Comparison between theophylline and an adenosine non-blocking xanthine in acute asthma


ABSTRACT: Enprofylline, a drug without adenosine antagonism and theophylline, a potent adenosine antagonist, were compared, double-blind, randomized, in acute asthma (n=33). The drugs were given intravenously as loading over 10 min followed by maintenance infusion for 24 h. Mean final plasma levels were very high with enprofylline (14 mg/l), and larger than calculated with theophylline (16 mg/l). Seven patients had maximum levels of enprofylline ranging between 16 and 42 mg/l. Extreme plasma levels of enprofylline were not associated with any theophylline-like central nervous system excitatory effects related to seizure-inducing ability. Some irregularities in the heart rhythm did not raise clinical problems and no significant difference between enprofylline and theophylline was recorded. At 1 h patients on enprofylline (mean plasma level: 5.7 mg/l) and theophylline (12.2 mg/l) had improved their peak expiratory flow rates by 31% and 15% (p<0.05), respectively. The improvement in lung function after 24 hours did not differ between treatments suggesting that the high levels of enprofylline were supramaximal for its anti-asthma effects in this situation. In conclusion, with enprofylline it is demonstrated that an adenosine non-blocking xanthine derivative may lack CNS-excitatory effects, but be more potent than theophylline in the treatment of acute asthma.


The pharmacology of enprofylline, 3-propylxanthine, is the basis for the original proposal that adenosine antagonism is an undesirable characteristic of anti-asthma xanthines [1]. While being a more potent airway anti-inflammatory and relaxant drug [2, 3] enprofylline differs from theophylline, 1, 3 dimethylxanthine, in several extrapulmonary effects. Thus enprofylline seems to lack diuretic, free fatty acid releasing, gastric secretory, and excitatory central nervous system behavioural effects [1, 2]. These differences may be explained by enprofylline being a poor and theophylline a potent antagonist of inhibitory actions of the purine nucleoside adenosine [1, 2]. Of particular importance for the use of xanthines without adenosine antagonism in acute asthma is their potential lack of CNS-excitatory effects [1, 2, 4]. There are also pharmacokinetic differences between enprofylline and theophylline. Enprofylline is largely eliminated by active renal secretion and is more rapidly eliminated than theophylline which undergoes liver metabolism [2, 5].

The present study set out to compare the efficacy and side-effects of enprofylline and theophylline in patients with acute asthma. Both drugs were given as an initial bolus followed by a 24 hour infusion regimen aiming at maintaining enprofylline at a plasma level about 4 µg·ml⁻¹ and theophylline at about 10 µg·ml⁻¹. Calculation of doses was based on previously published data on the clearances of the drugs [5]. Thus theophylline was maintained at or slightly above therapeutic levels. However, with enprofylline remarkably high plasma levels were attained. Besides giving information on clinical efficacy the present study provides side-effects and safety data for this novel type of xanthine compound in severely ill patients.

Patients

The trial was designed as a double-blind and randomized parallel group comparison of intravenously administered enprofylline and theophylline. Thirty-three adult patients, (17 female and 16 male) with a mean age of 49 years gave their informed consent to participate in the study. They were on maintenance treatment for their asthma with inhaled β₂-receptor agonist (27/33), inhaled steroid (18/33), oral steroid (12/33), oral β₂-receptor
agonist (3/33), and oral theophylline (4/33). All of them had an acute asthmatic attack with a peak expiratory flow rate (PEF; l/min⁻¹) less than 50% of the predicted normal value (mean 28%) and a pulse rate (HR) above 100 beats per min (mean 110 beats per min). Four patients were admitted to the hospital twice for treatment of an acute asthma attack. On the second occasion they were, according to protocol, given alternative treatment but considered to be new patients. The total number of admissions was thus 37; 18 were treated with enprofylline and 19 with theophylline (table 1). In addition to asthma, 11 patients had chronic bronchitis and 1 had emphysema. Apart from 3 patients with well-compensated cardiac insufficiency and 1 patient with mild hypertension controlled with metfurside (Baycaron®), all were free from significant cardiac, liver, renal or thyroid diseases.

The study was approved by the Norwegian Drug Control Authority and was performed in accordance with the Declaration of Helsinki.

