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Dependence of the Renal Excretion of Theophylline on its Plasma Concentrations and Urine Flow Rate in Asthmatic Children

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Abstract—The dependence of the renal excretion of theophylline on its plasma concentration and urine flow rate has been investigated in asthmatic children of either sex. One group (age 12·25 ± 0·80, mean ± s.d. n = 8) was given aminophylline intravenously (i.v.), while another (age 10·00 ± 3·64 n = 14) was given a sustained release preparation of theophylline orally (single dose and repeated doses). Unchanged drug (11·6% ± 1·75) was excreted in the urine corresponding to a renal clearance of 10·6 ± 1·6 mL $h^{-1}kg^{-1}$. Time dependence of the renal clearance of theophylline was found only after i.v. administration. Dependence of the renal clearance on urine flow rate was found both after i.v. administration and at steady state, but not after a single oral dose of theophylline. After oral administration, renal clearance of theophylline was higher at steady state than after a single dose (0·58 ± 0·06 L h^{-1} kg^{-1} vs 0·23 ± 0·03 L h^{-1} kg^{-1}), while urine flow rate was lower (1·1 ± 0·5 mL min^{-1} vs 1·8 ± 0·9 mL min^{-1}). High correlation of theophylline plasma concentration and theophylline excretion rate was obtained in 10 of 14 patients after administration of a single oral dose of the preparation (r = 0·8567 to 0·9830). There was no dose dependence of the renal clearance of the drug either after a single dose, or at steady state.

Theophylline metabolism in liver is known to be extensive and variable and the percentage of unchanged drug excreted in urine is dependent on age, being from 50 to 98% in premature neonates (Grygiel & Birkett 1980; Tserng et al 1981); 7·1 to 10·1% in children (Grygiel & Birkett 1980; Bonati et al 1981), 13·3 to 16·4% in adults (Tang-Liu et al 1982b; Rovei et al 1982) and 11·4% in the elderly (Antal et al 1981). The influences of urine flow rate (Levy & Koysooko 1976; Tang-Liu et al 1982a) and circadian rhythm (St-Pierre et al 1985) on renal clearance of theophylline have been investigated in adults.

The aim of the present work was to estimate renal clearance of theophylline in asthmatic children after oral administration of a single dose of the drug and at steady state, and to investigate the influence of urine flow rate on urinary excretion of theophylline and on its renal clearance, both after i.v. and oral administration. The correlation of renal clearance of theophylline with its plasma concentration, the dose of the drug and urine pH was also calculated. The study was undertaken to evaluate urine as an alternative biological fluid in pharmacokinetic investigations in asthmatic children.

Materials and Methods

Subjects

The investigation was carried out in two groups of hospitalized asthmatic children.

One group consisted of 8 children (4 male, 4 female), age 10–16 years (12·25 ± 0·80, mean ± s.d.), weight 30–49 kg (34·25 ± 2·3 kg). These children were given 5 mg kg^{-1} of aminophylline i.v.

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The second group consisted of 14 children (10 male, 4 female) age 5–15 years (10 ± 3·6, mean ± s.d.). These children were given different doses of an oral sustained release preparation (SRP) of theophylline (Durofilin, Zdravlje, Leskovac, Yugoslavia). One child was given 7 mg kg^{-1} of theophylline, 6 children 9 mg kg^{-1} and 7 children 11 mg kg^{-1} at 12 h intervals.

Clinical protocol

All the children refrained from xanthine-containing food and beverages for 48 h before and during the investigation. Before the study the children were tested both clinically and biochemically, blood and urine being monitored. None of the children had any sign of gastrointestinal, heart, hepatic or renal dysfunction. Creatinine clearance values were determined and found to be within normal limits in all the children. They were on standard clinical diet and received meals at 0700, 1200 and at 1800 h. Liquid intake was standardized to 50 mL of water after each urine sample, both after a single oral dose of the SRP of theophylline and at steady state. The same liquid intake was allowed after intravenous administration of the drug and plasma was collected just before the dose. After oral administration of the drug, plasma was collected just before the drug was given, and at 0·5, 1, 2, 4, 6, 8, 10 and 12 h after administration and urine was collected at specified intervals up to 12 h, both after a single dose of SRP of theophylline and at steady state (Fig. 1b). After the intravenous dose, plasma was also taken at the same times and at 24 h, and urine sampled up to 24 h. The study was approved by the Clinical Ethics Committee, and parental consent was obtained for each child who participated.

