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Effects of α-interferon on theophylline pharmacokinetics and metabolism

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1 The influence of α-interferon (Roferon-A®) on the pharmacokinetics and metabolism of theophylline was studied in healthy adults. Roferon-A was administered as an intramuscular injection (3×10^6 iu) once-a-day over 3 days. One week prior to and immediately after this course a single 20 min aminophylline infusion (4 mg kg^{-1}) was given.

2 Blood samples for theophylline analysis were taken over 48 h. Urine was collected up to 72 h and assayed for theophylline and its major metabolites 3-methylxanthine, 1,3-dimethyluric acid and 1-methyluric acid.

3 Pharmacokinetic parameters for theophylline in plasma were calculated. From urinary excretion data the overall metabolic clearance of theophylline and clearances for formation of the metabolites were calculated.

4 After interferon administration, there was a significant increase of approximately 15% in the mean values of the terminal elimination half-life, area under the curve and mean residence time of theophylline in association with a similar decrease in plasma clearance ($P < 0.05$). Formation clearances of the metabolites tended to be smaller after treatment, but only the change in the overall clearance of theophylline was significantly different ($P < 0.05$). There was no systematic shift in the metabolic pattern of theophylline.

5 Additional investigations of the influence of the duration of α-interferon treatment are necessary before definite conclusions can be drawn about the mechanism and the clinical relevance of the described interaction.

Keywords theophylline α-interferon interaction drug metabolism pharmacokinetics

Introduction

Theophylline (1,3-dimethylxanthine) is extensively metabolised by hepatic cytochrome P-450 dependent enzymes. Only about 10% of a theophylline dose is excreted unchanged in urine. About 15–20% is metabolised by demethylation to 3-methylxanthine (3-MX), approximately 30–40% is excreted as the oxidation product 1,3-dimethyluric acid (1,3-MU) and about 20–30% as 1-methyluric acid (1-MU) (Cornish & Christman, 1957; Jenne *et al.*, 1976; Lohman & Miech, 1976; Grygiel *et al.*, 1979; Jonkman *et al.*, 1981; Tang-Liu *et al.*, 1982; Birkett *et al.*, 1985).

Many factors affecting hepatic uptake and biotransformation in the liver can influence theophylline elimination, and interactions with various other drugs have been described (Jonkman & Upton, 1984; Jonkman, 1986). There is evidence that theophylline metabolism is impaired following infections, such as influenza.

Chang *et al.* (1978) first described prolonged theophylline half-lives (by 108 ± 121%) during acute respiratory viral infections in five out of six asthmatic children studied. Clark & Boyd (1979) reported similar findings. Kraemer *et al.* (1982) described symptoms of theophylline toxicity attributed to lowered theophylline clearance in 11 children during an influenza-B outbreak. Six had a titre to influenza-B of at least 1:4. The mean rise in serum theophylline concentrations following infection was 20 mg l^{-1}. No values for clearance or half-life were given. Walker & Middelkamp (1982) re-affirmed these findings. In one child total clearance decreased by 48% and in a second by 62% during infection. Koren & Greenwald (1985) described prolonged half-lives in three infants and in one child, but no pre-illness values were given. Although most of these communications are case reports and not systematic studies, there are clear indications of decreased theophylline elimination during infection. To explain these observations, it has been suggested that increased α-interferon production after these infections leads to a lowered activity of the hepatic P-450 systems. This might be a characteristic effect of interferon (Mannering *et al.*, 1980). To test this hypothesis we investigated the effect of parenteral administration of interferon (Roferon-A®, F. Hoffmann-La Roche) on the activity of the hepatic P-450 systems.

Methods

Subjects

The study was designed to include 12 subjects. Subjects with febrile illnesses within 14 days prior to the start of the study were excluded. Eleven of the originally enrolled 16 subjects completed both parts of the trial. They were healthy, young non-smoking volunteers (10 men and one woman) aged between 21 and 26 years (mean 22.2 ± 1.4 years) with weights between 63 and 79 kg (mean 69.0 ± 5.0 kg) (See also Table 1).

They were judged to be healthy by a physician based on pre-treatment medical history, normal physical examination, ECG and general laboratory tests including creatinine clearance. No medication was allowed for 7 days prior to the study.

