THE USE OF AMINOPHYLLINE BY INHALATION

The use of aminophylline by inhalation has been investigated on a limited number of occasions. The majority of the work reported occurred in the late 1940s (Segal, 1944; Prigal *et al.*, 1947; Segal *et al.*, 1949; Taplin *et al.*, 1949). In 1976 Stewart and Block proposed several hypotheses as to why this method of delivering the drug had no therapeutic role. However they chose to use 62.5 mg of aminophylline as their maximum dose and delivered it by a standard nebuliser (Stewart & Block, 1976).

To assess the dose limitations for nebulisation we have studied eight normal volunteers, four females and four males aged 23 to 33 years. They all gave written informed consent and the study was approved by the hospital's ethics committee.

We decided to nebulise 250 mg, 500 mg and 1000 mg of the drug. The maximum solubility of aminophylline is approximately 1 g in 4 ml of solution and therefore each dose was adjusted with saline to a volume of 4 ml. We used an 'Inspiron Incentineb' nebuliser which is a self-activating device. The volunteers were taught to activate the nebuliser in time with inspiration and consequently very little solution was lost to the atmosphere prior to entering the oropharynx. As a result it took approximately 0.5 h to completely nebulise. Each dose was given 2 h apart and blood levels were taken at 0, 15, 30, 60 and 120 min after the onset of administration of each solution. At the same time spirometry recordings were taken primarily to monitor bronchial irritation. A record was also kept of other side effects including taste, cough, nausea and dyspnoea. The volume of solution not nebulised was measured after each inhalation. From this the actual mean doses effectively nebulised were calculated to be 225 mg, 423 mg and 856 mg. The theophylline levels were measured by the EMIT (Syva) system with the assayist being unaware of the study design.

All volunteers found the taste unpleasant but tolerable and that it worsened as the concentration was increased. After 3 min of nebulisation the taste became less noticable. The incidence of cough during the nebulisation period was low but also increased as the concentration rose. There was no nausea or dyspnoea. Although the study was not designed to ascertain the bronchodilatory effect of nebulised aminophylline it was interesting that one volunteer had a rise of 21% in her baseline FEV_1 and on further questioning revealed that she occasionally wheezed when exercising. Her maximum theophylline blood level was 4.5 μg/ml. In the other volunteers there was no significant fall in FEV_1 or VC when compared to baseline with the mean maximal fall of FEV_1 being 7.5%.

The mean blood level results are shown in Figure 1 which shows a sharp rise during nebulisation followed by a plateau phase. The maximum mean level measured was 3.3 μg/ml and the range of individual maximum levels was 1.6 to 7.6 μg/ml.

From this data it would appear that the most acute rise occurs during the delivery phase. This may represent absorption at the level of the alveolus where

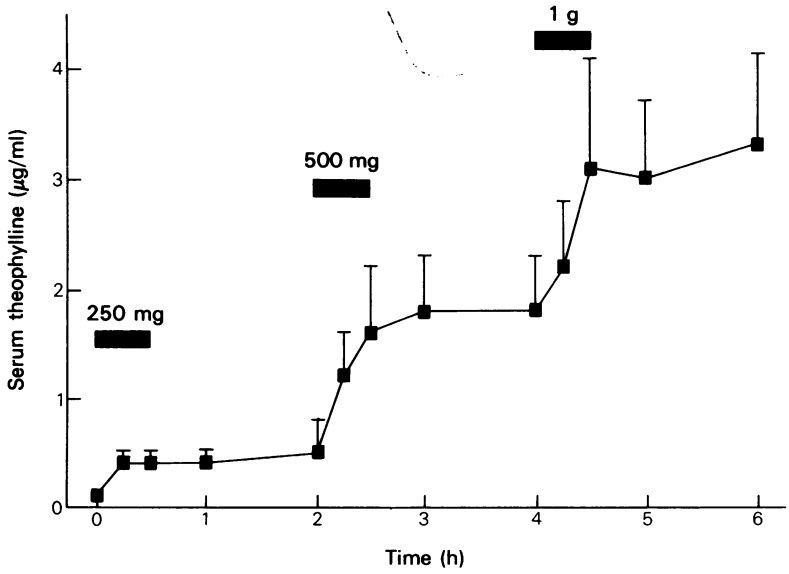

Figure 1 Mean serum theophylline levels (with s.e. mean) following inhalation of three doses of theophylline over a 30 min period at 0, 2 and 4 h.

accessibility to the circulation is greater than elsewhere in the bronchial tree. The plateau phase following this suggests a subsequent slower absorption, possibly from the bronchial mucosa of larger airways. It would seem unlikely that there is significant absorption from the gut and oropharynx as less than 2% of nebulised solution enters this region, whilst 11% or greater enters the airways (Lewis, personal communication; Lewis *et al.*, 1981).

