

Influence of Food on the Absorption Rate and Bioavailability of a Sustained Release Theophylline Preparation

S. PEDERSEN and J. MOELLER-PETERSEN

Dept. of Paediatrics and Dept. of Clinical Chemistry, Aalborg Hospital, Aalborg, Denmark

Six children and six adults were given a single dose of a sustained release theophylline preparation (Nuelin Retard®) after an overnight fast and later after a standardized breakfast. Food significantly reduced the absorption rate of theophylline whereas the extent of absorption of theophylline was unaffected by food. Under steady state treatment the fluctuations in the serum levels of theophylline were small when the tablets were taken after meals twice a day showing that this dose regimen was sufficient. No characteristic absorption or elimination phases were seen during the steady state dose interval, and the time to peak serum theophylline level showed great variation. Serum theophylline control about 4 h after fasting intake of the tablet is recommended.

Key words: absorption rate; bioavailability; food; sustained release theophylline.

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While the absorption of theophylline from ordinary tablets is unaffected by food (6), the rate of absorption of theophylline from the sustained release preparation Nuelin Retard® (Riker) is considerably delayed when the tablets are taken after a meal as compared to fasting intake of the tablets (3). As tablets are often taken with food it is important to know in detail how the absorption of theophylline from sustained release preparations is changed when the tablets are taken after meals.

Therefore, the aims of the present study were:

- 1) to investigate the effect of food on the absorption rate and bioavailability of the sustained release theophylline preparation Nuelin Retard in children and adults.
- 2) to measure steady state serum concentrations of theophylline during a dose interval when all doses of a multiple dose regimen of Nuelin Retard were taken with food.

PATIENTS AND METHODS

Five boys and one girl aged 8-11 years (mean = 11.2) and four men and two women aged 28-32 years (mean = 29.8) participated in the study. Apart from asthma in the children all participants were in good health. One adult was a smoker. Informed consent was obtained from all the participants and the children's parents.

On day 1 Nuelin Retard was given at a mean dose of 11.9 (range 11.0-12.9) mg/kg to the children and at a mean dose of 10.7 (range 10.0-11.4) mg/kg to the adults as a single dose in the morning together with 200 ml of water. The participants were fasted for 10 h prior to dosing and for 4 h after dosing.

Serum theophylline concentrations were determined before tablet administration and 2, 4, 6, 8, 12, 16, 20, 24 and 30 h afterwards. After a 24-h wash out period the procedure was repeated in the same 12 patients (day 3),

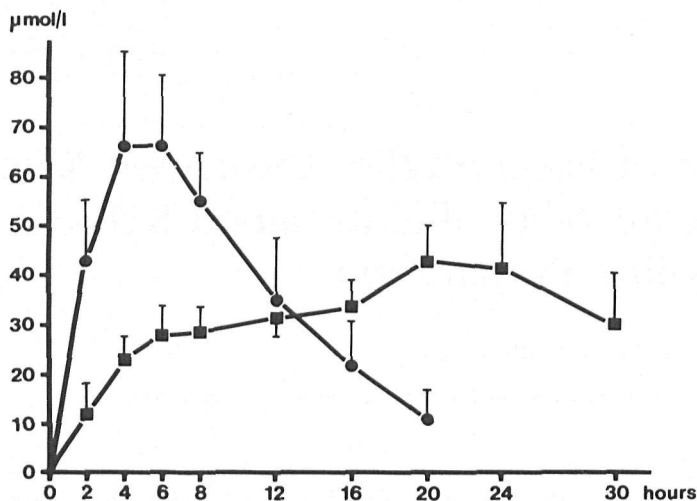


Fig. 1. Serum concentrations of theophylline (mean and SD) in six children taking a single dose of the sustained release theophylline preparation Nuelin Retard® under fasting conditions (●) and after breakfast (■).

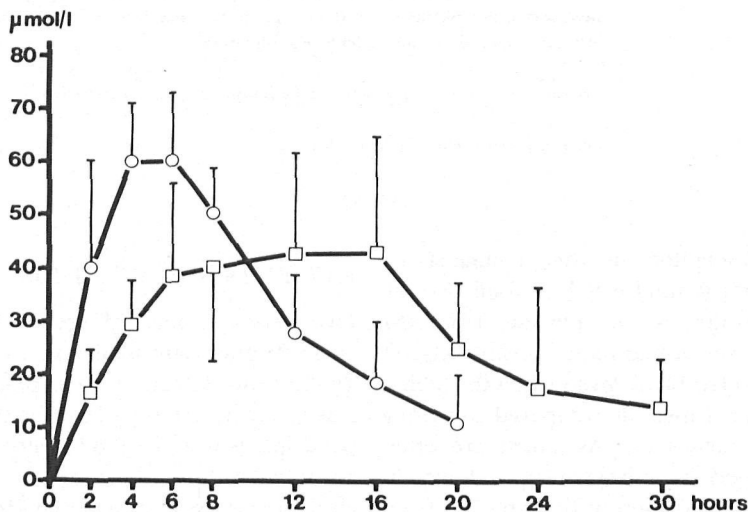


Fig. 2. Serum concentration of theophylline (mean and SD) in six adults taking a single dose of the sustained release theophylline preparation Nuelin Retard® under fasting conditions (○) and after breakfast (□).

but this time the participants received a large standardized breakfast before taking their tablets. The children received 10.6–15.1 kcal/kg (mean 13.1) and the adults received 7.2–9.8 kcal/kg (mean 8.2). In all cases the composition of the breakfast was so that 19–20% of the calories were made up of fats, 68–70% of carbohydrates and 12–13% of proteins.

