Effect of theophylline and enprofylline on bronchial hyperresponsiveness

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ABSTRACT The effect of increasing intravenous doses of theophylline and enprofylline, a new xanthine derivative, on bronchial responsiveness to methacholine was studied in eight asthmatic patients. Methacholine provocations were carried out on three days before and after increasing doses of theophylline, enprofylline, and placebo, a double blind study design being used. Methacholine responsiveness was determined as the provocative concentration of methacholine causing a fall of 20% in FEV₁ (PC₂₀). The patients were characterised pharmacokinetically before the main study to provide an individual dosage scheme for each patient that would provide rapid steady state plasma concentration plateaus of 5, 10, and 15 mg/l for theophylline and 1.25, 2.5, and 3.75 mg/l for enprofylline. Dose increments in the main study were given at 90 minute intervals. FEV₁ showed a small progressive decrease after placebo; it remained high in relation to placebo after both drugs and this effect was dose related. Methacholine PC₂₀ values decreased after placebo; mean values were higher after theophylline and enprofylline than after placebo (maximum difference 2.0 and 1.7 doubling doses of methacholine); the effect of both drugs was dose related. Thus enprofylline and theophylline when given intravenously cause a small dose related increase in FEV₁ and methacholine PC₂₀ when compared with placebo.

Theophylline is widely used as maintenance treatment for patients with moderately severe asthma.¹ In addition to causing dose related bronchodilatation,² theophylline provides some protection against the effects of constrictor agents such as histamine and methacholine.³⁻⁷ Enprofylline, a recently developed xanthine derivative, is three to five times more potent as a bronchodilator than theophylline,^{8,9} and might have advantages over theophylline if central nervous system side effects are less.¹⁰

In the present study increasing doses of enprofylline and theophylline were given intravenously to patients with asthma to examine the protective effect of theophylline and enprofylline on bronchoconstriction induced by inhaled methacholine and to relate this to the plasma concentrations of the two drugs. Before the study the pharmacokinetics of both drugs were determined for each patient so that individualised drug doses could be given and plasma concentrations held within narrow limits.

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Methods

PATIENTS

Eight asthmatic men (mean age 29, range 23-34 years) gave their written, informed consent to participate in the study. The clinical characteristics of each patient are shown in table 1. Patients had to show an increase in forced expiratory volume in one second (FEV₁) of at least 15% after 200 µg terbutaline. All patients had increased bronchial responsiveness to methacholine (a provocation concentration causing a fall of 20% in FEV₁ (PC₂₀) below 4 mg/l; see "Provocation tests" below).

Asthma was well controlled in all subjects by a small dose of an inhaled bronchodilator or a prophylactic drug (sodium cromoglycate or an inhaled corticosteroid) or both. Two patients took theophylline as maintenance treatment; this was withheld for at least one week before each study day. No patient was receiving regular oral steroids.

PROVOCATION TESTS

Slow inspiratory vital capacity (VC) and FEV₁ were measured with a water sealed spirometer. Increasing concentrations of methacholine were inhaled from a

Table 1 Clinical data on the patients

Patient No	Age (y)	VC (l)	FEV ₁ (l)	FEV ₁ (% pred)	% increase above initial FEV ₁ after terbutaline*	Methacholine PC ₂₀ (mg/ml)
1	34	5.40	3.25	71	18	0.78
2	29	5.50	3.00	66	40	0.10
3	24	5.50	3.40	71	25	0.24
4	32	4.90	2.10	53	18	0.10
5	23	5.40	3.60	71	19	1.07
6	29	5.30	3.25	77	21	1.41
7	25	6.30	4.30	89	16	0.18
8	33	3.70	2.20	62	37	0.03
Mean	29	5.25	3.14	70	24	0.24†
SD		0.74	0.72	11	9	

*The terbutaline effect was tested on a separate study day. The inhaled dose was 0.50 mg (two puffs).

†Geometric mean value.

VC—vital capacity; FEV₁—forced expiratory volume in one second; PC₂₀—provocation concentration causing a 20% fall in FEV₁.

Wiesbadener Doppelspray (Wiesbadener Inhalator-Vertrieb, Wiesbaden, West Germany) with an airflow of 8 l/min. The output of the nebuliser was 0.12 (SEM 0.02) ml/min. The aerosols were inhaled during tidal breathing, with the patient wearing a nose clip. Doubling concentrations of methacholine from 0.032 to 8 mg/ml were inhaled for two minutes at five minute intervals until the FEV₁ had fallen by 20% from the FEV₁ after a control inhalation of saline 0.9%.

