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Kaliuretic effect of short-term theophylline in healthy subjects

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Abstract

In a two-way crossover non-randomized design, the kaliuretic effect of sustained-release theophylline (T) 300 mg every 12 h for 3 days was compared with furosemide (F) 40 mg once a day for 3 days, on the urinary potassium excretion rate of 10 healthy nonsmoker males. The individual base lines of urinary potassium excretion rate (UKER, mg/min); urine flow rate (UFR, ml/min) and the 24 h total potassium excretion were established during a control period of 4 weeks. The net, as defined in the text, UKER and UFR of F were significantly higher than those of T, 0.212 ± 0.111 versus 0.111 ± 0.040 mmol/min and 10.44 ± 3.46 versus 1.36 ± 0.62 ml/min, respectively. However, T duration time, of both UKER and UFR, were significantly longer than that of F 7.21 ± 1.48 versus 3.24 ± 1.08 h. There was no significant difference in the 24 h net total potassium excretion between T and F, i.e. 47.69 ± 15.46 versus 41.25 ± 22.97 mmol, respectively. Potassium monitoring for patients who are on acute T is recommended.

Keywords: Theophylline; Furosemide; 24 h potassium excretion; Urine; Kaliuretic effect

1. Introduction

Hypokalemia frequently occurs during the management of acute severe asthma [1]. Hypokalemia has been associated with respiratory arrest [2]. β_2-adrenergic agonists and corticosteroids, both used in asthma management, but usually for a shorter period of time than theophylline, are known to cause hypokalemia [3,4]. In clinical studies, theophylline levels above the normal therapeutic range [10–20 mg/l] were usually associated with hypokalemia [5–7]. Even with theophylline levels within the therapeutic range, following acute therapy with theophylline infusion [8], a significant drop in plasma potassium (i.e. from 3.88 base line to 3.4 mmol/l) has been reported. Braat et al. [9] reported a 25% drop in the plasma concentration of potassium with theophylline concentrations as low as 2.22 and 7.71 mg/l, after a single PO 250 mg dose of theophylline. This hypokalemia could possibly be due to intracellular sequestration of potassium [5] or to depletion of potassium pools [10]. Since serum potassium concentration reflects only about 2% of the total body potassium (the remaining 98% of potassium is distributed in intracellular compartments), homeostatic mechanisms and acid–base imbalance render the serum potassium level an inaccurate indicator of total body potassium status. Since the kidney is a major potassium elimination pathway and the normal kidney does not have an efficient mechanism for potassium conservation [11], the 24 h potassium excretion may be considered a reliable indicator of total body potassium.

The purpose of this study was firstly to determine whether an average theophylline dosage of 300 mg every 12 h, can cause a significant increase in the urinary potassium excretion in healthy subjects and secondly to compare the kaliuretic effect of

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theophylline to that of a known kaliuretic loop diuretic such as furosemide with an average dosage of 40 mg every 24 h.

2. Materials and methods

2.1. Subjects

Ten healthy, nonsmoker males, volunteered for this study, the mean age ± standard deviation [S.D.] was 34 ± 10.5 year, ranging from 23 to 57 year, and the mean body weight was 73 ± 11 kg, ranging from 52 to 85 kg.

The procedures followed were in accord with the ethical standards of the institution's committee on human experimentation.

2.2. Procedure

In a two-way non-randomized crossover design, a sustained-release theophylline (T) 300 mg tablet (Theo-Dur, Key pharmaceuticals) was orally administered at 8:00 and 20:00 h for 3 days and furosemide (F) 40 mg tablet (Lasix, Hoechst) once a day at 8:00 h for 3 days. These dosages represented average dosage regimens for T and F. There was a 1 week washout period between the two treatments. Potassium concentrations were chosen to be monitored in urine rather than in serum, because serum potassium concentration reflects only about 2% of the total body potassium; the remaining 98% being distributed in intracellular compartments. Furthermore, homeostatic mechanisms and acid–base imbalance render the serum potassium level an inaccurate indicator of total body potassium status. The 24 h urinary potassium excretion monitored in this study was considered to be a more reliable indicator of total body potassium. In order to minimize the effect of circadian variation, urine samples—total urine output—were collected every day of the 3 day study period at 8:00; 8:30; 9:00; 9:30; 10:00; 10:30; 11:00; 11:30; 12:00; 13:00; 14:00; 15:00; 16:00; 17:00 and whenever available afterwards until 8:00 the following morning. The urine volume and pH of each sample was immediately measured and 10 ml aliquots were stored at −20° for K analysis. Urinary K concentrations were determined by Atomic Absorption (Perkin–Elmer spectrophotometer) with a hollow cathode lamp, air-acetylene flame; sensitivity 0.01 $mmoL^{-1}$ K for 1% absorption.

2.3. Urinary potassium excretion rate base line

Age and lean body weight correlate with the total potassium pools. To minimize the effect of wide ranges of age and body weight on potassium pools, every subject served as his own control. Each individual's base line data was collected, under a normal routine diet, plentiful fluid intake and routine daily activities for 28 days. The only restriction was in alcohol consumption and xanthine intake. The same restrictions of no alcohol consumption and no xanthines intake were applied for the whole study period including drug treatments and washout periods. Urine samples were collected every day of the 28 day study period at 8:00; 8:30; 9:00; 9:30; 10:00; 10:30; 11:00; 11:30; 12:00; 13:00; 14:00; 15:00; 16:00; 17:00 and whenever available afterward. The urine volume and pH of each sample were immediately measured and 10 ml aliquots were stored at −20° for potassium analysis.