**Methods**

Cannulas were inserted into the veins of both forearms, one for blood sampling and the other for administration of the treatment drug. Enprofylline was given as a loading dose of 2 mg·kg⁻¹, injected for 10 min, followed immediately by an infusion of 1 mg·kg⁻¹·h⁻¹. A clearance value for enprofylline of 0.25 l·kg⁻¹·h⁻¹ (range 0.17-0.33 l·kg⁻¹·h⁻¹) has been observed in healthy volunteers [5] and hence the dose regimen was estimated to give a plasma concentration of 4 mg·l⁻¹. The loading dose of theophylline was 4 mg·kg⁻¹ which was followed by an infusion of 0.5 mg·kg⁻¹·h⁻¹. A clearance value for theophylline of 0.05 l·kg⁻¹·h⁻¹ would then give a plasma concentration of 10 mg·l⁻¹. Infusion was continued for 24 hours or stopped earlier if the patient became well or if intolerable side-effects occurred.

Immediately after the start of the maintenance infusion 200 mg hydrocortisone (Solu-Cortef®) was given intravenously. This procedure was repeated after 8 hours. Together with the first hydrocortisone dose, 40 mg prednisolone was given orally. When considered absolutely necessary adrenaline (0.3 mg) was given subcutaneously 4 hours after starting infusions of xanthines. Oxygen (100%) 0.5 l·min⁻¹ was given via a nasal catheter during the first 4 hours, and if needed, continued throughout the trial.

PEF, HR, BP, clinical status, blood gases (repeated arterial punctures) and xanthine concentrations were recorded at 0, 1, 2, 4, 6, 12, 18 and 24 hours. A morning blood sample was used for clinical chemistry analyses. Adverse experiences were noted by questioning the patients about presence of symptoms: headache, tremor and nausea, at the same times, or after information was volunteered or observed during the trial. PEF was measured with a Wright peak flow meter. The highest of two consecutive readings was recorded. The blood gases were analysed by means of an automatic blood gases analyser (ABL1-Radiometer, Copenhagen).

The blood samples (5 ml) for determinations of the xanthines were collected in heparinized tubes (Venject®). After centrifugation the plasma was stored at -20°C pending analysis. The drug analyses were performed by liquid chromatography with coupled columns [6]. Selected (high) plasma concentrations of enprofylline were verified by gas chromatography and mass spectrometry (C. Lindberg and L.-E. Edholm, unpublished observations).

The patients were connected to a two-channel ECG tape recorder for continuous recording during 24 h (Del Mar Avionics Electrocardiorecorder model 445 B). This procedure could not be performed in 4 patients (1 on theophylline and 3 on enprofylline) due to a technical error. The 24 hour tapes were analysed on an Avionics Arrhythmia Analyzer (model 9000 A Trendsetter II System, Del Mar Avionics, Calif, U.S.A.). This system assumes that the investigator teaches the computer to recognize normal beats, ventricular extrasystoles and supraventricular extrasystoles [7]. The computer stops automatically and lights up for any of the following findings: ventricular bigeminy, ventricular pairs, R-on-T beats, ventricular tachycardia, single supraventricular beats, pairs and triplets, supraventricular tachycardia, pauses (defined as two seconds or more), bradycardia and two-R-R intervals.

The results of PEF, HR and arterial blood pressures (BP; mm Hg), as well as of the blood gas analyses (Paco₂, Paco₃, pH, and base excess (BE)) were compared for the

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### Table 1. – Patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>Enprofylline</th>
<th>Theophylline</th>
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<tbody>
<tr>
<td>Number of admissions:</td>
<td>18; 8/10</td>
<td>19; 12/7</td>
</tr>
<tr>
<td>Age, years; mean (range)</td>
<td>49 (18-78)</td>
<td>50 (20-78)</td>
</tr>
<tr>
<td>Height cm; mean (range)</td>
<td>170 (155-182)</td>
<td>173 (160-187)</td>
</tr>
<tr>
<td>Weight kg; mean (range)</td>
<td>72 (51-87)</td>
<td>72 (54-85)</td>
</tr>
<tr>
<td>Duration of asthma years; mean (range)</td>
<td>27 (3-40)</td>
<td>19 (1-62)</td>
</tr>
<tr>
<td>PEF l·min⁻¹; mean (sd)</td>
<td>138 (48)</td>
<td>141 (59)</td>
</tr>
<tr>
<td>PEF % of predicted normal; mean (sd)</td>
<td>29 (8)</td>
<td>28 (10)</td>
</tr>
<tr>
<td>Pulse rate beats per min; mean (sd)</td>
<td>107 (10)</td>
<td>114 (10)</td>
</tr>
<tr>
<td>Syst. blood pressure mm Hg; mean (sd)</td>
<td>143 (19)</td>
<td>150 (22)</td>
</tr>
<tr>
<td>Diast. blood pressure mm Hg; mean (sd)</td>
<td>90 (15)</td>
<td>88 (16)</td>
</tr>
</tbody>
</table>
Effects of Enprofylline at High Plasma Levels