Study drugs

Roferon-A® (= α-interferon; Ro 22-8181/626) containing 3×10^6 iu of lyophilized powder per 5 ml vial; batch number PT 3484 H 01, manufactured by F. Hoffmann-La Roche & Co., Basle, Switzerland. The vials were reconstituted just prior to use in 1.0 ml of sterile water.

Commercially available aminophylline was used as ampoules of 250 mg of aminophylline in 10 ml aqueous solution. All of the ampoules were from the same production batch.

Clinical procedures

The study was an open, comparative non-randomized, within subject, 2 week trial. The study protocol was reviewed and approved by the Leicestershire Area Health Authority Ethics Committee. After a laboratory screen on day 1 the subjects received on day 2 of the study an intravenous infusion of 4 mg kg^{-1} aminophylline over approximately 20 min. On days 8–10 an intramuscular injection of 3×10^6 iu α-interferon was given. On day 10 aminophylline was again infused as on day 2.

Blood samples (10 ml) were obtained on days 2–4 and days 10–12 at 0, 1, 2, 3, 4, 5, 6, 8, 10, 24, 28, 32, 36 and 48 h after theophylline administration. Plasma was collected after centrifugation at 1500 *g* and stored at −20°C until analysis. On the days of blood sampling urine was also collected from −2 to 0, 0–2, 2–4, 4–6, 6–10, 10–24, 24–36, 36–48, 48–60 and 60–72 h.

The subjects maintained a standardized diet throughout the trial, excluding methylxanthine-containing beverages during 72 h before and on all of the sampling days. The subjects did not take other drugs during the study. They were not allowed to drink alcoholic beverages in the 72 h before and on any of the sampling days.

Bioanalytical methods

Theophylline in plasma A selective and sensitive high performance liquid chromatographic method (h.p.l.c.) was used for the measurement of theophylline in 250 μl plasma (Jonkman *et al.*, 1980). Characteristic features of the assay method are: detection limit: 0.05 mg l^{-1}; lower limit of quantitation: 0.25 mg l^{-1}; recovery: 88.3 ± 1.8% (mean ± s.d.); intra-day reproducibility: 0.8% (C.V.); inter-day reproducibility: 1.0% (C.V.); accuracy: 0.8%.

Theophylline and metabolites in urine A modification of a previously reported method was used for the simultaneous determination of theophylline and its major metabolites in urine (Muir *et al.*, 1980). The method had the following characteristics: lower limit of quantitation of all compounds: 2 mg l^{-1}; recovery: for 3-MX: 86%;

for 1,3-MX: 86%; for 1-MU: 67%; for 1,3-MU: 78%; intra-day reproducibility: for 3-MX: 6.6% (C.V.); for 1,3-MX: 7.7% (C.V.); for 1-MU: 9.1% (C.V.); for 1,3-MU: 8.3% (C.V.).

Data analysis

The area under the plasma drug concentration-time curve (AUC) from the time at which infusion was started until the end of plasma sampling, and the area under the first moment curve during the same time interval (AUMC), were calculated using the linear trapezoidal rule. Extrapolation of both areas to infinity was done using the rate constant calculated by log-linear regression of the terminal elimination phase (Riegelman & Collier, 1980). The elimination half-life ($t_{½}$) was calculated from the terminal elimination rate constant. From AUC and AUMC and taking into account the dose and the duration of infusion, the mean residence time (MRT), plasma clearance (CL) and steady-state volume of distribution (V_{ss}) were derived (Gibaldi & Perrier, 1982).

From the urinary excretion data, the cumulative amounts of theophylline and the major metabolites were calculated. The formation clearance of each metabolite (CL_M) was calculated as the product of the molar fraction of the dose excreted as the metabolite and the clearance of theophylline. The renal clearance of theophylline (CL_R) was calculated as the product of the fraction of the dose excreted unchanged in urine and the clearance. The total metabolic clearance of theophylline (CL_M) was calculated by subtracting the renal clearance from the total clearance. Pharmacokinetic parameters before and after interferon administration were compared statistically using Student's *t*-test for paired observations ($\alpha=0.05$).

Results

Clinical observations

Five of the originally enrolled 16 subjects withdrew during the study for several reasons that were not related to the study medications.

All of the volunteers who received the second treatment developed symptoms attributable to interferon. These comprised influenza-like symptoms with myalgia, chills, sweats and feeling febrile. Generally, the symptoms decreased with successive doses as tolerance developed.

