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# The new trends in theophylline therapy

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## Abstract

Sustained-release theophylline pellets formulation for once-daily evening administration significantly improved patients compliance and adjusted serum levels profile of the drug. The patients conversion from i.v. to p.o. therapy is one of the most critical steps in the treatment of asthma according to its chronopathophysiological character.

In our study we have examined safety and efficiency of this conversion in twelve hospitalised asthmatic patients who were given the new sustained-release theophylline pellets formulation for once-daily evening administration. The lung function parameters (FEV<sub>1</sub>, VC, RV, and Rt) and serum theophylline concentrations were monitored. So, the values obtained for the last day of i.v. therapy and the fifth day of p.o. therapy were compared. We found that 75% of the patients had no change or improved lung function on the conversion.

Our results indicate that this conversion from i.v. to p.o. theophylline therapy is safe and could be efficacious. Also, the maximum theophylline serum levels could safely be predicted by measuring only one serum concentration in p.o. therapy with sustained-release theophylline pellets formulation for once-daily evening administration.

**Key words:** theophylline, sustained-release, pellets, asthma, theophylline serum concentrations, lung function parameters, once-daily evening administration

## Introduction

Asthma is a chronic inflammatory disease of the airways, characterised by hyper-responsiveness to a variety of stimuli (1). Clinically, these features are manifested by attacks of cough, wheezing, and dyspnoea. The nocturnal worsening of asthma is a common event in asthma patients. It has been recognized since the 5<sup>th</sup> century A.D. by Aurelianus Caelius (2). Nocturnal asthma, defined as an exacerbation of asthma at night, is associated with increases in symptoms and need for medication,

increased airway responsiveness and worsening of lung function (3).

The mechanisms of nocturnal asthma are intimately related to circadian rhythms, which influence inflammatory cells and mediators, hormone levels and cholinergic tone. Patients with nocturnal asthma symptoms may have greater night-time activation of inflammatory cells and mediators, lower levels of epinephrine and increased vagal tone (4).

In the long term treatment, especially in patients with nocturnal asthma, theophylline has a major impact on lung function parameters. This observation corresponds well to the hypothesis of a predominantly antiinflammatory action of theophylline (5). Theophylline is not only a bronchodilator but also has other effects (inhibition of mediator release, enhancement of mucociliary clearance, enhancement of diaphragmatic contractility) that are potentially beneficial to asthmatic patients. An important feature of oral controlled-release theophylline therapy is timing of drug administration. Because airway reactivity increases and airway caliber decreases at night, it has been suggested that the greatest benefit is derived from theophylline when peak serum concentration is reached during the night or the early morning.

It has been confirmed that once-daily theophylline (Th) regimens are as effective as twice daily regimens for control of chronic asthma in adult patients (6,7,8).

In the studies where the once-daily theophylline formulation was administered in the evening, there were significant benefits in spirometric values and symptom control in favour to the once-daily regimen (8,9,10). This confirmed the dynamic nature of the asthma process, in other words that the patients' greatest physiological needs for bronchodilatation are between 2 and 8 a.m. In order to achieve effective theophylline serum concentrations (STCNs) within the range of 8-20 mg/l once-daily dosing requires single doses greater than 600 mg of theophylline, which presumes linear and pH independent drug release from a dosage form.

New sustained-release theophylline pellet formulation for once-daily evening administration meets these requirements, providing STCNs profile adjusted to the chronopathophysiological character of asthma.

In order to individualize theophylline dosage, estimation of minimum and maximum STCNs is essential. Whereas the minimum (trough) concentration can readily be estimated from the pre-dose level for sustained-release theophylline pellets formulation, the nocturnal maximum concentration can be predicted by taking one blood sample between 7 and 9 a.m. The resultant STCNs represent 90% of the maximum STCNs, with a range of 80 to 100% in individual subjects.

The safe clinical conversion from i.v. aminophylline to this sustained-release theophylline pellets formulation for once-daily evening administration could have multiple advantages for the patients, providing most suitable conditions for the chronic treatment, and was examined in this study.