Log dose methacholine was plotted against FEV₁ and the provocation concentration of methacholine required to produce a fall in FEV₁ of 20% measured by interpolation.¹¹

The theophylline and enprofylline concentrations in plasma were determined by a high pressure liquid chromatography method.^{12,13}

STUDY DESIGN

Pharmacokinetic indices for each individual were measured on separate days after an intravenous bolus of 2 mg/kg theophylline and 1 mg/kg enprofylline. Total body clearance, volume of distribution at steady state, and volume of the central compartment were calculated from the drug plasma time-concentration curve.

The challenge tests were carried out on three days, before and after theophylline, enprofylline, and placebo. After baseline lung function measurements an inhalation provocation test with methacholine was carried out. Baseline FEV₁ values on the three study days had to be within 10% of the mean value for the three days, and the initial methacholine PC₂₀ values had to be within one dose step on the three days. After the baseline measurement an infusion was given over a total period of 270 minutes. An intravenous bolus dose of drug was given initially over three minutes to raise the plasma xanthine concentration to the first plateau level. The bolus dose was immediately followed by an exponentially decreasing dose by infusion during the succeeding 87 minutes. The procedure was repeated at

90 and 180 minutes¹⁴ in an attempt to achieve the three successive concentration plateaus with increasing doses of drug. The plasma concentrations aimed for were 5.0, 10.0, and 15.0 mg/l for theophylline and 1.25, 2.50, and 3.75 mg/l for enprofylline. The drug doses needed to achieve these goals were calculated from the pharmacokinetic measurements for all the subjects and prepared by the pharmacist in individual bottles for each subject to ensure that the study was blind for both the investigators and the patients.

The inhalation provocation with methacholine was repeated on three occasions for each drug 60 minutes after the start of each infusion at an increased drug concentration. The patients were not allowed to have beverages containing xanthine during the study days.

STATISTICAL ANALYSIS

Methacholine PC₂₀ values were log transformed. The response to theophylline and enprofylline was expressed as the difference between log PC₂₀ on the active treatment days and the placebo days. Change in FEV₁ values was expressed as a percentage of the baseline value on each day. With these as dependent variables, analysis of variance was carried out with treatment and dosage step as independent variables,¹⁵ followed by Duncan's multiple range test to establish differences between groups. Linear regression analysis was used to relate plasma xanthine concentration to change in FEV₁ and methacholine PC₂₀ (baseline measurements being excluded).

Results

THEOPHYLLINE AND ENPROFYLLINE PLASMA CONCENTRATIONS

Plasma concentration remained stable during the continuous infusion period after each increment. The mean plasma concentrations (table 2) deviated little from the concentrations we aimed at (theophylline 5.3, 10.2, 15 mg/l; enprofylline 1.2, 2.4, 3.7 mg/l).

Table 2 Plasma xanthine concentration at measurement of methacholine PC₂₀

Patient No	Theophylline (mg/l)			Enprofylline (mg/l)		
	Dose step			Dose step		
	1	2	3	1	2	3
1	5.7	10.4	16.5	1.3	2.6	4.1
2	5.5	11.0	15.6	1.5	3.1	5.1
3	5.1	10.8	14.7	1.3	2.8	4.2
4	5.7	10.1	14.2	1.4	2.6	3.9
5	5.3	10.7	15.9	1.1	2.4	3.5
6	5.0	9.2	14.0	1.0	2.3	3.5
7	4.5	9.0	13.2	1.1	2.3	3.6
8	5.3	10.4	15.6	1.0	1.5	2.0
Mean	5.3	10.2	15.0	1.2	2.4	3.7
SD	0.4	0.7	1.1	0.2	0.5	0.9

PC₂₀: see table 1.

CHANGE IN FEV₁ AND METHACHOLINE PC₂₀

Mean baseline values of FEV₁ and methacholine PC₂₀ on the three study days did not differ significantly (table 3). Mean change in FEV₁ and PC₂₀ from baseline after increasing dosages of active drug and placebo are shown in figures 1 and 2.

Placebo

After placebo FEV₁ decreased gradually and non-significantly from 68% predicted before methacholine challenge to 58% before the fourth challenge. Geometric mean methacholine PC₂₀ decreased from 0.25 mg/l to 0.10 mg/l after the fourth challenge ($p < 0.01$).

Theophylline and enprofylline

There was a dose related effect of both drugs on FEV₁ by comparison with the change after placebo (analysis of variance, $p < 0.01$). There was a significant relation between the increasing FEV₁ and the increasing plasma concentrations for both drugs ($r = 0.57$ for theophylline and 0.46 for enprofylline; $p < 0.01$). The increase in FEV₁ achieved significance after the first

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dose increment for theophylline ($p < 0.05$) and after the second for enprofylline ($p < 0.01$).