2.4. Statistical analysis

The base lines of UKER, UFR and 24 h potassium excretion for each subject were established by plotting the mean ± 2.0 S.D. of UKER, UFR and 24 h potassium excretion for pooled 28 day urine samples against mean clock time. All 28 days were included in the base-line to minimize the variation in potassium excretion measurements. Significant changes reflecting drug effect were calculated by computing the net effect of T and F on UKER, UFR and 24 h potassium excretion, by subtracting the upper limit of the base line [mean + 2 S.D.] from the observed values, at the same mean clock time. The drug duration time was taken to be the time within which significant net changes in the UKER, UFR and 24 h potassium excretion, were observed. Analyses of variance with repeated measurements were computed using SAS (Cary, NC). A value of $P < 0.05$ was considered significant.

3. Results

The individual base lines for UFR and UKER with respect to clock time followed circadian rhythm profiles. The peak rate time [acrophase] was at noon and the trough [nadir], was at midnight (Fig. 1).

The mean net changes in UKER and UFR under the effect of T were significantly lower than those of F, i.e. 4.30 ± 1.57 versus 8.28 ± 4.35 and 1.36 ± 0.62 versus 10.44 ± 3.46 ml/min, respectively, but significantly greater than the base line. Also T has a significantly longer duration time of kaliuretic effect than F, i.e. 7.21 ± 1.48 h versus 3.24 ± 1.08 h. There was no significant difference between T and F in the mean total amounts of potassium excreted over 24 h, i.e. 47.69 ± 15.46 mmol for T and 41.25 ± 22.97 mmol for F [Table 1].

There was a steady decline in the mean diuretic and kaliuretic effects of both drugs during the 3 day period (Fig. 2).

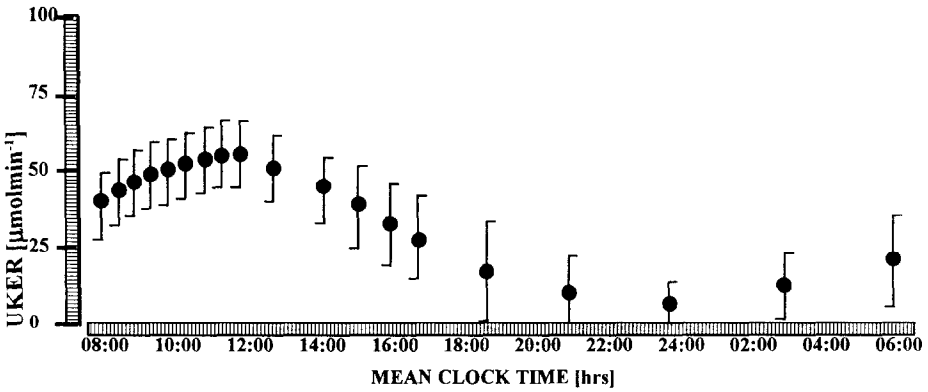

Fig. 1. The circadian profile of the urinary potassium excretion rate base-line (mean ± S.D.) of 10 subjects over a 28 day study period.

4. Discussion

In the present study, there was a significant increase in UKER from the normal base line following acute administration of both theophylline and furosemide. UKER under the influence of theophylline was half of that of furosemide. The daily potassium excretion was significantly higher than the base-line for both theophylline and furosemide, but did not differ significantly between both drugs. Following administration of an average daily dose, theophylline concentrations within the therapeutic range may increase 24 h potassium excretion by increasing the glomerular filtration rate [12] and decreasing tubular reabsorption of potassium [13], thus aggravating or provoking a decrease in potassium blood levels as previously reported. The diuretic and kaliuretic effects of both drugs declined over the 3 days trial period, inspite of the expected increase in theophylline plasma concentrations.

This decline could possibly be due to intracellular sequestration of potassium [5]. Even in plasma, decreases in plasma potassium levels (i.e. from 3.88 base line to 3.4 mmol/l) have been reported with theophylline levels both within the therapeutic range [8] and below it [9].

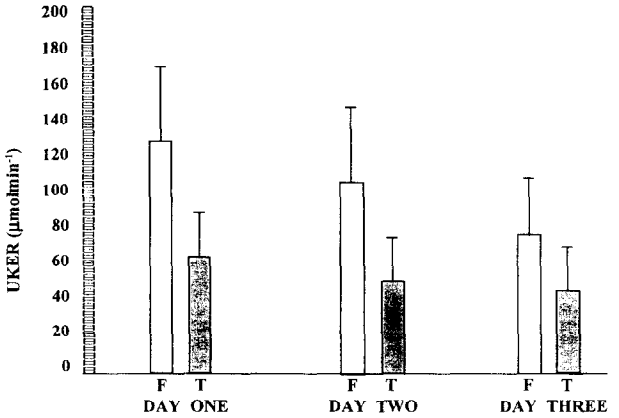

Fig. 2. The decline of diuretic and kaliuretic effects of furosemide and theophylline following their oral adminstration over a 3 day study period. □ Furosemide urine potassium excretion rate, ■ Theophylline urine potassium excretion rate.

With average dosage regimens for both theophylline and furosemide, (300 mg twice a day and 40 mg once a day, respectively), no significant difference was observed in their net daily potassium loss. However, 24 h potassium excretion was significantly higher than the base-line for both theophylline and furosemide. Thus, potassium monitoring is recommended for patients who are on acute theophylline therapy.

Table 1
Comparison between the daily kaliuretic effects of theophylline and furosemide (mean ± S.D.)

	24 h urinary potassium excretion [mmol/day]	
	Net theophylline effect	Net furosemide effect
Day 1	59.85 ± 18.38	63.47 ± 20.78
Day 2	47.69 ± 15.46	41.25 ± 22.97
Day 3	39.78 ± 12.46	37.25 ± 17.64

Net effect = effect greater than the upper limit of the mean urinary potassium excretion base line (+2 S.D.) = 46.87 mmol/day.

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