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J. MOORE (Salt Lake City, Utah)
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EFFECT OF UNEQUAL TWICE DAILY THEOPHYLLINE ON THE CIRCADIAN VARIATION IN THE EXPRESSION OF $\beta_2$-ADRENOCEPTOR SITES ON PERIPHERAL MONONUCLEAR LEUCOCYTES (MNL)

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KEY WORDS  
circadian variation, $\beta_2$-adrenoceptors, peripheral mononuclear leucocytes (MNL), nocturnal asthma, theophylline

INTRODUCTION

The reaction of hormone receptors to systemically administered drugs may be studied on intact mononuclear leucocytes (MNL). $\beta_2$-adrenoceptors respond to $\beta$-sympathomimetics with a so called "down-regulation", i.e. a decrease of the number of expressed receptor sites (Aarons et al 1983). The opposite effect, receptor "up-regulation" may be achieved with $\beta$-blockers such as propranolol (Aarons et al 1980). Theophylline may interact with the intracellular cAMP system which in MNL is coupled among others to $\beta_2$-adrenoceptors. This drug is currently being recommended for the prevention of nocturnal asthmatic attacks (Barnes 1984). It is of interest, therefore, to study the effect of therapeutic theophylline concentrations on the circadian variation in the expression and function of $\beta_2$-adrenoceptor sites (Pangerl et al 1986, Haen 1987) in male asthmatic patients suffering from nocturnal asthma (Haen et al 1988).

MATERIALS AND METHODS

Four so far untreated male asthmatic patients, 19-27 years of age, were given 1050 mg/day theophylline (Bronchoretard®, Klinge Pharma Munich/FRG). The dosage was divided in 1/3 (350 mg) at 08h00 and 2/3 (700 mg) at 22h00 because of the circadian variation in the serum concentration/time profile of this drug (Scott et al 1981). Before treatment and on day 7 venous blood was drawn at 14h00, 18h00, 22h00, 02h00, 06h00, 10h00, and again at 14h00. The blood specimen were immediately assayed for the number of high affinity $\beta$-adrenergic binding sites (B-max) on intact lymphocytes, using a receptor binding assay (Anhäuserl et al 1988) with $^{125}$I-cyanopindolol, a $\beta$-antagonist. $\beta_2$-adrenoceptor coupled adenylyl cyclase was stimulated by incubating the intact cells with $10^{-7}$ mol/l isoprenaline for 5 minutes at 37°C; the increase of intracellular cAMP above basal values was determined by radio-immunoassay after cell disruption.

Directly after venopuncture respiratory function was assessed using a computer based, room-restricted spirometer. Among other variables the best of three peak expiratory flow (PEF) readings was recorded.
The subjects were asked to follow a regular lifestyle for the two weeks preceding the study with bed rest between 23h00 and 07h00. On the day of the study the subjects stayed in the clinical pharmacological research unit of the hospital. They continued to follow their normal daily routine. Subjects were asked to record meal times, the consumption of alcohol and caffeine. All were non-smokers.

Circadian variations were statistically validated by the single cosinor method (Halberg et al 1967) and by analysis of variance (anova). Significance limit was $p<0.05$.

RESULTS

The theophylline dosing scheme resulted in plasma drug concentrations of 8-13 ug/ml on day 7 (Fig. 1). Respiratory function markedly improved, which matched the subjective relief of complaints. Especially the "nocturnal dip" in peak expiratory flow was much less pronounced (Fig. 2) indicating that theophylline was most effective between 02h00 and 06h00 when plasma drug concentrations were in the upper range (Fig. 1).

![Fig. 1. Theophylline plasma concentration in male asthmatic patients on day 7 of 1050 mg/d theophylline ($\bar{x} \pm SE$).](image)

![Fig. 2. Peak expiratory flow of male asthmatic patients before and on day 7 of 1050 mg/d theophylline ($\bar{x} \pm SE$).](image)
The circadian variation in the expression of $\beta_2$-adrenoceptor sites was preserved after treatment with theophylline (Fig. 3). Peak daytime values, however, were reduced resulting in a smaller circadian range of 63.1-139.0 % of 24h-mean (compared to 59.1-155.2 % of 24h-mean before treatment). The 24h-mean itself was lowered from 1014±119 sites/cell to 853±87 sites cell ($\bar{x}$±SE) equivalent to a receptor down-regulation of 15.9 % (not significant).

![Fig. 3. $\beta_2$-Adrenoceptor density on peripheral mononuclear leucocytes of male asthmatic patients before and on day 7 of 1050 mg/d theophylline ($\bar{x}$±SE).](image)

In spite of the reduced $\beta_2$-adrenoceptor density during the day basal cAMP contents of the cells were equally elevated throughout the 24 hours (Fig. 4). The circadian variation was preserved with a 24h-mean increased from 4.8±0.4 pmol/10^6 cells to 8.3±0.6 pmol/10^6 cells ($\bar{x}$±SE, not significant). $\beta_2$-adrenoceptor coupled adenylate cyclase could still be stimulated by $10^{-7}$ mol/l isoprenaline to 9.6±0.6 pmol/10^6 (24h-mean ± SE) cells (increase of 1.3 pmol/10^6 cells compared to 2.0 pmol/10^6 cells before treatment, Fig. 4, Haen et al 1988).

![Fig. 4. Cyclic AMP content of peripheral mononuclear leucocytes from male asthmatic patients on day 7 of 1050 mg/d theophylline before and after in vitro stimulation by $10^{-7}$ mol/l isoprenaline ($\bar{x}$±SE).](image)
DISCUSSION

A 25% down-regulation of \( \beta_2 \)-adrenoceptors by theophylline treatment was already described by Scarpace et al in 1982 in a non-chronobiological study. Such an effect could be mediated via stimulation of catecholamine secretion by theophylline (Hedquist et al 1978) and/or via an increased intracellular cAMP content, since a cAMP dependent protein kinase has been suggested to be responsible for receptor down-regulation (Helmreich & Pfeuffer 1985). The adrenoceptor down-regulation by theophylline is clinically irrelevant in asthma therapy, since respiratory function is on the contrary markedly improved. However, the reduced response of the adenylate cyclase system to \( \beta \)-adrenergic stimuli (as compared to pretreatment, Haen et al 1988) may be relevant to a combination of theophylline with \( \beta \)-sympathomimetic drugs. \( \beta \)-Sympathomimetics may increase the effectiveness of a theophylline therapy, but both drugs are less than additive in effect.

REFERENCES


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