## Subjects and Methods

Twelve hospitalised asthmatic patients (reversibility of the obstruction was proven by a beta-agonist inhalation) participated in the study. Mean patient's age 49,614,7 years (range 24-73 years), mean body mass was 76,713,8 kg (range 50-107 kg), eight were nonsmokers (six female and two male), and four smokers (one female and three male). Before the conversion, all the patients received i.v. aminophylline (250 or 500 mg twice daily). Inhaled beta-agonists and inhaled or orally administered steroids (part of some patient's regular therapy) were continued throughout the trial. The patients were asked to keep their daily dosage of these medications constant, and it was supervised.

Drugs known to affect theophylline metabolism were not allowed during the trial.

The patients took their regular meals three times daily, additional food intake was not restricted (except xanthine containing foods and beverages), and was recorded; so

was the occurrence of possible side-effects.

One the conversion, the patients were administered (at 8 p.m., one hour after a meal) one or two capsules (each containing 375mg of anhydrous theophylline) of a sustained-release theophylline pellets formulation for once-daily evening administration (average dose of 8,642,17 mg, range 4,66 to 11,36 mg). Fixed dose of the preparation all the patients received for five subsequent days.

Blood samples for the STCNs determination were taken according to the following schedule:

- The last day of i.v. aminophylline at 8 p.m. (just before the first p.o. dose)
- Every day during five trial days at 8 a.m.
- Just before the fifth p.o. dose at 8 p.m.
- After fifth p.o. dose at 2 a.m.

Five milliliters of blood were taken, serum was separated, and frozen at  $-20^{\circ}\text{C}$  until analysed.

Theophylline in serum was determined by the spectrophotometric method (11)

The function parameters (spirometry) was used) were monitored for six days between 8 and 9 a.m. For the presentation of the results and the conversion safety assessment, we chose the lung function parameters (FEV1-forced expiratory volume in the first second, VC-vital capacity, RV-residual volume and RT-total resistance) for the last day of i.v. aminophylline, and the fifth day of p.o. sustained release theophylline pellets for once—daily evening administration.

## Experimental RESULTS and discussion

The main results are shown in tables, I, II and III, and in Figure 1.

**Table 1** - minimum (trough) serum theophylline concen-

**Table 1.**

Patient	Age (Yr)	Sex	Body mass (kg)	Th (mg/kg/day)	Smoking status (S-smoker, NS-nonsmoker)	C <sub>min.i.v.</sub> (mg/l)	C <sub>min.p.o.</sub> (mg/l)
M.A.	42	F	50	7.5	NS	3.8	7.1
R.R.	26	M	80	4.6	S	12.5	6.5
G.B.	24	M	73	5.1	S	6.2	4.5
K.K.	73	M	76	9.8	NS	8.3	13.8
K.N.	57	F	107	7.08	NS	7.0	7.1
T.R.	65	F	78	9.6	NS	8.1	11.2
G.A.	44	M	73	10.2	S	5.7	5.4
P.J.	50	F	76	9.8	NS	5.8	23.5
B.U.	48	M	94	8.0	NS	6.0	6.1
P.J.	63	F	71	10.5	NS	7.5	15.6
H.M.	46	F	76	9.8	NS	4.7	10.6
S.S.	57	F	66	11.3	S	5.7	8.3
Mean ± S.D.	49.6 ± 14.7		76.7 ± 13.8	8.6 ± 2.1		6.8 ± 2.2	10.0 ± 5.4

trations (STCNs) after i.v. aminophylline and p.o. sustained-release theophylline pellets formulation for once-daily evening administration, determined for twelve asthmatic patients

**Table 2** - Lung function parameters for the last day of i.v. aminophylline ( I ), and the fifth day of p.o. sustained-release theophylline (Th) pellets formulation for once-daily evening administration ( II )

**Table 3** - Steady state theophylline (Th) concentrations at 8 a.m. and 2 a.m., and their ratio, in sera of twelve asthmatic patients after five p.o. doses of a sustained-release theophylline (Th) pellets formulation for once-daily evening administration

**Figure 1.** Mean serum theophylline concentrations (STCNs) at 8 a.m., in sera of 8 asthmatic nonsmoking patients receiving p.o. sustained-release theophylline pellets formulation for once-daily evening administration

lets formulation for once-daily evening administration

Table I contains minimum STCNs after i.v. aminophylline, as well as after four p.o. doses of sustained-release theophylline pellets formulation. It can be seen that in the case of non-smoking patients the trough concentration rose, confirming the sustained-release properties of the formulation, while in the case of smoking patients indicated the need for the adjustment of the dosage and timing of the administration (increase the dose and administer one third in the morning)

During the study all the conditions were constant, so the clinician, on the basis of the lung function comparison, could draw a conclusion about possible change during the conversion (Table II). It can be seen that 75% of the patients had no change or improved lung function on the conversion.