EFFECTS OF ENPROFYLLINE AT HIGH PLASMA LEVELS

enprofylline group and for the theophylline group by using the t-test. The changes in these variables were analysed separately for the first hour and for the 24 hour maintenance infusion time. In addition, a repeated measurement analysis was performed, but the result from this did not differ in any important way from the univariate results and is not reported here. The results of the assessments of the clinical status were analysed by means of the chi-square test. The scores for side-effects for both treatments were compared by using the Wilcoxon test.

Results

Plasma concentrations

Mean and range of plasma concentrations for enprofylline and theophylline are shown in figure 1. Three patients had theophylline plasma levels above 5 mg·L\(^{-1}\) (5.4, 8.6, 22.0 mg·L\(^{-1}\)) on arrival at hospital although they had denied intake of theophylline. Theophylline rose to 31.8 mg·L\(^{-1}\) in the patient with a level of 22.0 mg·L\(^{-1}\). During the course of infusion the mean theophylline plasma level increased slightly (increment 4.1 mg·L\(^{-1}\) to 16.3 mg·L\(^{-1}\)) which is above the predicted value of 10 mg·L\(^{-1}\).

The mean plasma concentration of enprofylline after loading infusion was 5.5 mg·L\(^{-1}\) and after completion of maintenance infusion it had increased to 14.3 mg·L\(^{-1}\). Seven patients had maximum enprofylline plasma concentrations ranging from 16.1 to 42.1 mg·L\(^{-1}\) (four of these had 24 h ECG recording), while the remaining patients had maxima ranging from 5.7 to 13.0 mg·L\(^{-1}\). Two patients ending up with plasma levels of enprofylline (16.1 and 20.2 mg·L\(^{-1}\)) entered the study a second time. They then received theophylline and reached plasma levels of 14.7 and 10.8 mg·L\(^{-1}\), respectively.

Peak expiratory flow

At 1 h the mean increase in PEF was about twice as large with enprofylline (31%) as compared with theophylline (15%; p<0.05). The plasma levels at 1 h were 5.7±1.3 (Mean ±SD) mg·L\(^{-1}\) of enprofylline and 12.2±4.8 mg·L\(^{-1}\) of theophylline, respectively. The mean maximum increase in PEFR from the base-line values at entry of the study was 82% (p<0.001) and 80% (p<0.001) for the enprofylline and theophylline treatments, respectively (fig. 2). The mean increase, expressed as a change in relation to the predicted normal PEFR, was from 28% to 51% for either treatment. The improvement of the patients, as assessed by the physician, was not different between the two treatments. There was no significant difference between the effects of the two treatments on peak expiratory flow for the whole 24 hour period. Six patients (4 on theophylline, 2 on enprofylline) received adrenaline treatment. Adrenaline was given at 70 min (one theophylline patient) or beyond 4 h (5 patients).

Cardiovascular effects

Heart rate as monitored continuously by the ECG decreased slightly during treatment. Recordings from 4 of those patients reaching quite high plasma levels of

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**Fig 1.** - Mean plasma levels of enprofylline (---) and theophylline (—) are illustrated. The shaded area is the range.

**Fig 2.** - The mean improvements in PEFR during the course of treatment with enprofylline (-----) and theophylline (—) are illustrated. Bars indicate SEM.
enprofylline (range of maxima: 16-42 mg·l⁻¹) indicated a sinus tachycardia with heart rates higher (mean 127.2; 95% confidence limit 114.7-139.8, n=4) than patients with lower maximal enprofylline levels (mean 103.5; 95% confidence limit 91.9-115.1, n=9) (fig. 3). No significant difference was seen with regard to cardiac arrhythmias in these 4 patients compared with the rest of the group. Mean systolic and diastolic blood pressures decreased between 5 and 15 mm Hg after either enprofylline or theophylline and the decreases were not significantly different between the two treatments.

