difference between the two treatments. Tulobuterol and salbutamol were well tolerated and no side effects including tremors were noted.

Tulobuterol by oral and inhaled routes appears to produce a significant bronchodilator response without side effects and may prove a worthwhile addition to sympathomimetic bronchodilators currently on the market.

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Circadian variation in theophylline 'trough' serum concentrations

Jackson *et al.* (1984), in 'Is circadian variation in theophylline trough serum concentrations determined by time of dosing?', suggest the difference between the so-called serum 'trough' levels when 200 mg of a slow-release theophylline preparation, apparent if given at 11.00 h and 23.00 h, disappears when given instead at 05.00 h and 17.00 h. This conclusion is based on data obtained from single pre-dose blood samplings done just before the morning and evening ingestions during steady state conditions.

As recently reviewed (Jonkman & Smolensky, 1984; Smolensky & McGovern, 1985), many investigators have reported a significant difference in the pharmacokinetics of theophylline following morning vs evening oral administrations. In general, when sustained-release theophyllines are given at 07.00 h or 08.00 h to day-active asthmatic or healthy persons, the serum theophylline concentration increases more rapidly reaching a higher peak level than when the same dosage is given 12 h later in the evening. Although the mechanisms (such as circadian variation in gastrointestinal function, posture, meal timings and composition, etc.) contributing to the 24 h variation in the theophylline serum level are not yet understood, it nonetheless is now apparent based on published findings that the serum trough theophylline concentration

after intake of some sustained release preparations need not occur at the end of each dosing interval (Kramer *et al.*, 1980; Scott *et al.*, 1981; Samaan *et al.*, 1984). Due to delayed absorption especially during evening hours, serum concentrations may continue to fall for even up to about 4 h post-dosing (Kramer *et al.*, 1980; Scott *et al.*, 1981). Thus pre-dose serum theophylline concentrations may be higher than trough concentrations.

In order to avoid confusion, we recommend theophylline concentrations measured before morning and evening oral administrations be referred to as pre-dose serum theophylline rather than 'trough' concentrations.

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Circadian variation in theophylline ‘trough’ serum concentrations—a reply

Smolensky *et al.* (1985) correctly point out that the term ‘trough concentration’ is misleading when used to refer to pre-dose concentrations.

Concerning the validity of our approach, however, Smolensky *et al.* (1985) incorrectly infer that our study design (Jackson *et al.*, 1984) was not capable of detecting a meaningful difference between the two regimens. They also incorrectly state that single pre-dose samples were taken when in fact two were taken 24 h apart for each subject at each time during each regimen.

A change in the relationship between pre-dose concentrations effected by a change in the time of dosing was demonstrated by our study. This observation does not require any assumptions concerning the relationship between pre-dose and true trough concentrations, although a knowledge of the concentration-time profile over a 24 h period would undoubtedly give insight into the mechanisms involved.

As stated in our report we chose not to obtain multiple blood samples as we do not have a sleep laboratory and would therefore be unable to guarantee that samples would be obtained without sleep disturbance. In fact we used volunteers used to performing self venesection, regarding this as a logical extension of the concept of autorhythmometry developed by Halberg *et al.* (1972), who used the term to describe the self measurement of physiological and psychological variables as a function of time.

We also take issue with Smolensky *et al.* (1985) concerning another aspect of the methodology involved in the study of circadian variation.

They have used the $AUC_{(0-12)}$ as a measure of the extent of absorption (Kramer *et al.*, 1984) and referred in their letter (Samaan *et al.*, 1984) and review article (Jonkman & Smolensky, 1984) to reports using the same procedure. We feel this is misleading as the $AUC_{(0-12)}$ is influenced by the concentration at the time of dosing and the relative size of the unabsorbed fractions of doses remaining at both 0 h and 12 h.

When the unabsorbed (but potentially bio-available) fraction from the previous dosing interval equals the unabsorbed fraction at the end of the current dosing interval and the concentration at 0 h equals the concentration at 12 h, $AUC_{(0-12)}$ is a true measure of the extent of absorption. In circadian variation studies these assumptions are clearly invalid. Quite apart from the concentration differences between 0 h and 12 h (which can be corrected for), the unabsorbed fraction of the morning dose still to be absorbed at the time of the evening dose is likely to be much smaller than the analogous fraction of the evening dose. Thus $AUC_{(0-12)}$ should not be used as a measure of the extent of absorption in this context.

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