

Enprofylline – Effects of a New Bronchodilating Xanthine Derivative in Asthmatic Patients

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The bronchodilating effect of two doses of peroral enprofylline was compared with placebo in 24 asthmatic patients. Enprofylline produced significantly greater bronchodilatation than placebo. A dose of 2 mg/kg b.wt. and 4 mg/kg b.wt. caused a mean maximal increase in FEV₁ of 26% and 35%, respectively. The degree and the incidence of headache and nausea were estimated by means of a scoring system. Dose-related effects on both parameters were observed. Other side effects were negligible. In seven patients the mean plasma half-life of enprofylline was found to be 113 min. It is suggested that enprofylline should be studied further in patients suffering from obstructive lung disease.

Key words: adenosine antagonism; bronchodilator; enprofylline; half-life.

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Enprofylline (3-propyl xanthine) is a new compound which has proved to be a potent bronchodilator in man and animals (3, 6). In animals, enprofylline is devoid of theophylline-like CNS-stimulant behavioural effects (5, 6) and diuretic action (5). As it also has a negligible degree of metabolism (2), it should be able to lead to improvements in the asthma therapy with xanthines.

The present double-blind cross-over placebo comparison was designed to examine both the bronchodilator effect and the occurrence of significant subjective side effects of enprofylline in asthmatic patients. Plasma levels of enprofylline were analysed in all patients, and in a subgroup of seven, the plasma half-life was calculated.

PATIENTS AND METHODS

Thirty patients suffering from chronic, stable, obstructive lung disease gave their written informed consent to participate on 3 different days in a double-blind, cross-over comparison of placebo versus two doses of enprofylline.

The lung-function stability was controlled by demanding less than a 15% variation from the mean value of the morning recordings of FEV₁ obtained on the 3 examination days. If, after completing 3 examination days, the patient did not fulfil this stability criterion, he was asked to attend the clinic on a 4th day, when the lung function was again measured. The same criterion was then applied, taking the 4th day and 2 of the examination days into account. If the stability criterion was fulfilled, the odd day was repeated. The patient's lung function was otherwise regarded as unstable, and the patient was excluded from the study.

Twenty-four patients fulfilled the stability criterion as defined above; six of these 24 patients obtained a stable lung function after completing the 4th day of the trial (Fig. 1). Five patients had an unstable lung function and one patient left the trial for personal reasons.

The results are based on the 24 stable patients (14 males, 10 females). Their mean age was 46 years (range 24–55 years) and their mean weight 71 kg (range 54–111 kg). The mean duration of asthma was 16 years (range

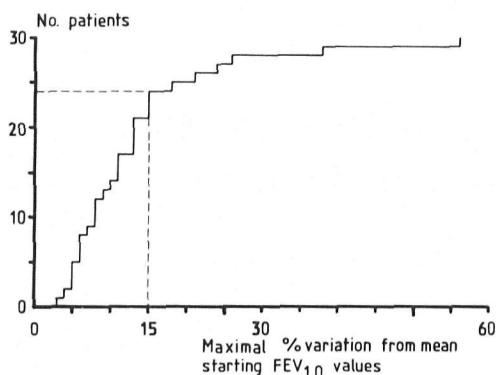


Fig. 1. Number of patients as function of their maximal daily variation. The stippled line corresponds to a maximal variation of 15%.

2–43 years). Sixteen patients suffered from extrinsic asthma defined as a typical anamnesis, a positive skin prick test to common allergens and specific plasma IgE concentration higher than 350 IU. Eight patients had intrinsic asthma.

The mean basal level of FEV₁ was 2.05 l, with a range of 1.25–3.8 l. Two patients had a basal level below 1.5 l. The mean expected level (FEV₁) was 3.41 l, with a range of 2.49–4.55 l. Basal FEV₁ in percent of the expected value was 60.1%. The mean reversibility (increase in FEV₁ 5 min after the inhalation of two puffs of terbutaline aerosol) was 32% (range 20–69%). All patients used sympathomimetics, 17 inhaled beclomethasone, 13 patients received theophyllines, four patients sodium cromoglycate, and two patients oral prednisone.

