Is Diurnal Variation in Absorption of Slow-Release Aminophylline an Age-Related Phenomenon?

A. Rodgers1, D. N. Bateman1, and K. W. Woodhouse2

Geriatric Pharmacology Research Group, Departments of 1 Clinical Pharmacology and 2 Medicine (Geriatrics), University of Newcastle upon Tyne, Newcastle upon Tyne, UK

Summary. To specifically assess the possible influence of ageing on the changes in theophylline absorption, the plasma concentration-time profiles of sustained-release aminophylline were studied in 8 young and 8 elderly subjects after 9 a.m. and 9 p.m. administration.

After 9 p.m. administration, in elderly subjects, maximum plasma theophylline concentrations (Cmax) were decreased, time to maximum concentration (tmax) was increased, and area under plasma concentration-time curve (AUC) was decreased compared to 9 a.m. dosing. This was true for single dose and at steady-state and suggests delayed and diminished absorption at night. No statistically significant changes were seen in the young subjects.

This study therefore suggests that time related changes in absorption may be more significant in elderly subjects, possibly due to postural differences after 9 p.m. dosing, and this should be borne in mind when prescribing.

Key words: aminophylline, geriatry; absorption, reversible airways obstruction

Aminophylline is widely used in the treatment of reversible airways obstruction, and is often prescribed at night to decrease or abolish nocturnal symptoms. The therapeutic range is generally accepted as being from 10-20 mg·l−1 [1, 2] though some patients will undoubtedly obtain benefit at lower levels. Toxic effects such as vomiting, tachycardia and CNS stimulation are likely to occur with increasing frequency and severity as plasma levels rise above 20 mg·l−1 [1].

The relatively rapid elimination of theophylline has led to the development of many sustained-release preparations in an attempt to decrease dosing frequency whilst maintaining stable plasma levels. Although much work has been performed with young subjects, little information is available regarding these preparations in elderly subjects.

It has recently been noted by several groups that pre-dose plasma levels are higher at 9 a.m. than at 9 p.m. in patients on twice daily dosing [3]. Possible explanations for this finding include decreased elimination at night; delayed absorption producing late peaks; or a combination of the two. Recent work has shown no difference in elimination of theophylline at night compared to during the day [4–6]. Furthermore, studies in our own department showed that this finding was true for both young and elderly subjects, and also suggested that theophylline clearance was not affected by age [7].

The study described here was therefore performed to investigate the possibility of delayed absorption of sustained release theophylline at night, both after single doses and at steady-state, and to examine the effects of ageing on absorption.

Methods

Subject Selection

Sixteen subjects were included in the study; 8 were healthy volunteers aged 20–33 years and 8 were elderly patients (aged 68–89 years) undergoing active rehabilitation in a rehabilitation unit because of poor mobility. Diagnoses in the elderly group included osteoarthritis, falls, cervical myelopathy and mild Parkinson's disease, but no subject suffered from any major systemic illness. Anyone suffering from conditions thought to interfere with theophylline absorption (e.g. previous gastric surgery, mal-
absorption) or elimination (e.g. cardiac failure, hepatic or severe renal impairment, acute respiratory infections) was excluded, as was anyone in whom aminophylline administration was thought to be hazardous (e.g. epilepsy, dysrhythmias, recent myocardial infarction or CVA, and aminophylline intolerance). Those taking drugs thought to interfere with gastrointestinal motility or theophylline metabolism were also excluded, and no subject ingested excess alcohol. All subjects were non-smokers and were judged to be normal by clinical, biochemical and haematological assessment.

Subject details are shown in Table 1. All subjects gave written informed consent prior to taking part, and the study was approved by the local ethical committee.

**Study Design**

The study was performed in two parts; initial single dose studies followed by steady-state studies.

**Single Dose.** Each subject received 225 mg sustained-release aminophylline (Phyllocontin Continus, Napp Laboratories) with 100 ml water at both 9 a.m. and 9 p.m. on two separate occasions, at least 5 days apart and in random order. Blood samples (6 ml) were taken via an indwelling forearm cannula into heparinised tubes pre-dose and at 1, 2, 3, 4, 5, 6, 8, 10, 12 and 24 h post-dose. Samples were centrifuged routinely within 10 min after collection and plasma stored at −20 °C prior to assay.

**Steady-State.** Subjects each received 225 mg sustained release aminophylline at 9 a.m. and 9 p.m. for 4 days to reach steady-state, and on day 5 studies were performed as after single doses at both 9 a.m. and 9 p.m.

During all parts of the study no attempt was made to control diet or activity, and subjects were encouraged to continue their normal routines. Content of meals was not controlled, but timing of meals was fairly consistent between both groups, breakfast being taken 1–1.5 h prior to 9 a.m. dose, and evening meal 2–3 h prior to 9 p.m. dose.

**Assay Method.** Theophylline assay was performed using a modification of the HPLC method of Orcutt et al. [8]. Precipitation was with 12% perchloric acid and mobile phase was 90% 0.01 M sodium acetate 10% Acetonitrile pH4. Standard curves were linear over the range 0–40 mg·l⁻¹ (r > 0.999) with a coefficient of variation between assays of 3.2% at 10 mg·l⁻¹.

**Kinetic Data.** These were obtained directly from plasma concentration/time curves, and AUC was calculated by the linear trapezoidal method. Statistical analysis was by Students t-test and significance was accepted as p < 0.05.

**Results**

No symptoms or adverse effects were noted after single dose studies, but during steady-state studies 6 subjects complained of restlessness and insomnia, 2 of mild nausea initially, and a further 2 complained of nausea and vomiting. These last subjects were subsequently found to be in the toxic range at steady-state with peak plasma levels of 28 and 29 mg·l⁻¹. This was unexpected after only 5 days treatment, as the dose used was the manufacturer's lowest recommended starting dose.

**Single Dose Studies**

In young subjects there was no statistically significant difference between 9 a.m. and 9 p.m. administration in maximum concentration (Cmax), time to maximum concentration (tmax) or area under plasma concentration time curve for the first 12 h after dosing (AUC) (Table 2).

In the eight elderly subjects, the maximum concentration was significantly lower (mean ± SEM 4.9 ± 0.5 mg·l⁻¹ vs 6.0 ± 0.5; p < 0.001) and reached significantly later (8.25 ± 1.03 h vs 5.13 ± 0.64 h: p < 0.05) after 9 p.m. administration. AUC (0–12 h) was also significantly reduced after 9 p.m. administration (31.2 ± 4.9 mg·h·l⁻¹ vs 37.9 ± 3.9: p < 0.05) (Table 2). These results indicate a decrease in the