Methacholine PC₂₀ differed progressively from the values seen after placebo with increasing plasma concentrations of theophylline and enprofylline (analysis of variance, $p < 0.05$), a significant difference being apparent at the lowest doses (theophylline 5.0 mg/l, $p < 0.01$; enprofylline 1.2 mg/l; $p < 0.05$). Change in methacholine PC₂₀ was related to plasma drug concentration ($r = 0.46$ for theophylline and 0.35 for enprofylline; $p < 0.05$ for both).

There were no significant differences between the effects of theophylline and enprofylline on FEV₁ or methacholine PC₂₀ at any of the three dose increments.

SIDE EFFECTS

Slight to moderate headache and nausea were noticed by three patients with the highest dose of theophylline and headache by three patients with the highest dose of enprofylline. One patient had a slight headache during the placebo treatment day.

Discussion

There was a progressive decline in FEV₁ and methacholine PC₂₀ after repeated methacholine challenges on the placebo day. The likely explanation for this decline is a cumulative bronchoconstrictor effect of methacholine, the interval between the challenges probably being too short for complete recovery. Consequently the present study cannot determine the maximal achievable bronchodilatation in these patients or the xanthine plasma concentration at which this occurs. Comparison of drug and placebo, however, in terms of change in FEV₁ and methacholine PC₂₀ provides a measure of xanthine induced protection, and the dose dependence of this effect can be assessed. Theophylline and enprofylline caused a dose related improvement in FEV₁ and methacholine PC₂₀ by comparison with placebo, significant

Table 3 Effect of increasing doses of theophylline and enprofylline on FEV₁ (mean (SD)) and methacholine PC₂₀ (geometric mean with geometric range of SEM in parentheses)

Xanthine plasma level	Saline		Theophylline		Enprofylline	
	FEV ₁ (%pred)	PC ₂₀ (mg/ml)	FEV ₁ (%pred)	PC ₂₀ (mg/ml)	FEV ₁ (%pred)	PC ₂₀ (mg/ml)
0	0.68 (0.04)	0.25 (0.15-0.40)	0.70 (0.04)	0.21 (0.13-0.33)	0.71 (0.05)	0.21 (0.15-0.30)
1	0.65 (0.04)	0.20 (0.14-0.31)	0.74 (0.03)	0.27 (0.19-0.39)	0.73 (0.04)	0.30 (0.21-0.44)
2	0.64 (0.04)	0.12 (0.07-0.21)	0.75 (0.03)	0.35 (0.23-0.51)	0.76 (0.04)	0.34 (0.22-0.52)
3	0.58 (0.04)	0.10 (0.06-0.17)	0.75 (0.03)	0.32 (0.23-0.46)	0.78 (0.05)	0.28 (0.19-0.41)

Abbreviations as in table 1.

Fig 1 Effect of increasing theophylline and enprofylline plasma concentrations (by comparison with placebo) on FEV₁, expressed as the percentage change from baseline. The bars indicate standard errors. The drug plasma concentrations 1, 2, and 3 correspond to 5.3, 10.2, and 15.0 mg/l for theophylline and 1.2, 2.4, and 3.7 mg/l for enprofylline.

differences being seen with relatively low plasma concentrations of both drugs.

Several studies have shown a moderate protective effect of theophylline against histamine³⁻⁷ and metha-

choline^{4,7} provocation; few have looked at the effect of increasing doses of theophylline on bronchial reactivity. Cockcroft *et al*⁷ found significant protection against histamine provocation only when serum theophylline concentrations were above 10 mg/l. In another study⁷ no correlation was detected between the protective effect of theophylline on histamine challenge and theophylline plasma concentration, possibly because the comparison was between and not within subjects. In a recent report Magnussen and coworkers¹⁷ showed dose related protection of theophylline against histamine challenge and significant protection with low plasma theophylline concentrations (6 mg/l), in accordance with our results. In our study the maximum protective effect (that is, difference from placebo) was 2.0 doubling doses of methacholine for theophylline and 1.7 for enprofylline.

We conclude that although theophylline and enprofylline provide dose related protection against methacholine the effect is relatively small. Both drugs provide some protection at relatively low plasma concentrations. Increasing the plasma concentration of theophylline from 10 mg/l to 15 mg/l and of enprofylline from 2.5 to 3.7 mg/l did not lead to any appreciable further protection. The results are in accordance with recent evidence that most of the possible bronchodilator effect of theophylline is achieved at relatively low plasma concentrations.^{18,19}

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Fig 2 Effect of increasing theophylline and enprofylline plasma concentrations (by comparison with placebo) on methacholine PC₂₀, expressed as the change in methacholine doubling doses from baseline. The bars indicate standard errors. The drug plasma levels 1, 2, and 3 correspond to 5.3, 10.2, and 15.0 mg/l for theophylline and 1.2, 2.4, and 3.7 mg/l for enprofylline.

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