No patients suffered from heart, liver or kidney diseases, nor did they have any current infections or a history of migraine or seizures. No pregnant women were included.

The patients were randomly given enprofylline in a dose of 2 mg/kg b.wt. or 4 mg/kg b.wt. or placebo on 3 different days. The tablets looked identical in order to maintain the double-blind character of the study.

The two different doses and the placebo were coded for each patient and dispensed in a ran-

domized sequence for the 3 days. A duplicate set of tablets was prepared in case the patient needed to repeat 1 day because of instability. The code was known only to a pharmacist who was not involved in patient care or in the evaluation.

All oral medication, except glucocorticoids and beta-receptor stimulants, had to be discontinued 56 h before attendance at the clinic. Ten hours before the visit, the patients were taken off oral beta-receptor stimulants and spray treatment with sympathomimetics, antimuscarinics and/or glucocorticoids. If necessary, a rimiterol spray (Pulmadil®) was permitted up to 4 h before the visit to the hospital. On each visit the patient was asked about his drug intake during the last 24 h before attending the clinic.

Beverages containing xanthine-like compounds, i.e., coffee, tea, coca-cola and chocolate, were not ingested the preceding night nor on the day of the trial.

Data collection

The patients stayed in the clinic from 8.00 a.m., when the tablets were administered, until 12.00 noon. The maximal FEV₁ values of three attempts were read directly from graphs drawn by a Wedge Bellows spirometer (Vitalograph) immediately before drug intake and every half hour. All values were corrected to BTPS values. After each determination of pulmonary function, a 5 ml venous blood sample mixed with heparin (Venoject® system) was obtained from an antecubital vein. The plasma was separated by centrifugation (5 min, 3700 r.p.m.) and analysed for enprofylline content by HPLC technique. Blood pressure and heart rate were measured before and 2 and 4 h after drug intake.

Every 60 min the patients were questioned in a standardised manner about adverse reactions (headache, nausea and palpitations) experienced during the preceding hour. Symptoms were graded on the following scale: 0 = absent, 1 = slight, 2 = moderate, 3 = severe.

To determine the half-life of enprofylline in patients, blood samples were obtained from nine patients every second hour until 8.00 p.m.

Statistics

Differences were determined with the Student's *t*-test for paired and unpaired samples. A difference corresponding to a *P*-value of less than 0.05 was considered significant.

RESULTS

Spirometry

Fig. 2 shows the spirometric values obtained after the two doses of enprofylline and placebo. A dose of 2 mg/kg resulted in significantly ($P < 0.05$) higher mean values than those achieved with placebo after 60, 90, 120, 150 and 180 min. A dose of 4 mg/kg resulted in significantly ($P < 0.05$) higher mean values than those with placebo after 60, 90, 120, 150, 180, 210, and

Time (min)	Placebo	2 mg/kg	4 mg/kg
0	2.05 $\pm$ 0.92	2.02 $\pm$ 0.77	1.97 $\pm$ 0.77
30	2.13 $\pm$ 0.88	2.16 $\pm$ 0.78	2.12 $\pm$ 0.79
60	2.07 $\pm$ 0.78	2.24 $\pm$ 0.79	2.28 $\pm$ 0.78
90	2.05 $\pm$ 0.84	2.36 $\pm$ 0.88	2.24 $\pm$ 0.74
120	2.01 $\pm$ 0.81	2.37 $\pm$ 0.86	2.26 $\pm$ 0.76
150	2.10 $\pm$ 0.88	2.29 $\pm$ 0.86	2.34 $\pm$ 0.76
180	2.08 $\pm$ 0.82	2.32 $\pm$ 0.80	2.35 $\pm$ 0.77
210	2.03 $\pm$ 0.83	2.18 $\pm$ 0.73	2.36 $\pm$ 0.78
240	2.15 $\pm$ 0.78	2.15 $\pm$ 0.72	2.39 $\pm$ 0.79

240 min. A dose of 4 mg/kg also produced significantly ($P < 0.05$) higher mean values than 2 mg/kg after 210 and 240 min. (See Table 1).