Ventricular extrasystoles (VES) were seen in 16/18 patients treated with theophylline and in 10/15 patients treated with enprofylline. Single as well as bigeminal, paired and R-on-T beats were frequent. Brief episodes of nonsustained ventricular tachycardia were seen in one patient on theophylline and in two on enprofylline. Supraventricular extrasystoles were present in all but one patient on theophylline. Supraventricular tachycardia was found in 6/18 patients on theophylline and 6/15 patients on enprofylline, with maximum heart rates of 193.5 and 171.8 beats per min, respectively. Brief episodes of AV block II with 2:1 conduction were seen in two patients on enprofylline. No statistically significant difference in any of the analysed arrhythmias was observed between the two treatments.

<table>
<thead>
<tr>
<th>Table 2. - Number of patients with adverse experiences</th>
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<tbody>
<tr>
<td>Enprofylline</td>
</tr>
<tr>
<td>dizziness</td>
</tr>
<tr>
<td>headache</td>
</tr>
<tr>
<td>paraesthesia</td>
</tr>
<tr>
<td>unspecified tremor</td>
</tr>
<tr>
<td>dyspepsia</td>
</tr>
<tr>
<td>nausea</td>
</tr>
<tr>
<td>vomiting</td>
</tr>
<tr>
<td>general discomfort</td>
</tr>
<tr>
<td>chest pain</td>
</tr>
<tr>
<td>hypotension</td>
</tr>
<tr>
<td>sweating</td>
</tr>
<tr>
<td>vasovagal reaction</td>
</tr>
<tr>
<td>patients with adverse reactions</td>
</tr>
<tr>
<td>patients treated with antiemetics</td>
</tr>
<tr>
<td>patients treated with analgeses</td>
</tr>
<tr>
<td>patients with adverse reactions at entrance</td>
</tr>
</tbody>
</table>

* Scores significantly larger than theophylline data (p<0.001).

Clinical chemistry and blood gases

The clinical chemistry tests showed normal values and a few near-normal values. It was noted that also in the seven patients with high levels of enprofylline normal clinical chemistry was obtained. Plasma potassium was not unduly reduced in these patients (mean (sn)) 4.00 (0.45) mmol·l⁻¹; n=7 (normal range 3.5-5.0 mmol·l⁻¹). Blood gases (Pao₂ and Paco₂), pH and base excess improved during treatment and were not significantly different in the two treatment groups. (Data not shown).

Adverse experiences

Adverse reactions such as headache and nausea were frequent and more so with enprofylline than with theophylline (table 2). The nausea induced by enprofylline appeared to be concentration dependent. Patients with a plasma level of enprofylline above 10 mg·l⁻¹ had a higher incidence of nausea than those below 10 mg·l⁻¹, who had nausea scores equal to theophylline-treated patients. The scores for subjective non-specific tremor tended to decrease during treatment. In no case was enprofylline treatment associated with arousal effects. Notably in those seven patients with plasma levels of enprofylline between 16 and 42 mg·l⁻¹ there were no signs of CNS excitation, odd behaviour, agitation or seizures that are associated with toxic levels of theophylline [8].

Discussion

Theophylline dose-regimen

There was a tendency for the theophylline plasma level to increase with time suggesting that a maintenance infusion of less than 0.5 mg·kg⁻¹·h⁻¹ of theophylline may be adequate in patients with acute asthma. It was noted that among those patients who denied recent intake of theophylline, three had significant plasma levels of this drug, including one value of 22 mg·l⁻¹. Analyses of theophylline plasma levels prior to infusion therapy may be mandatory if potentially toxic plasma levels (>20-30 mg·l⁻¹) are to be avoided.

Enprofylline dose-regimen

The intravenous maintenance infusion of enprofylline produced plasma levels that by far exceeded the predicted ones (fig. 1). Since elimination of enprofylline is almost entirely dependent on renal excretion [5], the present data suggest that the renal drug handling mechanism utilized by enprofylline is significantly compromised in patients with an attack of acute severe asthma. The active secretion of a drug in the kidneys is in principle saturable and dose-dependent pharmacokinetics of enprofylline after high oral doses has been described (unpublished observations by Laursen and Borg). The present results may in part be related to reduced urine production in patients with acute severe asthma [9].

Among these reaching particularly high levels of enprofylline (16-42 mg·l⁻¹) there was a slight over-representation of old and obese patients and all patients received the antiemetic drug metoclopramide. This drug may also have affected the elimination of enprofylline since it has been shown to reduce significantly renal
plasma flow in man [10]. Clearly, the maintenance infusion dose-rate of enprofylline must be considerably reduced in acute asthma.