We would recommend that at least 500 mg can be nebulised with safety and that it is probably safe to give 1000 mg particularly if one were to use a conventional nebuliser. At both doses it is doubtful if significant blood levels would be achieved.

These studies show that much larger doses than have been previously used can be successfully inhaled without inducing significant systemic or local side-effects in normal subjects. In particular no bronchoconstriction was seen. This study supports the possibility of achieving substantial local levels of drug with concomitantly low levels in the blood. Therefore we are now undertaking further studies to assess the feasibility of using this method of medication in treating asthmatic subjects. The major limitations for this may well be the taste and the potential hazard of sensitization to the ethylenediamine component of aminophylline.

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References

LEWIS, R.A., FLEMING, J.S. & TATTERSFIELD, A.E. (1981). The effect of temperature and humidity on the distribution of inhaled particles. *Eur. J. resp. Dis.*, **62**, Suppl. 13, 133.

PRIGAL, S.J., BROOKS, A.M. & HARRIS, R. (1947). The treatment of asthma by inhalation of aerosol of aminophyllin. *J. Allergy Immunol.*, **18**, 16–28.

SEGAL, M.S. (1944). Advances in inhalation therapy, with particular reference to cardiorespiratory diseases. *New Engl. J. Med.*, **231**, 553–556.

SEGAL, M.S., LEVINSON, L. & BRESNICK, E. (1949). Evaluation of therapeutic substances employed for the relief of bronchospasm: 6. Aminophylline. *J. clin. Invest.*, **28**, 1190–1195.

STEWART, B.N. & BLOCK, A.J. (1976). A trial of aerosolised theophylline in relieving bronchospasm. *Chest*, **69**, 718–721.

TALPIN, G.V., GROPPER, A.L., SCOTT, G. & HAGEMAN, J.R. (1949). Micropowered aminophylline or theophylline inhalation therapy in chronic bronchial asthma. *Annals of Allergy*, **7**, 513–523.

COMPARISON BETWEEN AIRWAYS RESPONSE TO AN α-ADRENOCEPTOR AGONIST AND HISTAMINE IN ASTHMATIC AND NON-ASTHMATIC SUBJECTS

There is now *in vitro* evidence for the existence of a population of α-adrenoceptors in human lung tissue, both central (Kneussl & Richardson, 1971) and peripheral (Black *et al.*, 1981). There is, in addition, evidence for a change in α-receptor number in pulmonary disease states on the basis of animal studies (Barnes *et al.*, 1980). The results of *in vivo* studies however, have been conflicting. There are reports of the existence of α-adrenoceptors in the airways of asthmatic subjects (Snashall *et al.*, 1978), non-asthmatics (Anthracite *et al.*, 1971) and neither (Stone *et al.*, 1973).

Bronchoconstriction in response to inhalation challenge with histamine has become a diagnostic feature of asthma (Salome *et al.*, 1980). However, there is a certain population of non-asthmatic subjects who bronchoconstrict in response to histamine challenge. A positive response to histamine challenge thus does not always serve to distinguish asthmatic from non-asthmatic subjects.

This study examines the airways response to inhalation of methoxamine in both asthmatics and non-asthmatic subjects and compares it to the responses to histamine provocation.

The subjects were 10 known asthmatics, 4 females and 6 males aged 21 to 54 years, and 10 non-asthmatics, 5 females and 5 males, aged 24 to 56 years. All the asthmatic subjects were taking regular bronchodilator aerosol therapy, but none was steroid dependent. Nine of the asthmatic subjects and 5 of the non-asthmatics were atopic (that is, they reacted with a positive skin prick test to one or more 8 standard allergens). Informed consent was obtained from all subjects and the protocol was authorised by the