The mean maximum increases $\pm$ SD of FEV₁ as a percentage of the initial values were 11.9 ± 10.8 , 26.0 ± 18.5 , and 35.2 ± 26.4 for placebo and enprofylline in a dose of 2 mg/kg and 4 mg/kg, respectively. The mean maximum increases in FEV₁ after 2 and 4 mg/kg of enprofylline were significantly ($P < 0.05$) higher compared with placebo.

Plasma levels and half-life of enprofylline

2 mg/kg of enprofylline resulted in a maximum plasma concentration of 1.83 ± 0.67 μ g/ml (mean $\pm$ SEM) 120 min after intake, while 4 mg/kg resulted in a concentration of 3.32 ± 0.91 μ g/ml 180 min after intake. The mean maximum plasma concentrations reached at any time after administration were 2.11 ± 0.61 μ g/ml and 3.67 ± 1.16 μ g/ml after 2 and 4 mg/kg respectively. The period of time required in order to reach plasma peaks showed a broad distribution around 2 h after 2 mg/kg and a biphasic distribution around 150 and 240 min after 4 mg/kg.

In two of the nine patients in whom blood samples were collected during a period of 12 h after intake, it was not possible to identify an elimination phase due to delayed absorption. The determination of the half-life ($t_{1/2}$) for enprofylline is therefore based on results from

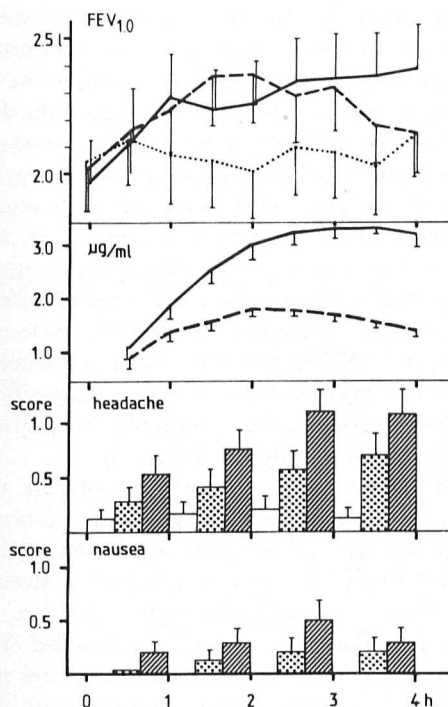


Fig. 2. Mean values for FEV₁, plasma concentrations, and side effects in 24 patients treated with enprofylline and placebo. Bars indicate SEM values.

Placebo: or □

2 mg/kg: - - - - - or ▨

4 mg/kg: ——— or ■

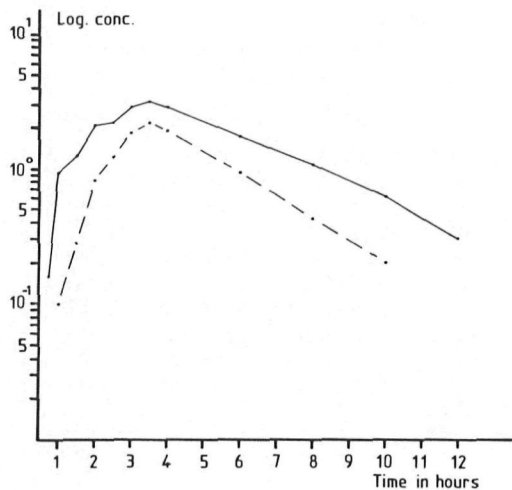


Fig. 3. Plasma concentrations obtained after two doses of enprofylline as function of time in a line-log scale.