After interferon there was a depression in lymphocyte count at 8 h which returned to normal by 24 h. A degree of tolerance also developed to this effect with successive doses.

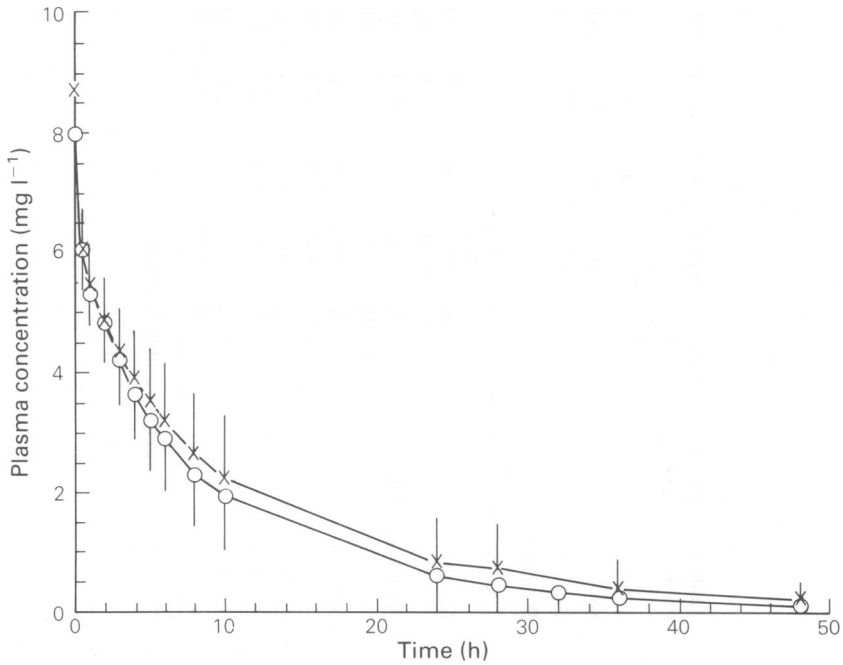

Figure 1 Time courses of theophylline plasma concentration after termination of infusion (mean data ± s.d. $n = 11$) before (○) and after (×) α-interferon treatment.

Table 1 Subject characteristics and pharmacokinetic parameters derived from plasma theophylline concentration data obtained before (A) and after (B) α-interferon treatment

Subject		02	04	05	06	07	09	10	11	12	15	16	*Mean ± s.d.*
Sex		M	M	M	M	M	M	M	M	M	F	M	
Age (years)		21	21	26	22	21	22	22	23	22	22	22	22.2 ± 1.4
Weight (kg)		68.5	64	77	65	69	66.5	69	79	69.5	68	63	69.0 ± 5.0
Theophylline dose (mg kg^{-1})		3.34	3.34	3.34	3.34	3.35	3.34	3.35	3.34	3.34	3.34	3.34	3.34 ± 0.00
$t_{½,z}$ (h)	A	8.95	7.01	5.59	9.85	4.02	5.20	4.60	4.80	7.66	16.47	3.78	7.08 ± 3.70
	B	10.00	6.25	5.26	11.66	4,75	5.76	5.97	5.36	10.22	19.32	3.98	8.05 ± 4.51*
AUC (mg l^{-1} h)	A	62.8	51.1	55.5	101.5	41.5	53.4	48.3	45.3	66.9	126.1	37.0	62.7 ± 27.8
	B	88.4	54.7	57.7	117.7	45.7	51.4	65.2	46.8	95.7	154.1	35.3	73.9 ± 36.4*
MRT (h)	A	10.62	9.34	7.18	14.59	5.89	7.54	6.46	7.04	9.78	22.54	5.46	9.68 ± 5.01
	B	14.36	8.89	8.01	16.78	6.60	7.60	8.05	6.70	14.60	26.76	5.49	11.26 ± 6.38*
CL ($l\ h^{-1}$)	A	3.65	4.19	4.63	2.14	5.57	4.16	4.79	5.83	3.47	1.80	5.70	4.18 ± 1.35
	B	2.59	3.91	4.45	1.84	5.05	4.32	3.54	5.64	2.43	1.47	5.99	3.75 ± 1.52*
V_{ss} (l)	A	36.65	38.57	27.66	30.85	31.78	30.42	30.01	39.88	32.86	40.25	29.99	33.54 ± 4.48
	B	35.31	34.05	29.84	30.63	32.38	31.99	27.80	36.93	34.94	39.17	32.02	33.17 ± 3.28