Analytical method

Plasma samples were obtained using heparin as an antico-

agulant. Urine samples were controlled for both volume and pH, and plasma and urine were frozen at −20°C until analysed (up to 14 days). Theophylline was determined by a spectrodensitometric method. Plasma theophylline was extracted from buffered plasma samples with chloroform, the solvent was evaporated to dryness and the residue was taken up in 100 μL of chloroform. Urinary theophylline was extracted from buffered urine samples with 2-propanol–chloroform (2:98, v/v), the solvent being evaporated to dryness, and the residue taken up in 200 μL of chloroform. Spots, 1 μL each, of the chloroform solution were applied to thin-layer chromatography plates, which were developed with the solvent system chloroform–carbon tetrachloride–methanol (8:5:1 v/v), and the spots were then scanned directly on the plate at 275 nm. The method is sensitive (5 ng, or 0·5 mg L^{-1} theophylline can be followed and detected), selective (different R_F values were obtained for the other xanthine derivatives and for theophylline metabolites), and reproducible (coefficient of variation of the values determined on different days was ⩽6·6%). The method was then compared with HPLC, RIA and the enzyme-multiplied immunoassay technique (EMIT), and good correlations found, especially with HPLC and EMIT (Pokrajac et al 1986).

Pharmacokinetic analysis

The urine flow rate (mL min^{-1}) and pH values were plotted against time. Renal clearance of theophylline was determined by dividing theophylline excretion rate for a 1 or 2 h interval by its plasma concentration at the midpoint of this interval, or from the slope representing theophylline urine excretion rate plotted against its plasma concentrations. Correlations between theophylline plasma concentrations and its renal clearance, as well as between urine flow rate and theophylline renal clearance were calculated using least squares linear regression analysis.

Statistics

The results were analysed statistically with Student's *t*-test or paired *t*-test.

Results and Discussion

The results of these investigations are summarized in Tables 1—4 and Figs 1—3. Time-dependence of renal theophylline clearance was observed in adults (Truitt et al 1951; Levy & Koysooko 1976; Jonkman et al 1981). Jonkman et al (1981) found a biphasic curve of theophylline excretion rate in urine after a single oral dose of the drug attributed to an increased diuretic effect of theophylline during the first hours after administration, when theophylline concentrations were greater than 7 mg L^{-1}; urine flow rate, excretion rate and renal clearance of theophylline were increased, although urine flow rate also depends on water and salt ingestion.

Table 1. Pharmacokinetic parameters after intravenous administration of theophylline: elimination half-life ($t_{\frac{1}{2}}$), clearance (CL), renal clearance (CL_r), extrarenal clearance ($CL_{ex.\ ren.}$) and drug fraction excreted unchanged (Fu).

Subject	$t_{\frac{1}{2}}$* (h)	CL* (L h^{-1})	CL_r (L h^{-1})	CL_r (mL $h^{-1}kg^{-1}$)	CL_r (%)	$CL_{ex.\ ren.}$ (L h^{-1})	Fu (%)
I	4·09	3·40	0·268**	7·59	7·79	3·13	7·82
II	9·49	1·80	0·367	6·87	20·38	1·43	18·69
III	5·50	4·26	0·335	9·57	7·86	3·92	7·87
IV	3·32	2·06	0·353	11·76	8·69	1·71	8·69
V	4·02	3·97	0·623	20·75	15·69	3·35	17·30
VI	4·09	3·61	0·282	8·07	7·81	3·33	7·43
VII	4·95	2·57	0·231	7·71	8·99	2·34	9·00
VIII	5·73	2·32	0·385	12·83	16·59	1·94	16·59
mean	5·15	2·99	0·355	10·64	11·72	2·63	11·67
±s.e.	0·68	0·32	0·042	1·63	1·77	0·32	1·73

* Plasma data. ** Renal clearance obtained from the slope of urinary excretion rate of theophylline vs its plasma concentrations.

Table 2. Renal clearance of theophylline and urine flow rate after administration of a single dose of a sustained release preparation of theophylline and at steady state.

	Single dose		Steady state	
Time (min)	CL_r (s.d.) (L h^{-1})	Urine flow rate (s.d.) (mL min^{-1})	CL_r (s.d.) (L h^{-1})	Urine flow rate (s.d.) (mL min^{-1})
60	0·29* (0·20)	0·97 (0·65)	0·30* (0·19)	0·75 (0·44)
120	0·28 (0·14)	1·52 (1·56)	0·28 (0·12)	2·21 (1·46)
240	0·35 (0·17)	2·46 (1·40)	0·37 (0·18)	1·94 (1·79)
360	0·34 (0·23)	1·33 (0·68)	0·27 (0·17)	1·09 (0·95)
480	0·32 (0·12)	2·25 (1·99)	0·28 (0·15)	1·50 (0·97)
600	0·28 (0·23)	0·93 (0·61)	0·26 (0·29)	1·04 (1·39)
720	0·26 (0·18)	1·00 (0·97)	0·17 (0·10)	0·41 (0·33)

* Renal clearance (mean values for the group) obtained by dividing theophylline urine excretion rate by its plasma concentration at mean time.

