecutive days. The patients were then given, in a random fashion using a double dummy technique, inhaled budesonide in three different doses 100 μg, 400 μg and 1600 μg (0.23, 0.93 and 3.72 μM respectively) and 1600 μg of oral budesonide. All drugs and placebo were administered each morning as a single dose at 08.00 h immediately after recording the first PEFR. An Air Med Mini Meter was used to detect changes in airflow obstruction. Prior to the study the patients had been taught how to use the peak flow meter correctly and how to record their results. The best of three successive attempts was chosen and recorded. Spirometric tests were repeated at hourly intervals for a 12 h period. Statistical significance was tested in all instances by means of Student's *t*-test (Snedecor, 1971).

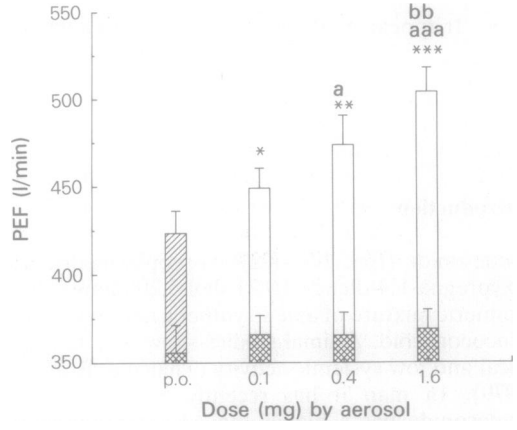

Figure 1 Mean ± s.e. mean maximum effect in PEF (l/min) by one oral (p.o.) and three inhaled doses of budesonide ($n = 12$).
$^*P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$ difference *vs* budesonide 1.6 mg p.o. a$P < 0.05$, aaa$P < 0.001$ difference *vs* budesonide 0.1 mg by inhalation. bb$P < 0.01$ difference *vs* budesonide 0.4 mg by inhalation.
The cross-hatched areas represent pretreatment mean maximum PEF + s.e. mean (l/min)

Results

None of the patients showed any untoward side-effects to any of the drugs given. All extrinsic asthmatic patients had evidence of a hypersensitivity diathesis; positive prick skin tests to a wide variety of allergens and blood eosinophilia. Electrocardiographs showed normal patterns in all patients except for patients 5 and 10 who had mild ischaemic changes. The chest radiographs were also normal except those of patients 7 and 11, which showed a moderate degree of hyperinflation. There was no clinical or bacteriological evidence of any chest infections. Initial PEFR values on the days in which prednisolone and inhaled budesonide were administered were not significantly different. The initial PEFR values for oral budesonide differed significantly from those of oral

prednisolone ($P < 0.05$), in spite of the small absolute difference in values, 16 ± 7 l/min (mean ± s.e. mean).

The maximum effect on PEFR produced by the different aerosol doses and the oral dose of budesonide is shown in Figure 1. All inhaled doses of budesonide produced a significantly greater increase in PEFR than did oral budesonide ($P < 0.05$; $P < 0.01$; $P < 0.001$). When the area under the curve for PEFR was calculated (Figure 2) a dose-response relationship could be seen between the different inhaled doses of budesonide. The smallest dose of inhaled budesonide (100 μg) was significantly more effective in relieving airflow obstruction than a markedly greater amount of oral budesonide (1600 μg).

The time course of response to oral prednisolone, oral budesonide and the three aerosol doses of budesonide is shown in Figure 3. The maximum increase in PEFR produced by 40 mg oral prednisolone was significantly greater than that produced by the different budesonide administrations ($P < 0.001$). The effect of prednisolone was still present during the second trial day which was used as a 'wash-out' day. However, it disappeared completely in all patients at the start of the second half of the study. A statistically significant increase in PEFR was produced 1 h after the inhalation of both 400 μg and 1600 μg, in the group of patients as a whole ($P < 0.05$, $P < 0.001$). Oral budesonide and 100 μg inhaled budesonide produced a significant increase in PEFR 2 h after their administration, as did oral prednisolone ($P < 0.05$; $P < 0.01$; $P < 0.001$). The duration of effect of inhaled budesonide was 11 h with the highest dose and 10 h with the lower 2 doses. The effect of oral budesonide also lasted for 11 h.