* : difference between A and B significant; $P < 0.05$

Plasma drug concentration data

Pharmacokinetic parameters for the 11 subjects from whom complete concentration-time profiles were available are shown in Table 1. After α-interferon treatment there were 10–15% increases in the terminal elimination half-life ($t_{½}$), AUC and MRT ($P < 0.05$); the total clearance showed a comparable decrease ($P < 0.05$).

In Figure 1 mean plasma drug concentration (± s.d.) *vs* time data are shown for the post-infusion period.

Urinary excretion data

Urine collections from nine subjects were complete over a 72 h period allowing calculation of the cumulative fractions of the dose excreted as unchanged drug and each metabolite. Complete recoveries were obtained after 48 h. The total urinary recovery in the period 0–72 h amounted to 94.5 ± 10.1% and 90.8 ± 14.1% before and after α-interferon treatment, respectively.

The mean (± s.d.) urinary recoveries of unchanged theophylline and major metabolites (expressed as molar fraction of theophylline dose) before α-interferon treatment were: theophylline 0.139 ± 0.039; 1,3-MU, 0.363 ± 0.070; 1-MU, 0.252 ± 0.070; 3-MX, 0.191 ± 0.030. After treatment the recoveries were: theophylline, 0.139 ± 0.036; 1,3-MU, 0.344 ± 0.068; 1-MU, 0.267 ± 0.069; 3-MX, 0.158 ± 0.050. None of the differences in recoveries before and after interferon administration was statistically significant.

The derived values for the overall metabolic and renal clearance of theophylline and formation clearances of the major metabolites are presented in Table 2. These clearance values tended to be smaller after interferon pre-treatment but only for CL_M was the difference statistically significant ($P < 0.05$). The changes in CL_M values associated with interferon administration for the individual subjects are shown in Figure 2.

Discussion

Changes in the metabolic clearance of theophylline associated with a variety of factors are very variable in their persistence. The effect of cimetidine, for example, is already maximal after 3 days of treatment and disappears after stopping the co-treatment, whereas altered theophylline clearance due to smoking can still be detected for several months after discontinuing smoking (Jonkman & Upton, 1984; Powell, 1984). As it was unknown to what extent and how long interferon would influence theophylline pharmacokinetics, it was decided to determine the baseline pharmacokinetics of theophylline for all subjects before administering interferon.

The dose of theophylline chosen for this study was low in order to avoid complications related to the non-linearity of both renal and metabolic elimination processes (Jonkman *et al.*, 1981). Peak plasma drug concentrations were generally lower than 10 mg l^{-1}, that is, well below the reported K_m value of 24 mg l^{-1} (Wagner, 1985). The observed concentration profiles of theophylline are in line with the results of many previous studies (Hendeles & Weinberger, 1983). This is also the case for the pharmacokinetic parameters shown in Table 1. Only the terminal half-life of subject 15 was outside the normal range (4–12 h), as were her AUC and clearance values.

As shown in Table 1, treatment with interferon caused small, but statistically significant, changes

Table 2 Clearance values (l h^{-1}) of theophylline and formation clearances of its major metabolites before (A) and after (B) α-interferon treatment

Subject		04	06	07	09	10	11	12	15	16	*(Mean ± s.d.)*
CL_M	A	3.85	1.74	5.11	3.87	4.27	5.58	3.01	1.49	5.37	3.81 ± 1.49
	B	3.60	1.57	4.61	4.00	3.18	5.22	2.10	1.16	5.39	3.43 ± 1.55*
CL_R	A	0.49	0.50	0.80	0.61	0.75	0.63	0.45	0.31	0.56	0.56 ± 0.15
	B	0.50	0.33	0.70	0.52	0.50	0.51	0.39	0.31	0.73	0.50 ± 0.15
$CL_{1,3\text{-}MU}$	A	1.05	1.00	1.85	1.72	2.37	2.04	1.34	0.61	2.11	1.56 ± 0.59
	B	1.15	0.78	1.75	1.20	1.48	2.22	1.09	0.37	2.02	1.34 ± 0.59
$CL_{1\text{-}MU}$	A	1.05	0.36	1.78	1.17	1.40	1.76	1.01	0.21	1.99	1.19 ± 0.62
	B	1.08	0.50	1.12	1.35	1.00	1.60	0.75	0.19	2.34	1.10 ± 0.63
$CL_{3\text{-}MX}$	A	0.74	0.39	1.37	0.73	0.81	1.38	0.81	0.31	1.13	0.85 ± 0.38
	B	0.62	0.38	0.69	0.60	0.58	0.96	0.36	0.12	1.58	0.65 ± 0.42

