Once nightly sustained release theophylline in elderly subjects

A recent paper (Steffensen & Pedersen, 1986) has suggested that once nightly sustained release theophylline therapy (Uniphyllin, Napp Laboratories) produces 'very reliable' absorption profiles in adults, though demonstrates unpredictable absorption in children. Our clinical impressions of this product in elderly patients are that absorption is not very reliable, and we present some data to support this contention. Indeed the data from Steffensen & Pedersen (1986) show a wide range of $C_{\max}$ and $t_{\max}$ after nocturnal administration despite an 8 h fast pre dose, and a 4 h fast post dose. This situation is unlikely to arise in clinical practice and we have attempted to assess absorption under more normal conditions.

We have studied seven elderly patients (age 69–86, median 80 years) without asthma, in a rehabilitation unit, undergoing active rehabilitation for primarily musculoskeletal problems. None suffered from any significant systemic illness nor was taking any medication currently known to interfere with either absorption or elimination of theophylline. All were non-smokers, and gave written informed consent for the study which was approved by the local ethics committee.

Plasma concentration-time profiles for theophylline were investigated for each subject after the ingestion of 400 mg sustained release theophylline (Uniphyllin, Napp Laboratories) at 21.00 h with 100 ml water. Studies were performed in all subjects after single dose, and after dosing to steady state with 400 mg daily for 5 days. No restrictions were imposed on diet or activity throughout the study. Samples were collected at intervals throughout a 24 h period (0, 1, 2, 3, 6, 9, 12, 15, 18, 21 and 24 h) and centrifuged routinely within 10 min. Plasma was stored at -20°C until assay performed. Theophylline assay was by h.p.l.c. using a modification of the method of Orcutt *et al.* (1977). Standard curves were linear over the range $0\text{--}40\text{ mg l}^{-1}$ ($r > 0.999$) and coefficient of variation between assays was 3.2% at 4 mg l^{-1} and 3.8% at 20 mg l^{-1} .

There was clearly wide variation in $C_{\max}$, $t_{\max}$ and AUC_{0-24} after single dose and at steady state (Table 1). The time spent within the generally accepted therapeutic range of $10\text{--}20\text{ mg l}^{-1}$ at steady state was also very variable, ranging from 1.5–16.5 h which is clearly unsuitable for a preparation to be used once daily for the 24 h control of asthmatic symptoms. It is unlikely that dose

Table 1 Pharmacokinetic data

	$C_{\max}$ (mg l^{-1})	$t_{\max}$ (h)	AUC^*_{0-24} ($\text{mg l}^{-1}\text{h}$)	Time therapeutic (h)	Peak/trough ratio
Single dose					
Median	8.9	9	133.3	—	—
Range	7.3–14.3	6–18	90–148	—	—
Steady state					
Median	18.5	9	205.1	8.5	2.8
Range	14.3–27.2	3–12	171.5–579.5	1.5–16.5	1.5–3.3

$C_{\max}$ = Maximum plasma concentration

$t_{\max}$ = time to maximum concentration

AUC^*_{0-24} = Area under plasma concentration time curve for 0–24 h corrected to standard 70 kg subject by

$\text{AUC}^* = \text{AUC} \times \frac{\text{Subject weight}}{70} \text{ (kg)}$

Time therapeutic = time plasma concentration within generally accepted range of $10\text{--}20\text{ mg l}^{-1}$

Peak/trough ratio = $\frac{\text{Maximum plasma concentration}}{\text{Minimum plasma concentration}}$

adjustment will correct this, as the peak/trough ratios were high (median 2.5, only one < 2) and therefore it would not be possible to maintain plasma levels within a range of 10–20 mg l⁻¹ throughout the 24 h period.

In conclusion, we would suggest that this preparation given once nightly cannot be relied upon to produce predictable absorption profiles in elderly subjects, and is unlikely to be suitable for the 24 h control of symptoms in these patients. In our opinion, this study demonstrates the wide variability found in elderly subjects and emphasises that results obtained in young adults should not be extrapolated freely to include the elderly.

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Once nightly sustained release theophylline in elderly subjects— a reply

We find the comments of Rodgers and colleagues (1988) very interesting, though difficult to interpret in detail because individual profiles are not given. It appears that the profiles in elderly patients are more in accordance with those in children rather than those in young adults. This strongly supports the suggestion we made in our paper on Uniphyllin: 'That all SRT products should be thoroughly tested in the age groups in which they are going to be used'.

It would be interesting to know whether the bioavailability of Uniphyllin was complete and reliable in elderly patients since this was the case in both children and young adults. Finally, the finding that therapeutic theophylline concen-

trations could not be maintained for 24 h with once daily dosing of Uniphyllin is in full agreement with our data in both children and young adults where about 80% of the total dose was absorbed within 8 h, leaving only 20% of the dose for the remaining 16 h.

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