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THE BRONCHODILATOR EFFECT OF NAB 365

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1 Dose response relationships for salbutamol and a new bronchodilator drug NAB 365 have been obtained in patients with reversible airways obstruction. These show that the latter is about one hundred times more potent than the former.

2 NAB 365 has a very long half-life. The implications of this are discussed.

Introduction

Among the new specific β_2-adrenoceptor stimulants which have been synthesized recently, NAB 365 (Boehringer Ingelheim Ltd) is one which is effective in very small doses (Nolte, Ulmer & Krieger, 1974; Nolte & Laumen, 1974). The base has a molecular weight of 277 and its chemical structure is shown in Figure 1. It differs from salbutamol in having chlorine atoms attached to the benzene ring in the 2 and 5 positions whilst in the case of salbutamol one of these positions only is occupied by a primary alcohol group.

Pharmacokinetic studies in man (Thomae, unpublished observations), using radioactively-labelled base, showed the drug to be well absorbed when administered by mouth, the maximum plasma concentration being reached in approximately 2 h; plasma concentration falls slowly with a half-life of 35 hour. Excretion is mainly through the kidney.

NAB 365 has been found to act predominantly on bronchial smooth muscle and to have little effect on the cardiac adrenoceptors (Englehardt, 1972). Initial reports on the dose effective in human subjects, however, were conflicting so the present work was carried out to define the effective clinical dosage and to compare the effects of the new drug with those of salbutamol.

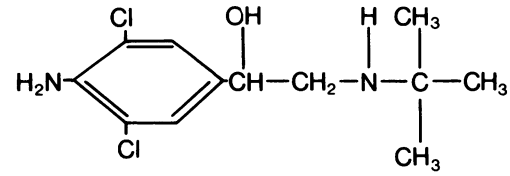

Figure 1 The structural formula of NAB 365.

Methods

Plan of the investigation

Experiments were carried out on two groups of ten selected patients with reversible airways obstruction. The first group of ten patients were given one tablet of NAB 365 (10 μg) every hour for 3 h and the second group were given similar tablets containing 20 μg of the drug in the same way. Thus the first group received a total dose of 30 μg and the second 60 μg of NAB 365. As controls both groups of patients were given placebo tablets on a different day. For comparative purposes tablets of salbutamol (2 mg) were administered instead of NAB 365 on a third day. The order in which the tablets of placebo, salbutamol or NAB 365 were allotted to each experimental day was varied at random for each patient so that neither he nor the operator knew which substance was being administered on any particular day. The patients were fully informed of the reason for the investigations and freely agreed to take part; all were familiar with the procedures used.

Choice of patients

The patients were admitted to hospital for investigation and treatment of chronic airways obstruction; most of these were intrinsic asthmatics and all had chronic obstructive bronchitis. The main criterion for admission to the trial was a 20% improvement in FEV_1 following the inhalation of

two puffs from a metered dose inhaler containing NAB 365 (fenoterol, 200 μg in each puff). A statistical summary of the responses in both groups of patients are shown in Table 1a and b together with their mean ages and physical characteristics.

Daily experimental routine and methods

Patients came to the laboratory at the same time each morning about one hour after a light breakfast; all bronchodilator drugs were withheld for the previous 12 h at least, with the exception of established constant steroid therapy. After resting in a comfortable arm-chair for 15 min, pulse rate was counted over 1 min and blood pressures measured by auscultation using a standard cuff and sphygmomanometer. Airways resistance (Raw) and thoracic gas volume (Vtg) were then measured using a body plethysmograph (Siemens) with the patient breathing at a rate of about 0.5 Hz (DuBois, Botelho & Comroe, 1956). Forced vital capacity (FVC) was then recorded using a dry spirometer (Vitalograph) and forced expiratory volume in 1 s (FEV_1) was estimated from this trace.

The first tablet was then administered.

The same set of measurements was made in the same order 1 h and 2 h after the control data and another tablet was given after each set. A fourth set of measurements was made 1 h after the third and then the patient was given isoprenaline (200 μg) from a metered dose inhaler. A final set of measurements was made 15 min later.