* : difference between A and B significant; $P < 0.05$

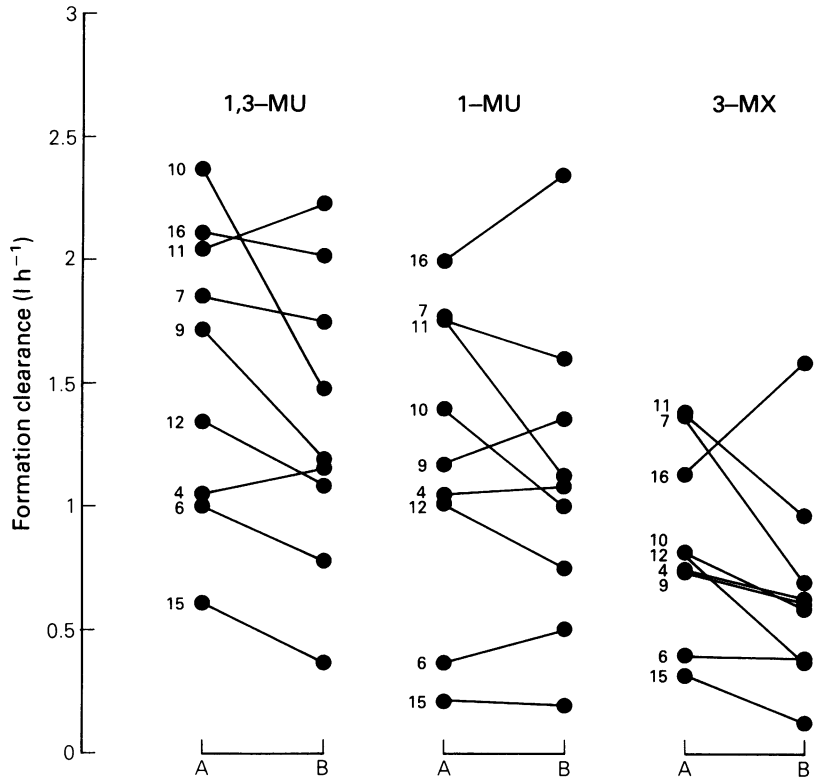

Figure 2 Changes in the formation clearance of theophylline metabolites during treatment with α-interferon (A = before treatment, B = after treatment).

in several parameters derived from the plasma drug concentration data. As the values of V_{ss} were identical before and after treatment, and relative changes in the other parameters are similar, it is apparent that the increases in AUC, $t_{1/2}$ and MRT are due to a decrease in clearance. As theophylline is eliminated mainly by biotransformation, this indicates that α-interferon treatment causes a lowering of drug-metabolizing enzyme activity. This is confirmed by the values of CL_M shown in Table 2.

Like antipyrine, theophylline is used as a marker drug to evaluate the influence of many factors on oxidative drug metabolism (Jenne, 1982; Teunissen *et al.*, 1985; Jonkman, 1986). It is generally assumed that different forms of the cytochrome P-450 system may be involved in the formation of the different metabolites of a drug. Evidence for this is available in the case of antipyrine (Danhof & Breimer, 1979; Teunissen *et al.*, 1983). Therefore, investigation of the different metabolic pathways should provide more specific information about the influence of specific factors on drug metabolism than information derived solely from parent drug data. Therefore, we calculated the formation clearance of the individual theophylline metabolites, reflecting the quantitative contribution of each metabolic route to the overall metabolic clearance of the drug. On average, interferon pre-treatment tended to reduce the formation clearances of 1,3-MU, 1-MU and 3-MX by 14%, 7.6% and 24%, respectively (Figure 2, Table 2), but these changes did not reach statistical significance.