STCNs in patients sera taken at 8 and 2 a.m., and their ratios are listed in Table III. As can be seen in eight non-

**Table 2.**

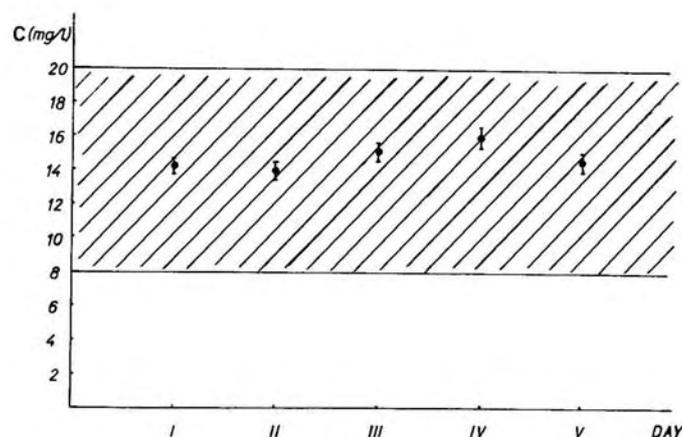
Patient	I				II				Conclusion
	FEV1	VC	RV	RT	FEV1	VC	RV	RT	
M.A.	81%	88%	113%	0.25	95%	94%	139%	0.29	no change
R.R.	71%	96%	185%	0.19	89%	91%	176%	0.18	no change
G.B.	89%	107%	179%	0.24	92%	111%	204%	0.18	improvement
K.K.	26%	61%	141%	0.60	35%	68%	181%	0.35	improvement
K.N.	55%	75%	181%	0.28	54%	65%	166%	-	no change
T.R.	57%	83%	190%	0.32	41%	75%	201%	0.34	worsening
G.A.	36%	79%	315%	0.60	35%	78%	376%	0.56	worsening
P.J.	60%	74%	332%	0.30	67%	94%	88%	0.20	improvement
B.U.	16%	45%	294%	1.54	55%	98%	160%	0.29	improvement
P.J.	24%	64%	335%	0.57	39%	59%	217%	0.80	no change
H.M.	36%	78%	260%	0.31	31%	75%	277%	1.16	worsening
S.S.	46%	85%	425%	0.45	80%	89%	258%	0.30	improvement

**Table 3.**

Patient	C <sub>8 a.m.</sub> (mg/l)	C <sub>2 a.m.</sub> (mg/l)	C <sub>8</sub> /C <sub>2</sub> (%)
M.A.	10.96	96%	12.80
R.R.*	9.38	8.84	105.11
G.B.*	6.03	8.51	70.86
K.K.	19.55	21.40	91.35
K.N.	7.67	7.93	96.72
T.R.	19.33	22.00	87.86
G.A.*	6.63	11.57	57.30
P.J.	20.80	25.40	81.89
B.U.	9.68	11.31	85.59
P.J.	15.21	17.64	85.56
H.M.	13.65	17.81	76.64
S.S.*	9.10	6.92	131.50

\* - smokers

Figure 1.



smoking patients, this ratio ranged between 76.64% and 96.72 (mean  $86.53 \pm 5.97$ ).

In Figure 1., non-smoking patients' 8 a.m. STCNs are given for the five trial days. It is shown that all the concentrations were within therapeutic range of theophylline (mean  $14.83 \pm 0.86$ ).

The results obtained indicate that this conversion from i.v. to p.o. theophylline therapy is safe and could be efficacious, and that maximum STCNs could be predicted by measuring 8 a.m. steady state concentration

## Conclusion

However, comparing individual STCNs with lung function parameters, one of the mayor conclusions in theophylline therapy arose.

This is that each patient must be treated individually in a context of SCTNs, lung function parameters and his specific needs for theophylline in the therapy of asthma.

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