

Effects of Enprofylline and Theophylline on Exercise-Induced Asthma

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Eight asthmatic out-patients with a history of exercise-induced asthma (EIA) were randomly treated with intravenously administered enprofylline 1.5 mg/kg b.wt., theophylline 5 mg/kg b.wt., and placebo immediately prior to a 6-min exercise provocation in this double-blind crossover comparison. A reduction in peak flow of more than 20 % was seen in all patients after placebo pre-treatment. Mean plasma concentrations at the start of the exercise test were 3.3 mg/l and 13.2 mg/l after 20 min infusion of enprofylline and theophylline, respectively. The corresponding figures 25 min later were 2.3 and 11.7, respectively. Maximal fall in peak expiratory flow (PEF) after exercise in percent of pre-exercise PEF was $49\% \pm 6\%$ (mean $\pm$ SEM), $39\% \pm 6\%$ and $24\% \pm 5\%$ after infusion of placebo, enprofylline, and theophylline, respectively. Theophylline produced a statistically significant better protection against EIA compared to enprofylline and placebo. Enprofylline produced a slight protection from EIA not statistically significantly different from placebo.

Key words: enprofylline; exercise-induced asthma; theophylline.

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Exercise-induced asthma (EIA) occurs in about 70-80 % of the asthmatic population and is particularly troublesome in asthmatic children (2, 8). In the search for effective antiasthmatic treatments many types of drugs have been investigated, and beta-adrenoceptor stimulants inhaled immediately before exercise have shown to be the most effective in preventing EIA, and methylxanthines in therapeutic doses have less but a clinically significant protective effect on EIA (1, 4, 15, 16, 17). The present study was undertaken in order to examine whether enprofylline (3-propylxanthine) - a new potent bronchodilator (10, 14) - is able to prevent EIA.

MATERIAL AND METHODS

Fifteen asthmatic out-patients with an anamnesis of EIA gave their informed consent to participate in the trial, which was approved by

the local ethical review committee of Copenhagen. Eight of these subjects (1 man and 7 women) responded with a fall in PEF of more than 20 % after exercise when pre-treated with placebo, and the evaluation is based on data from these patients only. Their mean age was 30 years (range 17-39 years), mean weight 62 kg (42-78 kg) and mean height was 168 cm (range 150-185 cm). Mean duration of asthma was 23 years (range 7-38 years). Seven patients suffered from extrinsic asthma, defined as a typical anamnesis, and a positive skin prick test to one or more common allergens; one patient had intrinsic asthma. The mean basal forced expiratory flow rate in the 1st sec (FEV₁) was 2.2 l (range 2.0-2.7 l) corresponding to 72 % of expected normal.

All patients used inhaled sympatomimetics, five took inhaled steroids, two used sustained released theophyllines, one patient took oral prednisone and one used oral terbutaline. On 3

consecutive days at 8 a.m. either enprofylline 1.5 mg/kg b.wt., theophylline 5 mg/kg b.wt. or placebo (isotonic saline) was given intravenously in random order during 20 min prior to the 6-min exercise provocation. Enprofylline, theophylline and saline were packed for each patient in identical ampoules in order to maintain the double-blind nature of the study. The code list was only known to a pharmacist not involved in the evaluation of the patients.

Venous blood samples (5 ml) were drawn immediately after infusion and 20 min after the start of the exercise. Plasma was stored at -20°C for later xanthine concentration determinations by means of the HPLC technique (7).

All oral medication except for glucocorticoids and beta-agonist stimulants were withdrawn 24 h prior to the study. No inhalation of beta-agonists was allowed until 8 h before the investigation. However, two puffs of a rimeterol aerosol (Pulmadil®) could be used until 4 h before the visit to the clinic. On arrival at the clinic the patients were asked about their intake of medication in the days prior to the study. FEV₁ and PEF were measured immediately before and after infusion and after 2, 4, 6, 8, 10, 15, 20, and 25 min after start of the 6-min exercise provocation using a Hewlett-Packard pneumotachygraph.

Adverse reactions to infusion were asked for before and after infusion and after exercise. Continuous ECG monitoring was performed in all patients during and after the exercise provocation. Exercise provocation test was performed using an ergometer cycle (Monark®) with a working load of 2–2.5 kp producing an increase in heart rate to more than 85 % of predicted age specific maximum (6). Variations in basal PEF should be within 15 % on the 3 days and if, however, variations were higher the odd day was repeated. The severity of EIA was determined by means of PEF and calculated after the formula:

and differences between mean percent fall after different pre-treatments were compared using a paired t-test (1). Furthermore, we determined the percent protection from EIA produced by the individual subjects (1). The percent protection was calculated as

$$\frac{\% \text{ fall after placebo} - \% \text{ fall after active drug}}{\% \text{ fall after placebo}} \times 100$$

RESULTS

Plasma concentrations

Enprofylline and theophylline plasma concentrations immediately after infusions were $3.3 \mu\text{g/ml} \pm 0.3$ (mean $\pm$ SEM) (range 2.23–4.63) and $13.2 \pm 0.1 \mu\text{g/ml}$ (range 8.48–17.96), respectively. Corresponding values 25 min after the start of exercise were 2.3 ± 0.2 (range 1.53–3.22) and $10.5 \pm 0.5 \mu\text{g/ml}$ (range 8.39–12.50).

