

Efficacy of enprofylline in acute airway obstruction

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The efficacy and safety of different regimens of intravenously administered enprofylline, an anti-asthma xanthine, were evaluated in a randomized open study, including 155 patients with acute exacerbation of obstructive lung disease. The regimen 2.5 mg/kg i.v. over 10 min was canceled after seven patients had been included, due to two cases of hypotensive/vasovagal reactions. The regimens 2.0 mg/kg/20 min and 2.5 mg/kg/20 min were significantly more effective with regard to bronchodilation than 2.0 mg/kg/10 min (PEF increase +35%, +30% and +17% respectively). Nausea and headache were the most common side effects (16-33% and 23-33% of the patients respectively on different regimens) with the lowest frequency on 2.0 mg/kg/20 min. Four additional hypotensive reactions occurred; one on each 2.0 mg/kg regimen and two on 2.5 mg/kg/20 min. The regimen 2.0 mg/kg/20 min was found to be the most favourable with regard to efficacy and side effects. Enprofylline i.v. was found to be an effective bronchodilating treatment of acute airway obstruction but the frequency of side effects has to be considered.

Key words: asthma; bronchodilator; enprofylline; xanthine.

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Enprofylline (3-propylxanthine) is a xanthine derivate which is found to have a bronchodilating effect similar to that of theophylline at 3-5 times lower plasma concentrations (4-7). Previous studies have shown that when enprofylline is administered intravenously in a dose of 1.5-2 mg/kg body weight to patients with acute asthma it is associated with an improvement of lung function similar to that from a "standard dose" of theophylline (2.5 mg/kg) to patients who are on oral maintenance therapy with theophylline (1). The aim of the present study was to evaluate the efficacy and safety of various doses of enprofylline administered i.v. to patients with an exacerbation of their obstructive lung disease.

PATIENTS AND METHODS

A total of 155 patients (68 women) with an acute exacerbation of their obstructive lung disease gave their written informed consent to participate in this randomized open multi-centre study involving two Danish and five Swedish hospitals. The study was approved by the respective local Medical Ethics Committees. Patients with cardiac or renal diseases were excluded from the study. Demographic patient data and asthma medication 24 h prior to the study are given in Table 1. Each patient was randomized to one of three different enprofylline treatment schedules 2.0 mg/kg/10 min, 2.5 mg/kg/10 min or 2.5 mg/kg/20 min. Enprofyl-

Table 1

Demographic data and asthma medication given within 24 h before the study. Data are not included for three patients who were excluded from analysis of "efficacy of treatment due to protocol violation"

Patients	152	
men	86	
women	66	
Age (years)*	55	(20-74)
Height (cm)*	170	(147-193)
Body weight (kg)*	771	(0-121)
Steroids		
oral	22 %	
aerosol	47 %	
Beta-2-agonist		
oral	76 %	
aerosol	71 %	
nebulised	18 %	
Oral theophylline	63 %	
Antiallergic medication	2 %	
Anticholinergic medication	1 %	

*mean (range)

line was administered as an i.v. solution, 10 mg/l, by means of a constant infusion pump (Injectomat-S3). The regimen 2.5 mg/kg i.v. over 10 min was cancelled after seven patients had been included, due to two cases of vaso-vagal/hypotensive reactions. It was replaced by 2.0 mg/kg/20 min. The data from the mentioned seven patients, and three other patients (non-valid due to protocol violation), were not included in the statistical analyses of efficacy of bronchodilation.

The peak expiratory flow (PEF, l/min, mini-Wright peak flow meter), heart rate (HR, beats/min, i.e. peripheral pulse rate) and blood pressure (BP, mmHg) were recorded before treatment, immediately after completion of the infusion and 60 min after the start of the infusion. Venous blood samples for analysis of plasma xanthine concentrations were drawn 60 min after the start of the infusion. At this time the patients were also asked about the possible occurrence and severity of adverse experiences and their overall opinion of their clinical condition. The intensity scores "none, mild, moderate, severe" were used. The patients were also asked to score the outcome of their clinical status after therapy according to a graded scale

"markedly improved, improved, unchanged, deteriorated, markedly deteriorated".

Statistics

Changes in PEF, HR and BP were analysed by means of t-tests. Analyses of variance of PEF and HR values were performed. Non-parametric tests were used for scoring and adverse experiences. A *P*-value < 0.05 was considered to be statistically significant.

