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The pharmacokinetics of lysine theophylline, a new soluble theophylline, in human volunteers

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Summary

A comparative study of the pharmacokinetics of lysine theophylline and aminophylline in normal subjects reveals no significant difference. If lysine theophylline is shown to have the same clinical efficacy as aminophylline, the hypersensitivity reactions associated with the latter could be avoided.

KEY WORDS: pharmacokinetics, lysine theophylline, aminophylline.

Introduction

The aqueous solubility of theophylline is poor and consequently its injectable preparations are formulated as double salts. The most widely used of these is aminophylline, a combination of ethylenediamine and theophylline. Ethylenediamine has no therapeutic action, but its presence increases the solubility of theophylline 20-fold. However, it has been demonstrated that ethylenediamine can give rise to contact dermatitis (Rudzki and Kleniewska, 1970; White, Douglas and Main, 1978) and administration of intravenous aminophylline preparations has been associated with urticaria (Booth, Coleman and Mitchell, 1979) and other hypersensitivity reactions (Wong, Lopapa and Haddad, 1971). It would therefore be advantageous if theophylline could be rendered more soluble without the use of ethylenediamine and this has been achieved using the essential amino acid lysine. In this study we have examined the pharmacokinetics of lysine theophylline in comparison with aminophylline as a prelude to clinical studies.

Methods

Six healthy non-smoking volunteers (2 female) gave their informed consent to participate in the study. The subjects ranged in age between 20 and 65 years (mean 33 years) and weighed between 60 and 80 kg. Each subject received a dose of theophylline equivalent to 250 mg as an intravenous infusion over 5 min on two occasions. Three subjects were given the lysine preparation first and aminophylline second and at least one week was allowed between administrations. After each infusion blood was taken, via an indwelling venous catheter, at 10, 20, 30 and 45 min and 1, 1·5, 2, 2·5, 3, 3·5, 4, 6, 8, 12 and 24 hr. After allowing the blood to clot, the serum was separated by centrifugation and was stored at −20°C until analysis for theophylline by enzyme immunoassay (EMIT, Syva Ltd, Maidenhead, Berkshire, U.K.).

The lysine theophylline preparation (25 mg/ml) was supplied by Laboratories for Applied Biology Ltd, and compared with aminophylline BP (25 mg/ml).

The serum theophylline/time curves were fitted to a two-compartment open model and pharmacokinetic parameters derived using the computer program STRIPE (Johnston and Woollard, 1982).

Results

After administration of the ethylenediamine formulation of theophylline the mean (±s.d.), elimination half-life in the subjects was 7·8±2·3 hr while after the lysine theophylline it was 8·2±3·2 hr. The difference was not statistically significant. The mean area under the concentration time curves (0–∞) for both preparations was almost identical, 80·5±23·3 $\mu g\ ml^{-1}$ hr for the aminophylline formulation and 80·0±21·0 $\mu g\ ml^{-1}$ hr for lysine theophylline. The mean serum theophylline concentrations after each preparation are displayed against time in Fig. 1.

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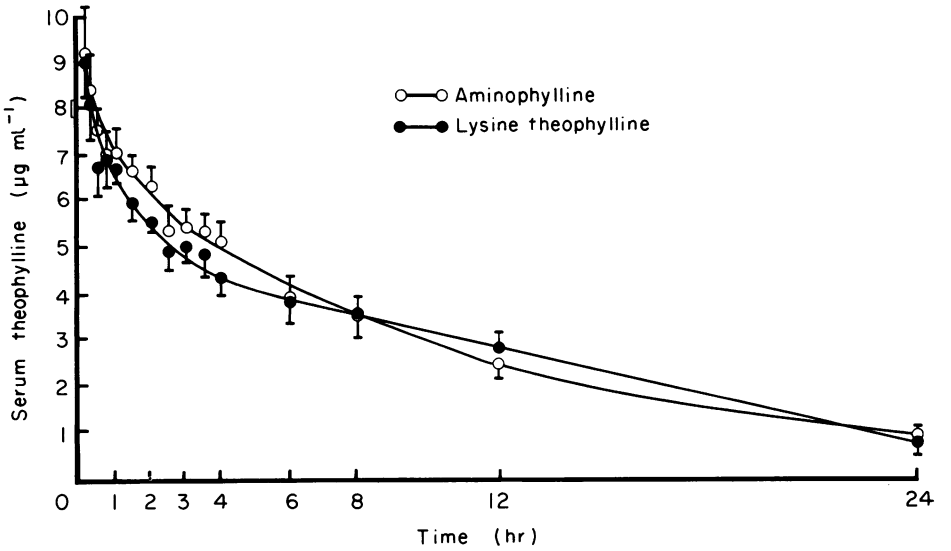

FIG. 1. Mean (±s.e.) serum theophylline levels seen in 6 subjects after aminophylline and lysine theophylline 250 mg i.v.

Discussion

The results of this normal volunteer study suggest that lysine theophylline has similar kinetic properties to aminophylline. Controlled clinical studies are required to demonstrate that it has similar clinical therapeutic efficacy when compared with aminophylline, and that absence of the ethylenediamine constituent reduces the incidence of hypersensitivity reactions. It is of interest that one of the 6 subjects was aged 65 years compared with a range of 20–32 years for the other 5 subjects, and his plasma half-life and areas under the plasma concentration curve were markedly greater than the rest. This confirms previous observations of the influence of age on theophylline kinetics (Antal *et al.*, 1981) and indicates the care that should be exercised in administrating theophylline preparations to elderly patients.

References

ANTAL, E.J., KRAMER, P.A., MERCIK, S.A., CHAPRON, D.J. & LAWSON, I.R. (1981) Theophylline pharmacokinetics in advanced age. *British Journal of Clinical Pharmacology*, **12**, 637.

BOOTH, B.H., COLEMAN, W.P. & MITCHELL, D.Q. (1979) Urticaria following intravenous aminophylline. *Annals of Allergy*, **43**, 289.

JOHNSTON, A. & WOOLLARD, R.C. (1982) STRIPE: an interactive curve fitting program for pharmacokinetic data (Unpublished).

RUDZKI, E. & KLENIEWSKA, D. (1970) The epidemiology of contact dermatitis in Poland. *British Journal of Dermatology*, **83**, 543.

WHITE, M.I., DOUGLAS, W.S. & MAIN, R.A. (1978) Contact dermatitis attributed to ethylenediamine. *British Medical Journal*, **1**, 415.

WONG, D., LOPAPA, A.F. & HADDAD, Z.H. (1971) Immediate hypersensitivity reaction to aminophylline. *Journal of Allergy and Clinical Immunology*, **48**, 165.

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