All subjects reached heart rate of more than 85 % of predicted maximum (mean 91 %). Mean room temperature was 23°C (range 22 – 24°C) and relative humidity 61 % (range 58–67 %). Placebo infusion produced a mean increase in PEF of only 5 % ($P > 0.1$) and 18 % ($P < 0.01$) and 14 % ($P < 0.05$) after theophylline and enprofylline administration (Fig. 1). Mean maximal increase in PEF during exercise showed no statistically significant differences between treatments. Maximal fall in PEF after placebo was $49 \pm 6\%$ (mean $\pm$ SEM) and $39 \pm 6\%$ and $24 \pm 5\%$ after enprofylline and theophylline respectively.

Theophylline had better EIA protective effects compared to placebo ($P < 0.001$) and to enprofylline ($P < 0.01$) (Fig. 2). No statistically significant differences were found between mean PEF fall after enprofylline and placebo (Fig. 2). The percentage protection against EIA produced by theophylline averaged 54 % and for enprofylline 24 % (Table 1).

$$\% \text{ fall} = \frac{\text{value immediately before exercise} - \text{lowest value after exercise}}{\text{value immediately before exercise}} \times 100$$

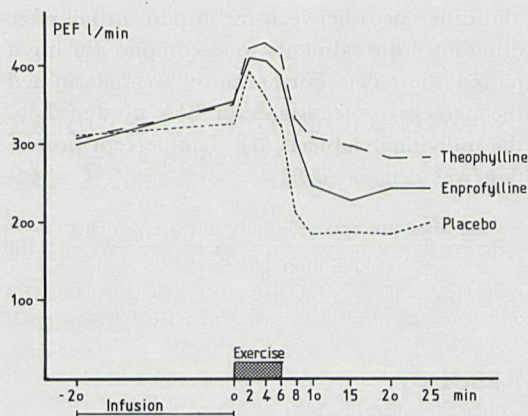


Fig. 1. Changes in mean PEF before and after infusion of enprofylline 1.5 mg/kg b.wt., theophylline 5 mg/kg b.wt. and saline during and after an exercise provocation ($n = 8$).

Side effects

Five patients experienced slight nausea after enprofylline infusion while two and one patient reported nausea after theophylline and placebo infusion, respectively. Four patients reported slight headache after enprofylline administration while one patient complained of headache after placebo infusion.

DISCUSSION

Two major hypotheses to explain the mechanism of EIA have been forwarded: airway cooling and/or loss of water from the bronchial mucosa (2). Most authors agree that EIA is a reflexion of non-specific bronchial hyperreactivity (1, 2) and a correlation between bronchial

hyperreactivity to histamine and EIA has been found (3, 5). We believe that airway cooling and heat loss from the airways of the subjects were identical during the 3 examination days, as room temperature, humidity and intra-individual heart rate varied insignificantly. Enprofylline at plasma concentrations of about one fourth compared to theophylline produced only a slight protection from EIA in contrast to the protection produced after theophylline infusion. These findings are somewhat surprising as enprofylline is about 3–4 times as potent in its bronchodilator effects compared with theophylline (11, 12). The protective effects of enprofylline on histamine-induced asthma have proved to be less than after theophylline pretreatment using similar doses as in our study (9). Van der Straaten et al. (18) found, however, that enprofylline and theophylline at mean plasma levels of 2.6 $\mu\text{g/ml}$ and 10.6 $\mu\text{g/ml}$, respectively produced slight protection on immediate bronchoconstrictory reaction after allergen inhalation, and a statistically significant inhibitory effect on the late bronchial reaction. A good correlation between plasma concentrations of theophylline and EIA protective effects exists (15), and higher plasma concentrations of enprofylline might produce better protection. Some authors claim that theophylline has EIA protective effects about twice that of bronchodilator effects at similar plasma levels (13). Furthermore, Bierman et al. (4) have found higher protective effects during continuous treatment with sustained release formulation compared to acute intravenous infusions after theophylline, indicating that the receptors involved in the mechanism producing EIA must be saturated before optimal protection can occur. That enprofylline seems to induce slightly more transient headache com-

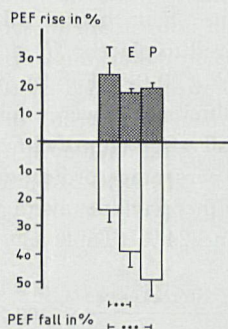


Fig. 2. Maximal rise and fall in PEF (mean + SEM) during and after exercise provocation, respectively.