Objective side-effects, especially tremor, tachycardia and irregularity of the pulse, were looked for. An attempt was made to quantify the degree of tremor. Tremor was absent when the extended fingers and arms were held perfectly steady; it was judged to be severe when it involved the whole arm. Between these two extremes, noticeable tremor was classified as obvious or doubtful.

Because many patients remark on the feeling of elation after taking β-adrenoceptor stimulant drugs, statements of alteration of mood volunteered by the patient were also noted.

Results

Low doses of NAB 365 (10 μg) (Figure 2a, b, c, d and e)

The changes in Raw after NAB 365 were negligible in eight of the patients, whilst a small fall was seen in the remaining two. A small fall in Vtg occurred after the drug so that the value of SGaw (the reciprocal of Raw x Vtg) rose in eight patients. The coincident increases in FEV_1 were statistically different from the control but not from the placebo results. The effects of salbutamol were similar but consistently better than those seen after NAB 365 in this dosage. The effects of the inhalation of isoprenaline at the end of each

Table 1 The mean predicted values of FVC and FEV_1 compared with the observed, and the effect of two puffs (400 μg) of fenoterol in two groups of ten patients (Group A: nine males, one female; Group B: five males, five females) with intrinsic asthma.

(a) *Low dose*

Group A

Age (years) (mean)	*Height (cm) (mean)*	*FVC (litres)*			*FEV_1 (litres)*		
		Predicted	*Observed*	*After NAB 365*	*Predicted*	*Observed*	*After NAB 365*
47-63 (54.3)	159-183 (172.0)	4.009	2.685*	3.360*	3.078	1.330*	1.830*

(b) *High dose*

Group B

Age (years) (mean)	*Height (cm) (mean)*	*FVC (litres)*			*FEV_1 (litres)*		
		Predicted	*Observed*	*After NAB 365*	*Predicted*	*Observed*	*After NAB 365*
33-62 (55.0)	151-181 (169.5)	3.759	2.080*	2.595*	2.702	1.140*	1.590*

* The changes after NAB 365 are significant ($P < 0.05$)