The magnitude of the changes observed in theophylline pharmacokinetics suggests that this interaction may be of only minor clinical relevance. Thus, the changes were of the same order as the normal intra-individual variation in the elimination rate of theophylline of around 10 to 15% (Milavetz *et al.*, 1987; Jonkman *et al.*, 1988). Thus, the changes observed in this study were similar to normal intra-individual variation and were much smaller than those observed after influenza infection. However, the duration of elevated interferon plasma/tissue concentrations might be relevant to the magnitude of any inhibitory effect. Thus, whereas viral respiratory infections, which usually last at least a week, decrease theophylline metabolism (although the

effect has only been documented in children), a single injection of influenza vaccine did not cause any change (Jonkman *et al.*, 1988). Taylor *et al.* (1985) reported that the continuous infusion of cloned human interferon in mice prolongs antipyrine half-life to a much greater extent than single daily doses of the equivalent amount.

In recent studies by Williams *et al.* (1987 a,b) a considerable influence of α-interferon on systemic theophylline clearance (2–5 fold reduction) was reported in patients with chronic active hepatitis B. Whether this increased influence may be ascribed to the different α-interferon dosage regimen used in that study (9 $\times 10^6$ iu, single dose), or to the pathology of the patients, is unclear. In the latter study *in vitro* experiments showed that the interaction is based on a non-competitive mechanism. One possible explanation, in the case of a low clearance drug like theophylline, is therefore a decrease in the amount of cytochrome P-450. With such a mechanism, it is possible that the interaction may depend on the dosage regimen.

Further studies of the influence of α-interferon treatment on cytochrome P-450 activity are indicated before definite conclusions can be drawn about the mechanism and the clinical relevance of the observed interaction.

References

Birkett, D. J., Dahlquist, R., Miners, J. O., Lelo, A. & Billing, B. (1985). Comparison of theophylline and theobromine metabolism in man. *Drug Metab. Dispos.*, **13**, 725–728.

Chang, K. C., Lauer, B. A., Bell, T. D. & Chaim, H. (1978). Altered theophylline pharmacokinetics during respiratory viral illness. *Lancet*, **i**, 1132–1133.

Clark, C. J. & Boyd, G. (1979). Theophylline pharmacokinetics during respiratory viral infection. *Lancet*, **i**, 492.

Cornish, J. J. & Christman, A. A. (1957). The metabolism of theobromine, theophylline and caffeine in man. *J. biol. Chem.*, **228**, 315–328.

Danhof, M. & Breimer, D. D. (1979). Studies on the different metabolic pathways of antipyrine in man. I Oral administration of 250, 500 and 1000 mg to healthy volunteers. *Br. J. clin. Pharmac.*, **8**, 529–537.

Gibaldi, M. & Perrier, D. (1982). *Pharmacokinetics*, 2nd ed. New York: Marcel Dekker Inc.

Grygiel, J. J., Wing, L. M. H., Farkas, J. & Birkett, D. J. (1979). Effects of allopurinol on theophylline metabolism and clearance. *Clin. Pharmac. Ther.*, **26**, 660–667.

Hendeles, L. & Weinberger, M. (1983). Theophylline; a 'state of the art' review. *Pharmacotherapy*, **3**, 2–44.

Jenne, J. W. (1982). Theophylline: a remarkable window to the hepatic microsomal oxidases. *Chest*, **81**, 529–530.

Jenne, J. W., Nagasawa, H. T. & Thompson, R. D. (1976). Relationship of urinary metabolites of theophylline to serum theophylline levels. *Clin. Pharmac. Ther.*, **19**, 375–381.

Jonkman, J. H. G. (1986). Therapeutic consequences of drug interactions with theophylline pharmacokinetics. *J. Allergy clin. Immunol.*, **78**, 736–742.

Jonkman, J. H. G., Schoenmaker, R., Greving, J. E. & De Zeeuw, R. A. (1980). Rapid and selective theophylline serum and saliva assay by means of high pressure liquid chromatography. *Pharm. Weekbl. Sc. Ed.*, **2**, 49–53.

Jonkman, J. H. G., Tang, D., Upton, R. A. & Riegelman, S. (1981). Measurement of excretion characteristics of theophylline and its major metabolites. *Eur. J. clin. Pharmac.*, **20**, 435–441.