** $P < 0.01$. *** $P < 0.001$.

Table 1

Number of patients with less than 10 % and more than 50 % protection (see text) after enprofylline and theophylline infusion followed by exercise provocation

	< 10 %	> 50 %	Mean
Enprofylline	3/8	1/8	24 %
Theophylline	0/8	4/8	54 %

pared with theophylline after single dose administration is consistent with earlier findings (9, 11, 12).

In conclusion, enprofylline appears to have less EIA protective effects compared with theophylline, but further studies with continuous treatment with enprofylline seem desirable for fully investigating the effects on EIA.

REFERENCES

1. Anderson, S., Seale, J. P., Ferris, L., Schoeffel, R. & Lindsay, D. A.: An evaluation of pharmacotherapy for exercise-induced asthma. *J. Allergy Clin. Immunol.* **64**, 612-624, 1979.
2. Anderson, S. D.: Current concepts of exercise-induced asthma. *Allergy* **38**, 289-302, 1983.
3. Anderton, R. C., Cuff, M. T., Frith, P. A., et al.: Bronchial responsiveness to inhaled histamine and exercise. *J. Allergy Clin. Immunol.* **63**, 315-320, 1979.
4. Bierman, C. W., Shapiro, G. G., Pierson, W. E. & Dorsett, C. S.: Acute and chronic theophylline therapy in exercise-induced bronchospasm. *Pediatrics* **60**, 845-849, 1977.
5. Chatham, M., Bleecker, E. R., Smith, P. L., Rosenthal, R. R., Mason, P. & Norman, P. S.: A comparison of histamine, methacholine, and exercise airway reactivity in normal and asthmatic subjects. *Am. Rev. Respir. Dis.* **126**, 235-240, 1982.
6. Cropp, G. J. A.: The exercise bronchoprovocation test: Standardization of procedures and evaluation of response. *J. Allergy Clin. Immunol.* **64**, 627-633, 1979.
7. Edholm, L. E.: Specific methods for theophylline assay in biological samples. *Eur. J. Respir. Dis.* **61**, Suppl. 109, 45-53, 1980.
8. Holgate, S. T.: Changing attitudes to exercise-induced asthma. *Br. Med. J.* **287**, 1650-1651, 1983.
9. Kluge, T. B. R., Oellerich, M. & Sybrecht, G. W.: Pharmacokinetics and effect of enprofylline compared to theophylline on histamine PC₂₀ in normal subjects. In Herzog, H. & Perruchoud, A. (eds.): *Respiration*. 3rd Congress of the European Society of Pneumology, Basel, September 1984, p. 27. S. Karger, Basel, 1984.
10. Laursen, L. C., Johannesson, N., Dirksen, A., et al.: Enprofylline - effects of a new bronchodilating xanthine derivative in asthmatic patients. *Allergy* **38**, 75-79, 1983.
11. Laursen, L. C., Johannesson, N., Fagerström, P.-O. & Weeke, B.: Intravenous administration of enprofylline to asthmatic patients. *Eur. J. Clin. Pharmacol.* **24**, 323-327, 1983.
12. Laursen, L. C., Johannesson, N., Søndergaard, I. & Weeke, B.: Comparison of oral enprofylline and theophylline in asthmatic patients. *Eur. J. Clin. Pharmacol.* **26**, 707-709, 1984.
13. Magnussen, H., Litt, M., Reuss, G., Stutz, P. & Kessler, K.: Theophylline efficacy in bronchial asthma: Bronchodilation versus protection. In Herzog, H. & Perruchoud, A. (eds.): *Respiration*. 3rd Congress of the European Society of Pneumology, Basel, September 1984, p. 34. S. Karger, Basel, 1984.
14. Persson, C. G. A.: Xanthines for asthma: Present status. *Trends. Pharmacol. Sci.* **3**, 312-313, 1982.
15. Philips, M. J., Ollier, S., Trembath, P. W., Boobis, S. W. & Davies, R. J.: The effect of sustained release aminophylline on exercise-induced asthma. *Br. J. Dis. Chest.* **75**, 181-189, 1981.
16. Pollock, J., Kiechel, F., Cooper, D. & Weinberger, M.: Relationship of serum theophylline concentration to inhibition of exercise-induced bronchospasm and comparison with cromolyn. *Pediatrics* **60**, 840-844, 1977.
17. Shapiro, G. G., McPhillips, J. J., Smith, K., Furukawa, C. T., Pierson, W. E. & Bierman, C. W.: Effectiveness of terbutaline and theophylline alone and in combination in exercise-induced bronchospasm. *Pediatrics* **67**, 508-513, 1981.
18. Van der Straaten, M., Pauwels, R., Van Renterghem, D., Johannesson, N. & Persson, C. G. A.: The effect of theophylline and enprofylline on allergen induced bronchoconstriction. *Folia Allergol. Immunol. Clin.* **XXX**, Suppl. al N. 4: 3, 1983.

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