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THE ACUTE AND CHRONIC BRONCHODILATOR EFFECTS OF EPHEDRINE IN ASTHMATIC PATIENTS

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1 In eight asthmatic patients, there was no change in the bronchodilator response to a single dose of ephedrine (22 mg) given alone or in a compound tablet, after treatment with ephedrine (11 mg three times a day) or one tablet three times a day for 2 weeks.

2 There was no deterioration in lung function during the 2 week treatment period with either ephedrine or the compound tablet.

3 An inter-patient variation was noted in the plasma ephedrine concentration required for bronchodilatation.

4 The half-life of theophylline did not change after chronic treatment with the tablets, one three times a day for 2 weeks.

Introduction

Ephedrine is still widely used in the treatment of reversible airways obstruction, usually in combination with theophylline and a barbiturate in compound preparations such as Franol (Winthrop) which contains ephedrine hydrochloride (11 mg), theophylline (120 mg) and phenobarbitone (8 mg).

Herxheimer (1946) reported that tolerance to the bronchodilator effects of ephedrine developed within 3-4 days in patients who required does of 60 mg or more three times daily. Pickup, May, Ssendagire & Paterson (1976) have shown that there is no change in the pharmacokinetics of ephedrine after chronic treatment with an ephedrine, theophylline, and barbiturate compound tablet (Tablets 4332, Boots Company Ltd) or with ephedrine alone in therapeutic doses. Tablets 4332 contain ephedrine hydrochloride 10 mg, theophylline (anhydrous) 125 mg and phenobarbitone 7.5 mg per tablet (Nix, personal communication).

The present study reports the acute and chronic bronchodilator response to tablets 4332 and ephedrine alone and assesses the relative importance of the other constituents in the compound tablet.

Methods

Eight subjects were studied as outpatients. All had reversible airways obstruction and had been shown to respond to the inhalation of salbutamol by an increase in forced expiratory volume in 1 s (FEV_1) and peak expiratory flow rate (PEFR) of at least 20%. All subjects gave their informed consent after explanation of the procedures to be performed. There were three different treatment regimens, each of 2 weeks' duration:

(a) Ephedrine HCl (11 mg three times a day, in solution of 5 ml of distilled water).
(b) One tablet 4332 (containing nominally ephedrine HCl 10 mg, theophylline 125 mg, and phenobarbitone 7.5 mg) three times a day.
(c) Their normal bronchodilator regimen (usually salbutamol) was administered between the ephedrine and tablet regimens, and thus for 2 weeks between (a) and (b) the subjects received no ephedrine-containing compounds.

During these three treatment periods, the subjects:

1. Made daily recordings of morning and

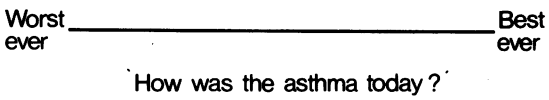

Figure 1 Line form of questionnaire used in the study.

evening PEFR using a Wright's peak flow meter.

2. Recorded the number of puffs of salbutamol aerosol (100 μg/puff) they required to remain free of wheeze (in addition to the ephedrine preparation they were already taking).
3. Answered the question 'How was the asthma today?' by marking a 10 cm line (Figure 1). This was scored by expressing the distance of their mark along the line as a percentage of 10 cm.

On the day immediately preceding, and the day immediately following the treatment periods with (a) ephedrine and (b) tablets 4332, a single dose of the respective drug (equivalent to 22 mg of ephedrine HCl ≡ 18 mg ephedrine base) was administered. All bronchodilator drugs (including ephedrine) were stopped from 18.00 h the night before and when the compound tablet was administered, all xanthine-containing compounds were also suspended for at least 12 hours. A cannula was inserted in a vein on the dorsum of the hand. FEV_1 and forced vital capacity (FVC) were measured with a dry spirometer (Vitalograph), PEFR with a Wright's peak flow meter, blood pressure by sphygmomanometry, and heart rate by palpation of the radial artery at the wrist. When steady baseline readings were obtained ephedrine HCl (22 mg in distilled H_2O) or two tablets 4332 (containing ephedrine HCl 22 mg) were given orally. The physiological measurements were repeated and a blood sample taken every 30 min for 3 h, and then hourly for a total of at least 8 hours. Plasma ephedrine was measured by gas-liquid chromatography (Pickup & Paterson, 1974) and when the tablets were given, plasma theophylline levels were also measured, by a modification of the spectrofluorimetric method of Schack & Waxler (1949). The results were analysed by the Student's paired *t*-test.