Table 3. Correlation of urine flow rate and renal clearance of theophylline after administration of a single dose of a sustained release preparation of theophylline.

Patients	Correlation coefficient	Regressional equation
1	0·6082	0·163x + 0·07
2	0·7175	0·026x + 0·12
3	0·2240	0·069x + 0·19
4	0·4461	0·020x + 0·40
5	0·2759	0·027x + 0·18
6	−0·0641	−0·039x + 0·26
7	0·3667	0·007x + 0·36
8	0·1463	0·021x + 0·16
9	0·1402	0·038x + 0·60
10	−0·0481	−0·023x + 0·25
11	0·4111	0·113x + 0·32
12	0·4076	1·210x + 0·05
13	0·5892	0·075x + 0·12
14	0·7904	0·110x + 0·08

Table 4. Individual values of renal clearance of theophylline and urine flow rate for 14 subjects after administration of a sustained release preparation of theophylline.

	Single dose		Steady state	
Subject	CL*$_r$ (L h^{-1})	Urine flow rate (mL min^{-1})	CL$_r$ (L h^{-1})	Urine flow rate (mL min^{-1})
1	0·35	1·56	0·56	1·45
2	0·22	1·85	0·49	2·56
3	0·42	2·20	0·01	1·74
4	0·35	1·80	0·89	2·03
5	0·17	1·45	0·26	1·02
6	0·30	1·46	0·76	1·25
7	0·73	4·13	0·25	1·70
8	0·22	1·28	0·32	0·83
9	0·64	2·27	0·11	1·49
10	0·28	0·82	0·71	0·76
11	0·09	2·51	0·50	2·67
12	0·06	1·69	0·77	1·96
13	0·27	1·50	0·16	0·47
14	0·18	1·49	0·04	0·38

* renal clearance was calculated from the slope of urine excretion of theophylline vs its plasma concentrations.

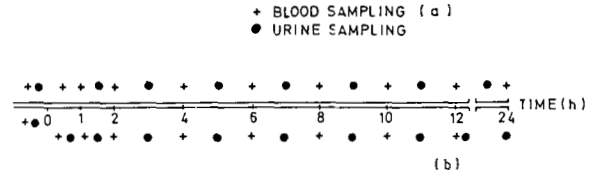

FIG. 1. Sampling times for plasma and urine after a) intravenous and b) oral administration of theophylline.

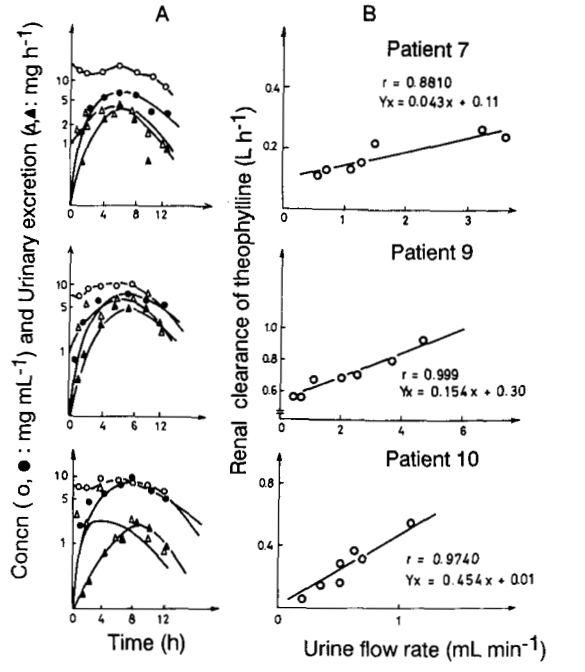

FIG. 2. Concentrations of theophylline in plasma and theophylline urinary excretion rate (dXu/dt) after administration of a single dose of a sustained release preparation of theophylline (●, ▲), and at steady state (○, △) (A). Relationship between renal clearance of theophylline and urine flow rate after administration of a single oral dose of the preparation at steady state (B). Examples are shown for 3 subjects.