RESULTS

The mean values $\pm$ SD for PEF and HR on admission to the study and the changes recorded 60 min later related to the different enprofylline therapies are given in Table 2. Because of a substantial difference between the HR values (*P* = 0.07) and a significant dependence between the baseline HR and change in HR (*P* < 0.001), the data from centre 2 and the data from the remaining centres were analysed separately. A similar subdivision was made for PEF, although no significant centre effect was detected.

The baseline PEF at centre 2 tended to be lower than at the other centres (mean 136 vs. 231 l/min), while the responses to enprofylline were similar. Compared with baseline values on admission to the study all three therapies were associated with a significant improvement in lung function (PEF) at 60 min. The mean increase in PEF with 2.0 mg/kg/10 min (+ 38 l/min = + 17%) was significantly less (< 0.05) than with 2.0 mg/kg/20 min (+ 69 l/min = + 35%) and 2.5 mg/kg/20 min (+ 65 l/min = + 30%). There was no significant difference between the two latter regimens with regard to change in PEF.

The heart rate on admission to the study was significantly higher at centre 2 than in the other centres, with a difference of 30 beats/min (bpm). Compared with baseline values on admission to the study the mean heart rate at centre 2 at 60 min was 13-32 bpm lower with the various therapies. The corresponding changes at the other centres varied between -2 and + 5 bpm.

All three therapies were associated with a similar decrease in systolic and diastolic blood pressures at 60 min ranging between 5 and 15 mmHg.

In the mean the patients rated their clinical condition at 60 min as slightly better than "improved", but there was no significant difference between the three regimens (Table 3). The three most common adverse experiences were headache, nausea and dizziness. The therapy 2.0 mg/kg/20 min was accompanied by the lowest frequency as well as the lowest mean in-

tensity score of adverse experiences, although there was no significant difference between the treatment groups (Table 4).

Cardiovascular effects were recorded in eight patients, aged 52-67 years, with various degrees of airway obstruction. They were distributed over several centers. One vasovagal reaction with BP fall to 80/60 occurred after 11 min infusion of enprofylline 2.0 mg/kg/20 min (blood sample for enprofylline concentration not taken). The other incidents all occurred after the infusion was completed. One vasovagal re-

Table 2

PEF and HR values on admission to the study and the changes observed 60 min after starting the i.v. of enprofylline infusions, 2 mg/kg/10 min, 2 mg/kg/20 min and 2.5 mg/kg/20 min. Values are mean $\pm$ SD. Centre 1 did not participate due to technical problems

	No of patients	PEF (l/min)	
		On admission to study	After 60 min
2 mg/kg/10 min			
all centres	51	220 $\pm$ 118	+ 38 $\pm$ 38
centre 2	10	118 $\pm$ 39	+ 51 $\pm$ 20
centres 3-8	41	245 $\pm$ 118	+ 35 $\pm$ 41
20 mg/kg/20 min			
all centres	43	196 $\pm$ 81	+ 69 $\pm$ 70
centre 2	12	163 $\pm$ 32	+ 69 $\pm$ 41
centres 3-8	31	208 $\pm$ 90	+ 69 $\pm$ 79
2.5 mg/kg/20 min			
all centres	49	215 $\pm$ 105	+ 65 $\pm$ 68
centre 2	9	121 $\pm$ 36	+ 70 $\pm$ 35
centres 3-8	41	235 $\pm$ 104	+ 64 $\pm$ 74 (n = 40)
All therapies			
all centres	144	211 $\pm$ 103	+ 57 $\pm$ 61 (n = 143)
centre 2	31	136 $\pm$ 41	+ 63 $\pm$ 34
centres 3-8	113	231 $\pm$ 106	+ 55 $\pm$ 67 (n = 112)
2 mg/kg/10 min			
centres 3-8	42	89 $\pm$ 14	2 $\pm$ 10
centre 2	10	115 $\pm$ 15	- 13 $\pm$ 15
2 mg/kg/20 min			
centres 3-8	31	93 $\pm$ 16	- 2 $\pm$ 9
centre 2	12	128 $\pm$ 11	- 32 $\pm$ 14
2.5 mg/kg/10 min			
centres 3-8	41	91 $\pm$ 18	5 $\pm$ 13
centre 2	9	120 $\pm$ 11	- 20 $\pm$ 15
All therapies			
centres 3-8	114	91 $\pm$ 16	2 $\pm$ 11
centre 2	31	122 $\pm$ 14	- 22 $\pm$ 16

Table 3

Patient's statement of clinical status 60 min after start of enprofylline infusion compared with before treatment

Score	Enprofylline regimen			
	2.0 mg/kg/ 10 min	2.0 mg/kg/ 20 min	2.5 mg/kg/ 20 min	2.5 mg/kg/ 10 min
1	16	19	22	2
2	31	19	21	4
3	5	5	7	1