Results

The FEV_1 readings, after suspension of all bronchodilators for 15 h, are seen in Table 1. They are well below the predicted normal; expressed as the mean percentage predicted FEV_1 the values were: before chronic ephedrine treatment, 44.1%; after chronic ephedrine treatment 55.3%; before chronic treatment with tablets 4332 44.0%; after chronic treatment with tablets 4332 47.1%. A significant rise occurred after a single dose of ephedrine or compund tablet. The figures for mean increase in PEFR and FEV_1 are derived by expressing the difference between the baseline value and the value obtained at the time of maximum plasma ephedrine concentration (which was usually the maximum improvement achieved, and also usually corresponded to the peak theophylline concentration) as a percentage of the mean of the two values (i.e.

$$\frac{(y-x) \times 100\%}{(y+x)/2},$$

where y is the new value and x is the initial value). This has been suggested by Cotes (1974) as a more valid method of expressing change in these measurements.

The mean increases in PEFR and FEV_1 achieved by ephedrine HCl (22 mg) before chronic therapy were 16.8% and 18.3% respectively, and after chronic treatment, 14.4% and 9.9% respectively.

Two tablets 4332 caused a greater mean increase in PEFR and FEV_1 than did ephedrine

Table 1 Mean (± s.e. mean) increase in PEFR and FEV_1 in each of the four single dose studies

Study	*Baseline PEFR (litres/min)*	*% Increase in PEFR*	*Baseline FEV_1 (litres)*	*% Increase in FEV_1*
Ephedrine (22 mg) acute*	261	16.8 (±9.4)	1.66	18.3 (±11.8)
Ephedrine (22 mg) chronic*	274	14.4 (±5.8)	1.85	9.9 (± 5.0)
Two tablets 4332 acute*	257	28.9 (±4.8)	1.61	30.0 (± 4.9)
Two tablets 4332 chronic*	261	32.8 (±6.9)	1.74	26.7 (± 7.9)

* Acute (or chronic): Before (or after) treatment with ephedrine HCl (11 mg three times a day) or one tablet 4332 three times a day for 2 weeks.

alone; the rises before chronic treatment were: PEFR 28.9% and FEV_1 30.0% and after chronic treatment 32.8% and 26.7% respectively. This greater response to the compound tablet did not achieve statistical significance but the probability of an additional effect from theophylline was supported by patient (L.H.) who failed to bronchodilate in response to ephedrine HCl (22 mg), but after two tablets showed an increase in PEFR of 20.0% and FEV_1 of 18.9% (the baseline spirometric values being within 15%).

Ephedrine HCl (22 mg) resulted in a significant mean increase in heart rate of 9.5 (±15) beats/min before, and 7.5 (±3.0) beats/min after chronic treatment. The corresponding increases for two tablets 4332 were 9.7 (±6.0) and 8.9 (±3.4) beats/minute. There was no significant difference between any of these four values, nor was there any significant change in mean systolic and diastolic blood pressure during the four studies.

Table 2 shows the mean values for PEFR, number of puffs of salbutamol used per day, and questionnaire score recorded by the eight patients during the treatment periods on (a) ephedrine (b) tablets 4332 and (c) their normal bronchodilator. There was no significant difference between the three regimens for any parameter. In addition, the mean PEFR in the first week of treatment did not differ from that in the second week with tablet or ephedrine alone.