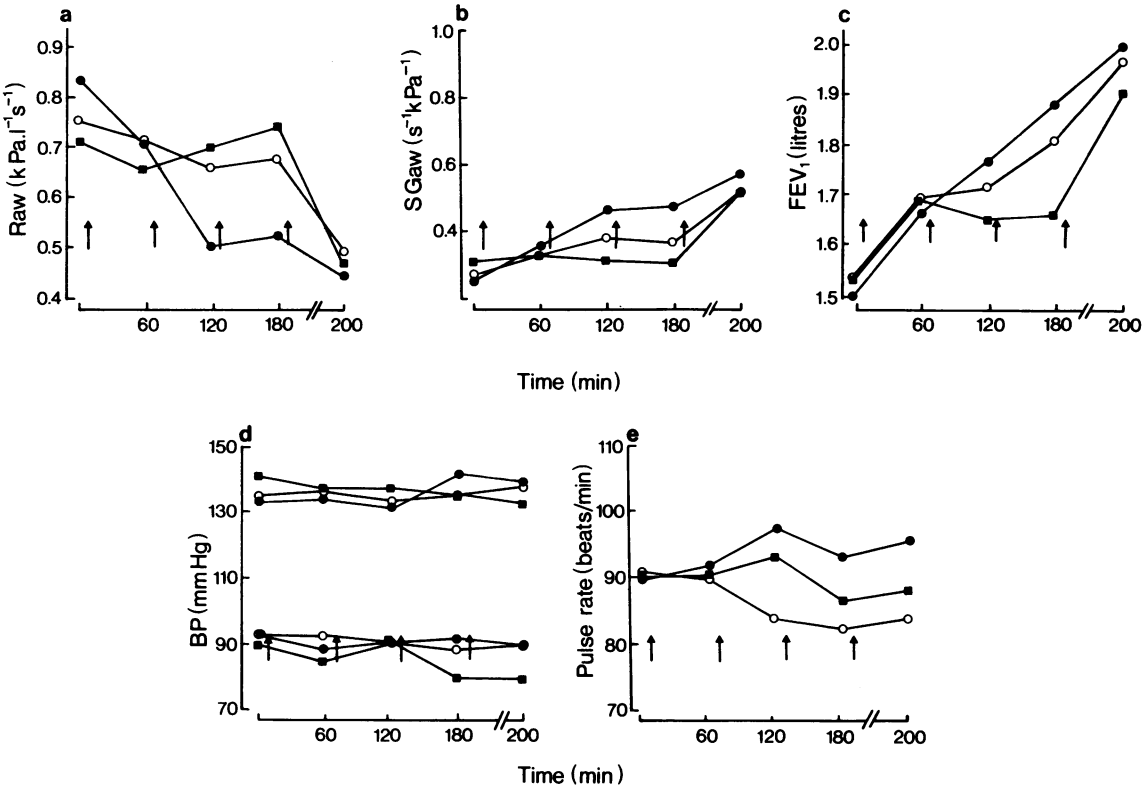

Figure 2 The effects of salbutamol (2 mg, •), NAB 365 (10 μg, ○) and placebo (▪) given at successive hourly intervals (↑) on airways resistance (Raw), specific airways conductance (SGaw), FEV_1, systolic and diastolic blood pressures and pulse rate. Isoprenaline (200 μg) was given by inhalation after the third hour.

experiment brought all the values close to the final values for salbutamol.

The effect on pulse rate of NAB 365 was not distinguishable statistically from that of salbutamol. The changes were never more than 5 beats/min. Similarly, both systolic and diastolic blood pressures tended to fall slightly during each experimental day. The most significant changes were seen in one patient whose blood pressures varied between 135/95 and 155/85 but without any relation to the drugs or placebo.

Side effects were not seen during or after NAB 365 but obvious tremor was recorded in four of the patients taking salbutamol; the tremor became apparent after the 4 mg had been given.

High doses of NAB 365 (20 μg)

Figure 3a, b, c, d and e shows that the response to increasing the doses of NAB 365 was to produce effects on all the variables measured which were almost the same as those of salbutamol. Raw fell, SGaw and FEV_1 rose in all the subjects and these changes were statistically different from the placebo results after the first dose of both the drugs. These changes were seen consistently in all the subjects. On average there was a progressive increase in pulse rate on NAB 365 which was also apparent in the case of the placebo and after salbutamol; this increase amounted to 7 beats/min though in two cases the increase was 15 beats/min. Similarly with blood pressures, after NAB 365 there was a mean change from 136/91 to 136/84 with a further fall to 136/81 after isoprenaline had been given. There were no striking exceptions to this general behaviour in any individual patient.

Side-effects of NAB 365 appeared in this group; obvious tremor of moderate severity was seen in two of the patients on NAB 365 and severe tremor in another. Moderately severe tremor was again seen in four of the patients after salbutamol; these included the three who showed tremor after