Jonkman, J. H. G. & Upton, R. A. (1984). Pharmacokinetic drug interactions with theophylline. *Clin. Pharmacokin.*, **9**, 309–334

Jonkman, J. H. G., Wymenga, A. S. C., Van der Boon, W. J. V., Beugelink, J. K. & Oosterhuis, B. (1988). No effect of influenza-vaccination on theophylline pharmacokinetics as studied by UV-spectrophotometry, HPLC and EMIT® assay methods. *Ther. Drug Monit.*, **10**, 345–348.

Koren, G. & Greenwald, M. (1985). Decreased theophylline clearance causing toxicity in children during viral epidemics. *J. Asthma*, **22**, 75–79.

Kraemer, M. J., Furukawa, C. T., Koup, J. R., Shapiro, G., Pierson, W. & Bierman, W. (1982). Altered theophylline clearance during an influenza B outbreak. *Pediatrics*, **69**, 476–479.

Lohman, S. M. & Miech, R. P. (1976). Theophylline metabolism by the rat liver microsomal system. *J. Pharmac. exp. Ther.*, **196**, 213–225.

Mannering, J. J., Renton, K. W., El Azhary, R. & Deloria, L. B. (1980). Effects of interferon-inducing agents on hepatic cytochrome P-450 drug metabolizing systems. *Ann. N.Y. Acad. Sci.*, **350**, 314–331.

Milavetz, G., Vaughan, L. M. & Weinberger, M. M. (1987). Stability of theophylline elimination rate. *Clin. Pharmac. Ther.*, **41**, 388–391.

Muir, K. T., Jonkman, J. H. G., Tang, D. S., Kunitani, M. & Riegelman, S. (1980). Simultaneous determination of theophylline and its major metabolites in urine by reversed-phase ion pair high performance liquid chromatography. *J. Chromatogr. Biomed. Appl.*, **221**, 85–95.

Powell, J. R. (1984). Smoking and theophylline clinical pharmacology. In *Sustained release theophylline in the treatment of chronic reversible airways obstruction*, eds Jonkman, J. H. G., Jenne, J. W. & Simons, F. E. R., pp 75–82. Amsterdam: Excerpta Medica.

Riegelman, S. & Collier, P. (1980). The application of statistical moment theory to the evaluations of *in vivo* dissolution time and absorption time. *J. Pharmacokin. Biopharm.*, **8**, 509–534.

Tang-Liu, D. D. S., Williams, R. L. & Riegelman, S. (1982). Non-linear theophylline elimination. *Clin. Pharmac. Ther.*, **31**, 358–369.

Taylor, G., Marafino, B. J. & Moore, J. A. (1985). Interferon reduces hepatic drug metabolism *in vivo* in mice. *Drug Metab. Dispos.*, **13**, 459–463.

Teunissen, M. W. E., Joeres, R. P., Vermeulen, N. P. E. & Breimer, D. D. (1983). Influence of 9-hydroxyellipticine and 3-methylcholanthrene treatment on antipyrine metabolite formation in rats *in vivo*. *Xenobiotica*, **13**, 223–231.

Teunissen, M. W. E., De Leede, L. G. J., Boeijinga, J. K. & Breimer, D. D. (1985). Correlation between antipyrine metabolite formation and theophylline metabolism in humans after simultaneous single-dose administration and at steady state. *J. Pharmac. exp. Ther.*, **223**, 770–775.

Wagner, J. G. (1985). Theophylline. Pooled Michaelis-Menten parameters (V_{max} and K_m) and implications. *Clin. Pharmacokin.*, **10**, 432–442.

Walker, S. & Middelkamp, J. N. (1982). Theophylline toxicity and viral infections. *Pediatrics*, **70**, 508.

Williams, S. J., Baird-Lambert, J., Cantrill, E. M. & Farrell, G. C. (1987 a). Interferon inhibits hepatic clearance of theophylline by a non-competitive mechanism. *Austr. New Z. J. Med.*, **17** (Suppl. 1): 128.

Williams, S. J., Baird-Lambert, J., Cantrill, E. M. & Farrell, G. C. (1987 b). Inhibition of theophylline metabolism by interferon. *Lancet*, **ii**, 939.

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