After day 3 all patients took Nuelin Retard twice a day for 4 days (a total of 8 doses). The tablets were taken immediately after supper and the standardized breakfast which were approximately 12 h apart. The children took 12.5–17.2 mg theophylline/kg/day (mean 14.7) and the adults 10.0–13.6 mg theophylline/kg/day (mean 10.7). Serum theophylline was then

determined before, and 2, 4, 6, 8, 10 and 12 h after dose No. 9 (day 8).

Throughout the investigation period no xanthine-containing food or drink was permitted. Serum theophylline concentrations were measured by a radioimmunoassay method (1). Side effects were recorded by the patients themselves and by the investigator. The results are given as mean $\pm$ standard deviation.

RESULTS

The serum concentrations of theophylline on days 1 and 3 are given in Fig. 1 (children) and Fig. 2 (adults).

The absorption rate of theophylline was significantly reduced by food in both children and adults. On day 1 the time to peak concentrations was 4.7 ± 1.0 h for both children and adults. On day 3 the children's peak time occurred significantly later than the peak time of the adults i.e. 21.3 ± 2.1 h versus 15.3 ± 5.9 h ($P < 0.01$ unpaired *t* test).

The mean peak serum level of theophylline of 71 ± 15 $\mu\text{mol/l}$ in the children on day 1 was significantly higher than the peak level of 48 ± 9 $\mu\text{mol/l}$ ($P < 0.01$ paired *t* test) on day 3. The peak levels of the adults on days 1 and 3 (64 ± 12 and 54 ± 17 $\mu\text{mol/l}$) were not statistically significantly different.

The extent of absorption of theophylline was not reduced by the intake of food. The areas under the time concentration curves (AUC) on day 1 and day 3 for the children were 800 ± 166 and 931 ± 133 $\mu\text{mol} \times \text{h/l}$ respectively, and for the adults 756 ± 203 and 888 ± 298 $\mu\text{mol} \times \text{h/l}$. The difference in AUC between days 1 and 3 were not statistically significant.

The steady state serum concentrations on day 8 are shown in Fig. 3. No characteristic absorption and elimination phase was seen. The theophylline levels showed little fluctuation during the 12 h interval with peak to trough differences of 15.2 ± 4.8 $\mu\text{mol/l}$ (children) and 20 ± 7.7 $\mu\text{mol/l}$ (adults).

On day 1 two children complained of dizziness, one of headache and one of stomach pain. During the two doses per day period two adults complained of dizziness.

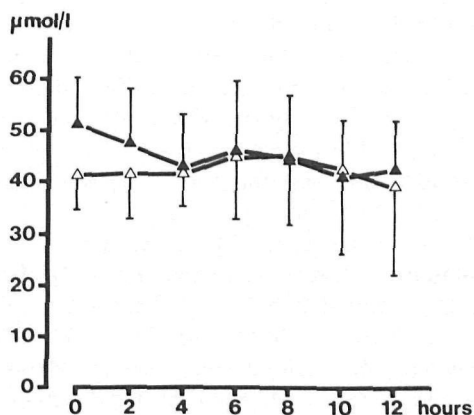


Fig. 3. Steady state serum concentrations of theophylline (mean and SD) in six children (▲) and six adults (△) taking the sustained release theophylline preparation Nuelin Retard® twice a day after meals.

DISCUSSION

The influence of food on the absorption rate and the peak serum levels of theophylline was not so pronounced in the adults as in the children. This may have been due to the fact that the adults' meals were comparatively smaller than the meals of the children.

The study implies the following clinical aspects:

1) Serum theophylline should be controlled 4 h after fasting intake of Nuelin Retard, because maximum serum theophylline levels will occur reliably about that time. An optimal time for serum theophylline control cannot be recommended when Nuelin Retard is taken with food because the time of peak serum theophylline level will then be unpredictable and perhaps dependent on the size of the meal.

2) The prolonged absorption after food requires that treatment with Nuelin Retard should be stopped for at least 48 h prior to bronchial provocation tests in order to ensure that all theophylline has been absorbed and eliminated at the time of the test.

3) In order to avoid high, potentially toxic serum concentrations of theophylline the possibility of a very sustained oral absorption of

theophylline should be taken into account when patients taking Nuelin Retard require continuous intravenous theophylline emergency treatment at hospital. Storms (4) reported a case of theophylline intoxication which might be ascribed to a very sustained absorption of another sustained release preparation.

4) As the bioavailability of theophylline was unaffected by food and the absorption of theophylline was made more protracted by food, Nuelin Retard should be taken twice daily after meals. On the basis of single dose absorption data 8-h dosing has been advocated in children with most sustained release theophylline products (5). If such absorption data came from fasting intake of tablets our study showed that this recommendation will have to be reconsidered. Furthermore, concomitant intake of food may reduce the frequency and severity of side effects (3).

5) The absorption rate and bioavailability of drugs may be influenced by the intake of food in many different ways (2), and therefore investigations of different formulations of sustained release theophylline preparations should

also include the effect of food on absorption and elimination.

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Address:

S. Pedersen, M.D.
Hobrovej 13
DK-9000 Aalborg
Denmark

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