Table 3 shows the approximate plasma levels of ephedrine at which 20% improvement occurred in PEFR and FEV_1 after a single dose of ephedrine HCl' (22 mg). There is a wide variation in this plasma level, and the patient mentioned above (L.H.) showed no response, even though the plasma ephedrine concentration was 80 ng/ml. Also shown are the peak plasma concentrations reached by the same patients during chronic therapy with ephedrine (11 mg three times a day)

Table 2 Recordings (mean (± s.e. mean)) during 2 weeks' treatment with three different regimens

Treatment period	*Peak flow rate (litres/min)*	*No. of puffs of salbutamol/day*	*Questionnaire score (%)*
(a) Ephedrine (11 mg three times a day)			
1st week	299 (±53)	3 (±1)	57.3 (±5.8)
2nd week	302 (±52)	3 (±1)	63.1 (±7.0)
Average	301 (±53)	3 (±1)	60.2 (±6.3)
(b) Tablets 4332 (one three times a day)			
1st week	306 (±55)	3 (±1)	57.3 (±8.4)
2nd week	292 (±54)	3 (±1)	54.2 (±7.0)
Average	299 (±54)	3 (±1)	56.0 (±6.9)
(c) Normal bronchodilator	307 (±57)	3 (±1)	59.4 (±6.8)

Table 3 Plasma ephedrine concentrations during chronic therapy

Patient	*Calculated maximum plasma concentration of ephedrine during treatment with ephedrine (11 mg three times a day) (ng/ml)**	*Measured plasma concentration of ephedrine for bronchodilatation (ng/ml)*
L.H.	52	>80
H.M.	71	40-70
J.B.	96	30-80
T.S.	75	65
P.W.	66	20
J.H.	80	50
D.S.	62	35
U.B.	55	50

* Pickup *et al.* (1975).

Table 4 Mean (± range) effect of chronic treatment with tablets 4332 on peak plasma concentration and half-life of theophylline.

Study	*Peak plasma concentration of theophylline (μg/ml)*	*Half-life of theophylline (h)*
Two tablets 4332 acute*	8.1 (6.2-9.3)	5.3 (4.0-8.8)
Two tablets 4332 chronic*	10.6 (7.2-14.0)	5.6 (3.0-6.0)

* Acute (or chronic): Before (and after) treatment with tablets 4332 (one three times a day) for 2 weeks.

calculated using the data obtained from the acute study (Pickup *et al.*, 1976).

Table 4 shows mean elimination half-life and peak plasma level (± s.e. mean) for theophylline, obtained from the single dose studies with two tablets 4332, before and after chronic treatment with the tablets three times per day. The higher mean value for plasma theophylline after chronic dosage (10.6 μg/ml) is due to residual theophylline from the final dose on the previous day, the mean initial concentration prior to the second study being 3.7 μg/ml. There is no significant difference between the mean half-life of theophylline before (5.3 h) and after (5.6 h) chronic treatment with tablets 4332, one tablet three times per day.

Discussion

Ephedrine has been used by Chinese physicians for over 5,000 years and in western medicine since the work of Chen & Schmidt (1924). Speizer, Doll, Heaf & Strang (1968) showed that almost 60% of patients who died from asthma in the period October 1966 to March 1967 had received ephedrine in some form in the last month of life. Although selective β_2-adrenoceptor stimulants have been widely promoted as the bronchodilators of choice, the current edition of MIMS (August 1974) lists over fifty preparations containing ephedrine or pseudo-ephedrine.