**Effects of the two xanthines on peak expiratory flow**

The exact mode of action of xanthines in asthma is not known. In particular, in severe asthma these drugs have a unique effect not produced by other antiasthma drugs even when given in combination at high doses [11]. Two multicentre studies on the effects of xanthines in acute asthma have recently been completed. One demonstrated that even after large doses of salbutamol had been given either iv (0.2-0.5 mg) or by inhalation (7-15 mg) theophylline produced a highly significant further improvement in lung function [12]. The other study showed that a single intravenous dose of enprofylline (2 mg kg⁻¹) was about equally effective as inhalation of 10 mg terbutaline [13]. In this study, enprofylline, consistent with its greater potency, see [2, 3, 14], improved PEFR more than theophylline during the first hours of treatment. Comparisons made beyond 4-6 h are complicated by the effects of the glucocorticoid treatment. The patients had no particular benefit from the very high (supra therapeutic) plasma levels of enprofylline.

At plasma levels corresponding to 50-100 mg·l⁻¹ and above of theophylline, enprofylline produced nausea and headache but it did not produce any of the characteristic signs of slight to severe CNS toxicity of theophylline (e.g., tremor, restlessness, anxiety, agitation, hallucinations and seizures). The lack of these effects is consistent with the view, also based on animal studies employing unlimited doses, that the difference in CNS-stimulant behavioural effects between enprofylline and theophylline is qualitative in nature [2, 4]. If it is further consistent with observations that theophylline is a potent antagonist of neuro depressant actions of adenosine whereas enprofylline lacks this antagonism [1, 2, 4].

A high frequency of arrhythmias among patients hospitalised for acute asthma has been reported [15]. None of the irregularities in the heart rhythm observed in this study raised any clinical problems and were therefore probably clinically unimportant. Previously, CONRADSON *et al* [16] have demonstrated that both enprofylline and theophylline when given together with terbutaline increase the frequency of ventricular arrhythmias. The clinical significance of these findings, which were obtained at low plasma levels of the xanthines, was considered minor [16].

It has been established that toxic levels of theophylline, in particular after an acute dose, are associated with hypokalaemia [17, 18], leading to conduction abnormalities and atrial and ventricular arrhythmias [17]. It is, therefore, of interest to note that with the present overdosage of enprofylline in severe asthma no such potassium lowering effect could be demonstrated.

In conclusion, the present study has demonstrated that intravenous enprofylline is effective in acute asthma but maintenance infusion of it may lead to unacceptably high plasma levels. At reasonable plasma levels side-effects of enprofylline did not differ from those of theophylline. At high levels enprofylline was without excitatory CNS side-effects. It is suggested that adenosine non-blocking xanthines may be without serious CNS side effects such as seizures in the treatment of asthmatic patients.

**Acknowledgements:** We thank Mrs I Källén for typing the manuscript.

**References**


RÉSUMÉ: Nous avons comparé, dans 32 cas 32 d'asthme aigu, au cours d'une étude en double aveugle et randomisée, l'Enprofylline et la Théophylline. Les produits ont été administrés par voie intraveineuse, sous forme d'une dose chargée pendant 10 minutes, suivie par une perfusion d'entretien pendant 24 h. Les taux plasmatiques moyens finaux s'avèrent très élevés avec l'Enprofylline (14 mg·l⁻¹) et plus élevés que ceux calculés avec la Théophylline (16 mg·l⁻¹). Chez 7 patients, les taux maximaux d'Enprofylline se situent entre 16 et 42 mg·l⁻¹. Des taux plasmatiques extrêmes d'Enprofylline sont sans relation avec des effets d'excitation du système nerveux central en rapport avec une possibilité d'induction de convulsions comme c'est le cas pour la Théophylline. Quelques irrégularités du rythme cardiaque n'ont pas entraîné de problème clinique et l'on a trouvé à cet égard aucune différence significative entre l'Enprofylline et la Théophylline. Après une heure, les patients sous Enprofylline (taux plasmatique moyen 5.2 mg·l⁻¹) et sous Théophylline (12.2 mg·l⁻¹) ont amélioré leur débit expiratoire de pointe de 31 et 15% respectivement (p<0.05). L'amélioration du débit expiratoire de pointe après 24 h est semblable avec les deux traitements, ce qui suggère que les taux élevés d'Enprofylline sont supra-maximaux pour son activité anti-asthmatique dans ce cas. En conclusion, l'Enprofylline est plus puissante que la Théophylline, n'aurait pas d'effets excitatoires sur le système nerveux central, et peut être adaptée pour un traitement intra-veineux bref initial dans l'asthme aigu. Eur Respir J., 1990, 3, 27-32.