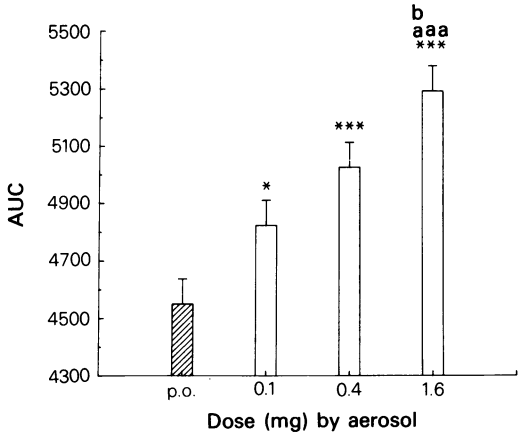

Figure 2 Mean area under curve (AUC) calculated on PEF for one oral and three inhaled doses of budesonide ($n = 12$).
*$P < 0.05$, ***$P < 0.001$ difference *vs* budesonide 1.6 mg p.o. aaa$P < 0.001$ difference *vs* budesonide 0.1 mg by inhalation. b$P < 0.05$ difference *vs* budesonide 0.4 mg by inhalation.

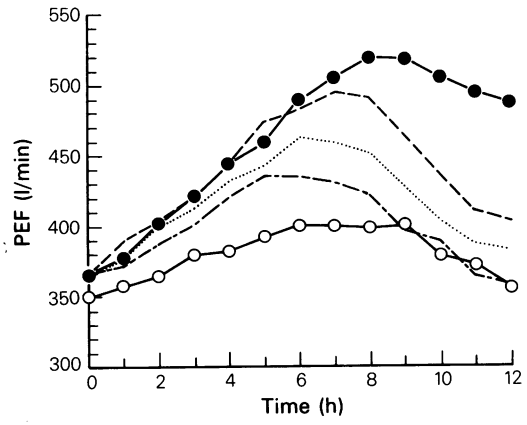

Figure 3 The time course of response (PEF, l/min) to oral prednisolone and budesonide in one oral and three inhaled doses. The range for s.e. mean was 9–22 l/min ($n = 12$).
●—● prednisolone 40 mg p.o., - - - - budesonide 1600 μg inhalation, ····· budesonide 400 μg inhalation, — - — budesonide 100 μg inhalation, O—O budesonide 1600 μg p.o.

Discussion

A simple test of pulmonary function, PEFR was chosen to detect changes in airflow obstruction as previous work had shown it to be a sensitive and reliable index of change in bronchial asthma (Ellul-Micallef *et al.*, 1974). In monitoring the effects of a drug in this condition it is perhaps more meaningful to use an easy, simple test frequently rather than the occasional elaborate work-out in the laboratory. In order to increase the availability of the drug to the lung and diminish the amount of oropharyngeal deposition, a tube spacer was interposed between the inhaler and the mouthpiece before budesonide was administered (Morén, 1978). Asthmatic patients not infrequently find difficulties in using a pressurized aerosol efficiently (Saunders, 1965) even when taught how to use it (Patterson & Crompton, 1976). The altered airway deposition of drug particles produced by the tube spacer seems to benefit such patients (Ellul-Micallef *et al.*, 1980b; Godden & Crompton, 1981).

It was possible to carry out an acute dose-response study with single doses of inhaled budesonide in our group of asthmatic patients because of careful initial selection. Our group of patients suffered from chronic bronchial asthma and all displayed small diurnal variations in their PEFR measurements prior to admittance to the study. They were 'stable' in the sense that their PEFR at the start of the trial had not been recently arrived at via a path of improvement or deterioration in their airflow obstruction. In this study prednisolone was used as a tool to select suitable patients.

The various doses of inhaled budesonide resulted in statistically significant differences in the maximum response in PEFR. No significant difference could, however, be detected between the various time intervals needed to attain the different peak effects on PEFR values. The duration of the effect of the drug administered appears to be influenced by the degree of peak effect achieved. The study showed a linear relationship in the maximum increase in PEFR produced by the different inhaled doses of budesonide.

The lowest dose of inhaled budesonide produced a more marked physiological effect than a much larger (× 16) oral dose of the drug. This seems to indicate that budesonide has a predominantly topical anti-asthmatic action in the lung. Budesonide is rapidly absorbed through the mucosa of the respiratory tract and there is little or no biotransformation of the drug in the lung (Brattsand *et al.*, 1983). It appears that the swallowed portion of the drug has very little effect (Ellul-Micallef *et al.*, 1980a). These findings agree with those of Ryrfeldt and his co-workers (1981) who showed that oral budesonide had a bioavailability of only 11%. It is now known that most of the budesonide absorbed from the gastrointestinal tract is rapidly and extensively metabolized by the liver (Andersson *et al.*, 1983). The above mentioned findings and the fact that budesonide has a half-life of only about 2 h in man would explain why budesonide seems to have such a low potential for inducing systemic effects (Johansson *et al.*, 1983).