In 1946 Herxheimer noted that patients who required doses of over 60 mg of ephedrine to produce bronchodilatation became resistant if this dose was given three times daily for 3-4 days. This phenomenon could be overcome by increasing the dose even further or withdrawing the drug completely for a short period. However, Taylor, Heinlich, Strick & Busser (1965) failed to show tachyphylaxis to ephedrine sulphate (1 mg/kg) in children who had been treated with ephedrine (12.5 or 25.0 mg three times a day) for 6 days. In spite of Herxheimer's observation, in practice ephedrine is administered continuously, though in smaller doses and usually in combination with theophylline and a barbiturate. Pickup *et al.* (1976) have shown no change in the pharmacokinetics of ephedrine after treatment for 2 weeks with ephedrine (11 mg three times a day) and have thus inferred that if tolerance does occur then it is due to a pharmacodynamic change rather than a pharmacokinetic one. In our patients we have been unable to demonstrate the development of tolerance measured either by a smaller bronchodilator response to a single dose of ephedrine after treatment for 2 weeks, or by deterioration in lung function during the 2 week period of treatment with ephedrine. This was so both for ephedrine alone and when administered in a compound tablet as tablets 4332. However, one of our patients (L.H.) showed no bronchodilator response to ephedrine (22 mg) either before or after chronic treatment, and yet when the tablet was given, responded in a normal manner, presumably due to the additional theophylline. In both studies the plasma ephedrine concentration was within the range reached by other patients. it may be that he falls into the group of patients described by Herxheimer (1946) which does not respond to smaller doses, and it was in these patients that the phenomenon of tolerance was noted. Ephedrine is thought to act mainly indirectly, i.e. by release of noradrenaline at sympathetic nerve endings. Presumably the higher the dose the more noradrenaline released, the greater the likelihood of depletion and hence tolerance. In the present study the dose of ephedrine given chronically was 11 mg three times a day and in the study of Taylor *et al.* (1965) 12.5 and 25 mg three times a day. Tolerance was reported by Herxheimer (1946) at 60 mg three times a day and therefore it is likely that it is a dose-related phenomenon.

There was a definite variation in the plasma ephedrine concentration required for effective bronchodilatation, varying from 20 ng/ml to greater than 80 ng/ml (Table 3). The plasma ephedrine concentration reached after a single dose of ephedrine (22 mg) or during treatment with ephedrine (11 mg three times a day (Pickup *et al.*, 1976)) exceeded these levels in most patients. We therefore deduce that the ephedrine content of tablet 4332 (one three times a day) or ephedrine alone (11 mg three times) will result in effective bronchodilatation in most patients.

Turner-Warwick (1957) showed that the bronchodilator plasma concentration of theophylline was approximately 10 μg/ml, though there was a wide range. Following two tablets, the maximum plasma levels of theophylline achieved ranged from 6.2-9.3 μg/ml. The mean half-life for theophylline was 5.3 h agreeing with the work of Jenne, Wyze, Rood & MacDonald (1972) and Mitenko & Ogilvie (1973). There is no previous data on the effect of theophylline on its own metabolism, but we have shown no change in half-life after two weeks' treatment with 120 mg three times a day.

In a previous multi-centre trial using only subjective assessment and a similar compound tablet (Franol), patients thought that the tablet gave better control of their asthma than ephedrine alone (Practitioner, 1963). In the present study a single administration of two compound tablets caused a greater average rise in PEFR and FEV_1 than the same amount of ephedrine, given alone,

and in one patient unresponsive to ephedrine, two tablets produced bronchodilatation. The larger response to tablets 4332 is presumably due to the additional theophylline, and the plasma levels measured after two tablets are sufficient to cause bronchodilatation. However, on chronic administration the tablets appeared no better than ephedrine as judged by questionnaire and twice daily PEFR testing. This discrepancy is no doubt due to the different doses used. While the two tablets given in the acute study resulted in an adequate plasma theophylline level for bronchodilatation, the regimen of one tablet three times a day (chronic study) would not achieve a bronchodilator concentration, and so no additional effect was seen on chronic treatment. It is of interest that in the present study the patients' assessment coincided with the objective measurements. The experience of Gandevia, Hume & Prime (1957) was different. They found that patients preferred phenobarbitone alone to theophylline or isoprenaline, even though the barbiturate had no beneficial effect on spirometric measurement. The patients' assessment of a bronchodilator drug is not solely due to a direct bronchodilator action on the lung, but may be considerably altered by central effects. It may be that the line questionnaire used in the present study is more precise than those used previously. However, the objective measurements all changed in the same direction, in contrast with the study of Gandevia *et al.* (1957) where there was a significant difference in lung function between regimens. It would be of interest to see if the line questionnaire would correlate with the reduced lung function associated with say, phenobarbitone as compared with theophylline, or whether it would reflect the central effects of the drug. There is some debate about whether compound tablets have any advantage over ephedrine alone. Some patients will prefer them presumably because of the central effects of the barbiturate. However, in patients requiring higher doses of ephedrine, the use of compound tablets to lower the dose of ephedrine might well prevent the development of tolerance on chronic treatment.

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