Scores: 1 = markedly improved, 2 = improved, 3 = unchanged, 4 = deteriorated, 5 = markedly deteriorated.

action with BP fall to 80/50 occurred after 2.0 mg/kg/10 min (plasma-enprofylline concentration 60 min after start of infusion 3.76 mg/l). Two moderate hypotensive reactions on 2.5 mg/kg/20 min with BP 110-120/60-70 were recorded (pl-enprofylline 4.79 and 4.98 mg/l and pl-theophylline 1.61 and 1.70 mg/l, respectively). The 2.5 mg/kg/10 min regimen, which was withdrawn, caused 2 vasovagal reactions. One with BP drop to 90/60 and one which was accompanied by a short unconsciousness. Data on BP and HR around the time of the latter incident is lacking. The patient soon recovered and never had to be admitted as in-patient. Pl-enprofylline concentrations were 6.35 and 6.33 mg/l and pl-theophylline 5.50 and 7.99 mg/l, for the last two patients, respectively. Further, atrial flutter was diagnosed with ECG in one patient and atrial fibrillation was clinically suspected in another. The arrhythmias were short-lasting and without haemodynamic effects.

The mean and range of plasma enprofylline concentrations at 60 min were 3.5 (2.3-5.4), 3.3 (2.2-5.0) and 4.6 (2.8-6.5) mg/l for the regimens 2.0 mg/kg/10 min, 2.0 mg/kg/20 min and 2.5 mg/kg/20 min, respectively. The mean plasma theophylline concentration for all patients at 60 min was 6.5 mg/l (range 0-26.4 mg/l) without significant difference between treatment groups.

DISCUSSION

The trial was designed to study the bronchodilating effect of enprofylline infusion in a sample

Table 4

Number of patients who reported headache and nausea at active questioning after enprofylline infusion i.v.

	2.0 mg/kg/ 10 min (n = 52)	2.0 mg/kg/ 20 min (n = 44)	2.5 mg/kg/ 20 min (n = 52)	2.5 mg/kg/ 10 min (n = 7)
Headache				
mild	9	9	14	-
moderate	4	1	2	2
severe	1	-	1	-
Total	14	10	17	2
Nausea				
mild	9	3	10	-
moderate	6	2	5	-
severe	2	2	2	2
Total	17	7	17	2

of patients resembling as much as possible the everyday patients treated for acute airway obstruction in the emergency room. Thus, not only asthmatic patients were included but also patients with chronic obstructive lung disease. This is in contrast to the study on which the chosen drug therapies were based (1). It is possible that the selection of the present heterogeneous study population with patients up to 74 years of age influenced the relationship between efficacy and adverse experiences.

The patients who received enprofylline 2.0 mg/kg during 20 min experienced a greater bronchodilating effect than those given the same dose during 10 min. This appears not to have been due to differences in the plasma concentrations of enprofylline between the groups. The more pronounced side effects experienced by patients during the shorter infusion period may, however, have affected the physical status and consequently the outcome.

The significantly higher mean HR on admission in centre 2, compared with the other centres, was related to the more severe airway obstruction in those patients. A significant reduction in HR after treatment was found at centre 2, in agreement with previous results (1). This was not observed in the somewhat less ill patients at the other centres. These effects on the heart were most likely due to a decreased sympathoadrenal activity following the improve-

ment in lung function. It can be speculated on whether enprofylline's positive chronotropic effect contributed to the relatively high heart rates that persisted after the improvement in lung function (3).

The side effects were similar to those reported with other xanthines, such as theophylline and caffeine (2). The frequency of atrial arrhythmias corresponds with that reported in patients with acute respiratory distress (8). However, the finding that enprofylline caused hypotensive/vasovagal reaction in six out of 155 patients (4%) is an important observation.

It appears that most of the hypotensive/vasovagal reactions were associated with relatively high enprofylline concentrations. The theophylline concentrations were relatively low in the four subjects who were on oral theophyllines. There is not enough data to suggest a possible enprofylline/theophylline interaction to have been responsible.

It is concluded that enprofylline is an effective bronchodilating xanthine when given i.v. to patients with acute airway obstruction. The frequency of vasovagal/hypotensive reactions must, however, be given consideration. Of the three different therapies that were fully investigated 2.0 mg/kg/10 min was less effective than 2 and 2.5 mg/kg/20 min. Since there were no significant differences between the two latter

therapies the dose of 2.0 mg/kg/20 min was estimated most favourable.

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