References

AGRUP, G., BJÖRNBERG, A., ELMROS, T., GROTH, O., HANNUKSELA, H., LASSUS, A., SALDE, L., SKOGH, M. & THOMSEN, K. (1981). Clinical trial of a potent non-halogenated topical steroid, budesonide. *Acta Dermatovener.*, **61**, 180–182.

ANDERSSON, P., EDSBÄCKER, S., RYRFELDT, A. & VON BAHR, C. (1983). *In vitro* biotransformation of glucocorticoids in liver and skin homogenate fraction from man, rat and hairless mouse. *J. steroid Biochem.*, **16**, (in press).

BALLE, V., PEDERSEN, V. & ENGBY, B. (1980). Allergic perennial and non-allergic vasomotor rhinitis treated with budesonide nasal spray. *Rhinology*, **18**, 135–142.

BRATTSAND, R., KÄLLSTRÖM, L., NILSSON, E., RYRFELDT, A. & TÖNNESSON, M. (1983). The deposition of budesonide in the lung in guinea pig and rat. *Eur. J. resp. Dis.*, Suppl. (in press).

ELLUL-MICALLEF, R., BORTHWICK, R.C. & McHARDY, G.J.R. (1974). The time course of response to prednisolone in chronic bronchial asthma. *Clin. Sci. mol. Med.*, **47**, 105–117.

ELLUL-MICALLEF, R., HANSSON, E. & JOHANSSON, S.A. (1980a). Budesonide: A new corticosteroid in bronchial asthma. *Eur. J. resp. Dis.*, **61**, 167–173.

ELLUL-MICALLEF, R., MORÉN, F., WETTERLIN, K. & HIDINGER, K.G. (1980b). Use of special inhaler attachment in asthmatic children. *Thorax*, **35**, 620–623.

GODDEN, D.J. & CROMPTON, G.K. (1981). An objective assessment of the tube spacer in patients not able to use a conventional pressurized aerosol efficiently. *Br. J. dis. Chest*, **75**, 165–168.

HARTIALA, J., VOTILA, P. & NIENSTEDT, W. (1979). Absorption and metabolism of intratracheally instilled cortisol and beclomethasone dipropionate in the isolated perfused rat lungs. *Med. Biol.*, **57**, 294–297.

JOHANSSON, S.A., ANDERSSON, K.E., BRATTSAND, R., GRUVSTAD, E. & HEDNER P. (1983). Topical and systemic glucocorticoid potencies of budesonide, beclomethasone dipropionate and prednisolone in man. *Eur. J. resp. Dis.*, Suppl. (in press).

MALM, L., WIHL, J.A., LAMM, C.J. & LINDQVIST, N. (1981). Reduction of metacholine-induced nasal secretion by treatment with a new topical steroid in perennial non-allergic rhinitis. *Allergy*, **36**, 209–214.

MARTIN, L., TANNER, R.J.N., CLARK, T.J.H. & COCHRANE, G.M. (1974). Absorption and metabolism of orally administered beclomethasone dipropionate. *Clin. Pharmac. Ther.*, **15**, 267–270.

MORÉN, F. (1978). Drug deposition of pressurized inhalation aerosols. *Int. J. Pharmac.*, **1**, 205–212.

PATTERSON, I.C. & CROMPTON, G.K. (1976). Use of pressurized aerosols by asthmatic patients. *Br. med. J.*, **1**, 76–78.

PIPKORN, U., RUNDCRANTZ, H. & LINDQVIST, N. (1980). Budesonide a new nasal steroid. *Rhinology*, **18**, 171–175.

RYRFELDT, A., ANDERSSON, P., EDSBÄCKER, S., TÖNNESSON, M., DAVIES, D. & PAUWELS, R. (1983). Pharmacokinetics and metabolism of budesonide, a selective glucocorticoid. *Eur. J. resp. Dis.*, Suppl. (in press).

SAUNDERS, K.B. (1965). Misuse of inhaled bronchodilator agents. *Br. med. J.*, **1**, 1037–1039.

SNEDECOR, G.W. & COCHRAN, W.G. (1971). *Statistical methods*. Ames: Iowa State University Press.

THALÉN, A. & BRATTSAND, R. (1979). Synthesis and anti-inflammatory properties of budesonide, a new non-halogenated glucocorticoid with high local activity. *Arzneim-Forsch/Drug Res.*, **29**, 1687–1690.

WILLEY, R.F., GODDEN, D.J., CARMICHAEL, J., PRESTON, P., FRAME, M. & CROMPTON, G.K. (1982). Comparison of twice daily administration of a new corticosteroid budesonide with beclomethasone dipropionate four times daily in the treatment of chronic asthma. *Br. J. dis. Chest*, **76**, 61–68.

(Received July 15, 1982, accepted October 29, 1982)