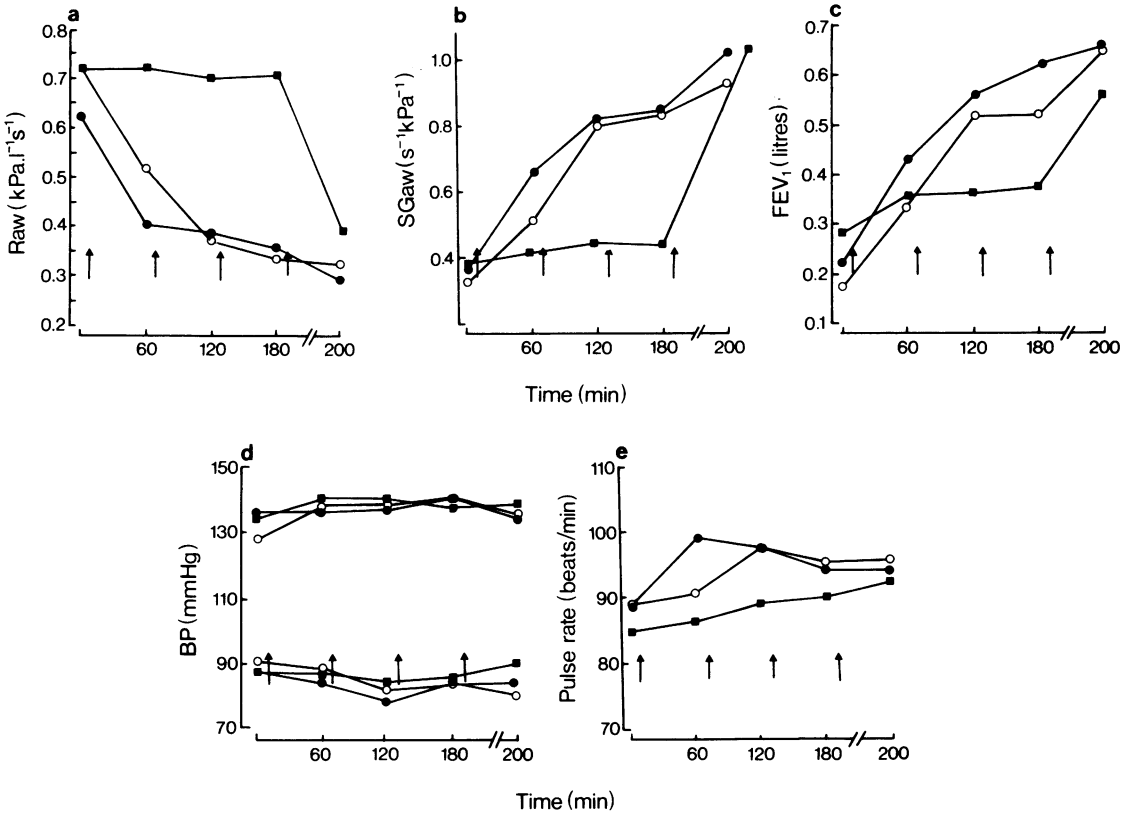

Figure 3 The effects of salbutamol (2 mg, •), NAB 365 (20 μg, ○) and placebo (▪) given at successive hourly intervals (↑) on airways resistance (Raw), specific airways conductance (SGaw), FEV_1, systolic and diastolic blood pressures and pulse rate. Isoprenaline (200 μg) was given by inhalation after the third hour.

NAB 365. The incidence of tremor would seem to be about the same after either of the drugs.

In this group of patients there was little change in any of the measurements after isoprenaline had been given except on the placebo day.

Discussion

The data obtained in these experiments are in the form of cumulative dose response curves. The great value of these is that they provide much the best information for comparing the activities of two drugs. They can show not only the differences between the doses necessary to produce effects of similar magnitude but also show the effects of increments in dosage. Our results show that on the basis of molecular weight, NAB 365 is about one hundred times more potent than salbutamol. The slopes of the dose-response curves in the second group of patients coincide closely. The striking difference in potency is presumably related to the difference in chemical structure which may permit NAB 365 to have a more ready access to the β_2-adrenoceptors. One criticism of these results is the implicit assumption that the maximum effect of the two drugs is apparent 1 h after administration by mouth. In the case of salbutamol the peak effect after a single dose was found 3 h after administration in one series (Kamburoff & Prime, 1970); the difference between the peak value and that at one hour was 5% in the case of FEV_1. Curti (1974) finds a similar pattern of activity in the case of NAB 365, so that we have some justification in concluding that these dose-response curves are reasonably accurate pictures of the relative potencies of the two drugs. Moreover, the effect of inhaling isoprenaline (200 μg) at the end of the experimental period showed that maximum bronchodilator effects of both salbutamol and the high doses of NAB 365 had been obtained.

The side-effects of the two drugs seem to be

similar in the doses we have used.

We conclude that NAB 365 is a very active bronchodilator drug having little effect on the cardiovascular system; an effective dose is in the region of 20 μg by mouth and this dose can be repeated at least 3 times a day. Its very long half-life in the circulation suggests that accumulation of the drug could occur in long-term treatment. More detailed studies in man are required to assess this possibility though Curti (1974) finds that administration of this dose over the course of 14 days is well tolerated.

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