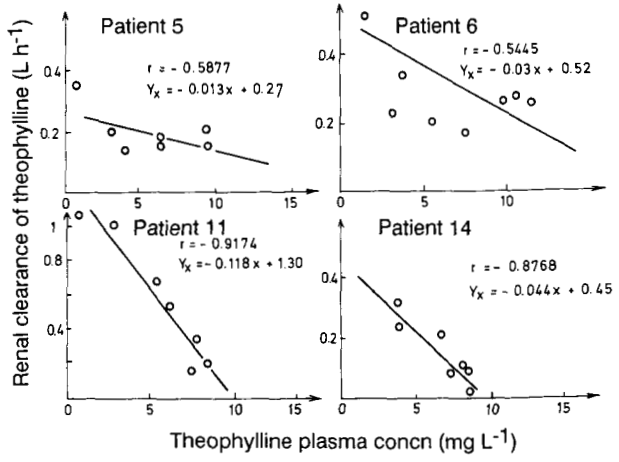

FIG. 3. Relationship between renal clearance of theophylline and its plasma concentrations (examples in 4 subjects, both after single oral dose and at steady state).

According to Shargel & Yu (1985), factors which increase urine flow rate, such as ethanol, high water intake and methylxanthines (caffeine and theophylline) ingestion, decrease theophylline reabsorption time and increase its excretion. For that reason, it is considered that renal clearance of drugs that are largely reabsorbed should be sensitive to change in urine flow. Examples of such drugs, that have urine concentrations which approach their unbound concentration in plasma, include ethanol, phenytoin and theophylline (Rowland & Tozer 1980).

In spite of the fact that even under controlled liquid intake urine flow rate can vary (Tang-Liu et al 1982a), we observed that, individually, in 10 patients, urine flow rate was significantly lower at steady state than after a single oral dose of theophylline ($P < 0.05$). The mean urine flow rate was 1.82 ± 0.9 mL min^{-1} ($n = 10$), and 1.1 ± 0.5 mL min^{-1} ($n = 10$), after a single oral dose or at steady state, respectively. These results indicate that after repeated administration tolerance of the theophylline diuretic effect occurs, but they do not support the hypothesis that renal clearance of

theophylline is dependent on urine flow rate because of its diuretic effect. Correlating urine flow rate with theophylline excretion rate and its renal clearance, we found high dependence only at steady state, when the diuretic effect is much lowered or negligible (Fig. 2).

Formation and elimination of the three main metabolites of theophylline are considered capacity-limited processes even within the therapeutic range of theophylline (Tang-Liu et al 1982b). Since the plasma concentrations of theophylline were significantly higher at steady state (C_{max} 12·47 ± 1·04 mg L^{-1}, for a t_{max} of 6 h) than after a single dose (C_{max} 8·71 ± 0·58 mg L^{-1}, for a t_{max} of 8 h) ($P < 0·05$), we propose a decreased metabolic clearance. However, it is possible that at steady state, at theophylline plasma concentrations higher than after a single dose, at lower urine flow rate and lower urine excretion rate of theophylline, the concentration gradient for reabsorption of theophylline is decreased, and its urinary excretion increases proportionally to the urine flow rate.

Tang-Liu et al (1983) found that renal theophylline clearance did not increase proportionally to the higher urine flow rate, which they explained by lower reabsorption of water, which decreased the tendency for theophylline reabsorption, and Cu/Cp ratio of theophylline (concentration in urine relative to concentration in plasma) was decreased. However, we found a linear increase of renal clearance with an increase of urine flow rate at steady state (Fig. 2), which is in agreement with the results of Levy & Koysooko (1976) in adults. We also found a high positive correlation of theophylline excretion rate with theophylline plasma concentration in 10 out of 14 children after administration of a single dose of SRP of theophylline ($r \geqslant 0·857$, $P < 0·01$). The correlation coefficient was from 0·197 to 0·676 in the four other patients. The renal clearance value was 0·37 ± 0·06 L h^{-1} or 11·32 ± 0·7 mL h^{-1} kg^{-1}, and was not significantly different from the value obtained after i.v. administration ($P > 0·05$). There was no positive correlation between theophylline plasma concentrations and renal clearance values, either after a single dose or at steady state. In nine patients we obtained negative correlation, which was high only in two patients ($r = -0·917$ and $r = -0·877$) and this could be the result of saturation during theophylline urine excretion (Fig. 3). We did not find statistically significant dependence between urine pH and urine flow rate on renal theophylline clearance. Also, there was no dependence of theophylline renal clearance on the dose of the drug, either after a single dose or at steady state, which is important in view of the different theophylline doses required to achieve therapeutic plasma concentrations in children.

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