2 mg/kg: -----
4 mg/kg: —————

seven patients (4 males and 3 females) with a mean age of 37 years (range 25–55 years) and a mean body weight of 75 kg (range 50–111 kg). A set of plasma concentration curves is illustrated in Fig. 3 for one patient. The value of $t_{1/2}$ was 113 ± 15 min (mean $\pm$ SEM).

Side effects

Determinations of blood pressure and heart rate showed no differences between placebo and active treatment with enprofylline.

Twelve patients complained of headache when given the low dose of enprofylline, 16 experienced headache after the high dose and three patients after the placebo. A dose of 2 mg/kg produced significantly ($P < 0.05$) higher scores than the placebo during the 4th h, whereas a dose of 4 mg/kg resulted in significantly ($P < 0.05$) higher scores than the placebo during the 1st, 2nd, 3rd and 4th h. Enprofylline in a dose of 4 mg/kg produced significantly ($P < 0.05$) higher scores than 2 mg/kg during the 3rd h (Fig. 2).

Five patients complained of nausea when given the low dose, nine with the high dose and no patients experienced nausea after receiving

placebo. One patient treated with the high dose vomited. 4 mg/kg resulted in a significantly ($P < 0.05$) higher score for nausea than the placebo during the 2nd, 3rd and 4th h (Fig. 2).

One patient developed palpitations after taking the placebo, while three developed palpitations after 4 mg/kg. One patient experienced slight dizziness after 2 mg/kg of enprofylline.

DISCUSSION

Various mechanisms have been proposed as explaining the pharmacological actions of theophylline. These include inhibition of the catabolism of cyclic AMP, mobilisation of intracellular calcium and antagonism of adenosine receptor-mediated effects (7). Of these mechanisms, only adenosine antagonism seems to be definitely produced at therapeutic concentrations of theophylline. Indeed, some well-known characteristics of theophylline, such as diuresis and CNS-stimulant behavioural effects, probably reflect adenosine receptor antagonism (1, 4). It is therefore particularly interesting that enprofylline did not, over a wide range of concentrations, antagonise the inhibitory effects of adenosine in smooth muscle (trachea) and nervous tissue (myenteric plexus) (5), and that it was devoid of theophylline-like natriuretic and CNS-stimulant behavioural effects (5). As enprofylline has, in addition, proved to be a potent bronchodilator in man and animals (6), it is suggested that adenosine antagonism is neither a necessary nor a desirable characteristic of xanthine anti-asthmatic drugs (5).

An earlier study, in which enprofylline was given as plain tablets on an empty stomach, showed a fast and complete absorption (2). But when enprofylline, as in this study, was given in the same type of tablets *after* breakfast, an irregular absorption pattern was obtained. This finding may be explained by the possibility that absorption of enprofylline from the stomach is negligible (2).

The spirometric data confirm that enprofylline is a bronchodilator. Due to the slow absorption of enprofylline, a clear dose response relation was not revealed during the 4 h of

observation. Significant adverse reactions were dose-related headache and nausea. It is known that non-users of theophylline may have transient adverse reactions when exposed to this drug. For this reason it is important to determine whether the number of theophylline non-users are overrepresented in the groups that complained of adverse reactions. Analysis revealed a small overrepresentation of patients who did not use theophylline in their daily medication in the group complaining of nausea, but no such finding in the group with headache. The cause of these side effects, their frequency and severity in relation to other bronchodilators, and the possibility that they are transient during long-term therapy cannot be settled on the basis of present information, but will be dealt with in future studies.

Enprofylline was shown to undergo a negligible metabolic degradation and has a high renal clearance (2). The pharmacokinetic information obtained in this study is consistent with previous results obtained from healthy volunteers (2).

Thus, the present study confirmed that enprofylline is a bronchodilator in asthmatic patients, that significant dose-related headache and nausea may occur and that the half-life of enprofylline in asthmatic patients is short.

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