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THE POSSIBILITY OF MEASURING THE SALIVARY CONCENTRATIONS OF THEOPHYLLINE IN BIOAVAILABILITY STUDIES

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The possibility of using the saliva in bioavailability studies of theophylline was investigated. Plasma and saliva concentrations were determined simultaneously and corresponding pharmacokinetic parameters were calculated and compared.

INTRODUCTION

The possibility of use of alternative biological fluids (saliva and urine at first) in compliance control, therapeutic monitoring and pharmacokinetic studies (1), bioavailability assessment (2,3), and in protein binding investigations (4), has been examined with many drugs, among which is theophylline (Th). Because of well-known characteristics of Th - narrow therapeutic range (1o-2o mg/l) (5), and large inter-

and intraindividual variations in clearance values in both children and adults (6,7)- there is a permanent need for monitoring Th levels in the therapy.
Saliva and its use in pharmacokinetic investigation of Th in therapy in both children and adult patients has been studied in many cases, although there are yet no any reliable or final conclusions on it.Lena et al.,(8), and Sharma et al., (9), suggested that saliva can be used in control of compliance only in children and adults, respectively, after administration of a sustained release preparation of theophylline (SRP of Th). However, Kelly et al., (10), confirmed that saliva can be used in pharmacokinetic assessment of elimination phase of Th after administration of a SRP of the drug, providing that necessary number of samples is collected. Investigations in adults (11), and in children (12), have resulted in conclusion that saliva can be used for therapeutic monitoring of Th instead of plasma, due to high correlation of Th concentrations in saliva and plasma, and low inter- and intraindividual differences in the P/S ratio. On the contrary to these results,Jackson et al., (13), and Munch et al., (14), in their investigations in adults, have found that measuring of the Th in saliva is not precise enough to give concentrations of the drug in plasma. Danhof and Breimer, (15), concluded that saliva can be of practical value in investigation of pharmacokinetics of elimination of Th, as well as of its absorption, which is of special importance as can be adopted in comparative bioavailability studies of different Th preparations.
The aim of this work was to investigate the possibility of measuring salivary instead of plasma levels

of Th after administration of a SRP of Th, as well as after intravenous administration of the drug,in order to calculate absolute bioavailability. For this purpose, correlation of Th concentrations in plasma and saliva, as well as P/S ratios, after both intravenous and oral administration of the drug-single dose and steady state after administration of a SRP of Th-have been determined (16).

SUBJECTS AND METHODS

Eight hospitalized patients with reversible chronic obstructive pulmonary desease (4 male and 4female) were included in the study. They aged from 27 to 74yr (52.2± 15.7, mean ± SD), with range of body masses from 62 to lol kg (72.2 ± 12.6), and all were nonsmokers. The patients were administered aminophylline intravenously in an average dose of 3.5 ± o.5 mg/kg (range from 2.45 to 4.oo mg/kg) which corresponded to 2.98 ± o.44 mg/kg (2.o9-3.48 mg/kg) of pure theophylline. After a wash-out period of two days, to these patients was administered SRP of Th (beed-filled gelatine capsules) at 12 hr intervals during 7 days, and in an mean dose of 5.25 ± o.76 mg/kg of Th (3.7 to 6.o mg/kg). At least 36 hr before, and during the investigation, all the patients refrained from xanthine-containing food and beverages. No other medication was given during the study. Saliva and plasma samples were collected simultaneously before the drug was given, and o.25, o.5, 1, 2, 4, 6, 8, 10, and 12 hr after intravenous administration, and 1, 2, 4, 6, 8, 10 and 12 hr after single dose of the oral preparation of Th and at steady state. Saliva collection was stimulated with a few drops of 20% citric acid solution. Plasma was obtained by centrifuging of he-

parinized blood samples.Both saliva and plasma samples were frozen at -20°C until analyzed.
Theophylline in the biological samples was determined by the spectrodensitometric method (17).
Area under the curve (AUC) was calculated by trapezoidal rule, and extrapolated to infinity by dividing last concentration with elimination rate constant.
Absolute bioavailability was calculated using standard equations (18), with correction for the dose administered and with terminal log concentration-numeric time rate constant for both intravenous and oral administration. An open two compartment open model was consistent with intravenous data, and an open one compartment pharmacokinetic model was adopted for kinetic analysis after administration of a SRP of Th.

RESULTS

Theophylline concentrations in both plasma and saliva against time, after both intravenous and oral administration of the drug, are shown in semilogarithmic plot for 6 patients in Fig.1. By the method of trapesoids, the individual AUC values were obtained after intravenous administration for plasma and saliva ($AUC_{iv.pl.}$ and $AUC_{iv.sal.}$), as well as after oral administration of a SRP of Th for plasma ($AUC_{or.pl.}$) and saliva ($AUC_{or.sal.}$). These results are shown in Table 1.The mean AUC values were: 48.25 ± 18.69 mgh/l (mean ± SD) $AUC_{iv.pl.}$, and 4o.2o ± 17.94 mgh/l $AUC_{iv.sal.}$ and 77.45 ± 43.25 mgh/l $AUC_{or.pl.}$ and 73.22 ± 41.54 mgh/l for $AUC_{or.sal.}$ The extent of bioavailability calculated for plasma and saliva was corrected for the dose administered,and with elimination rate constant (ß) after intravenous, or with the

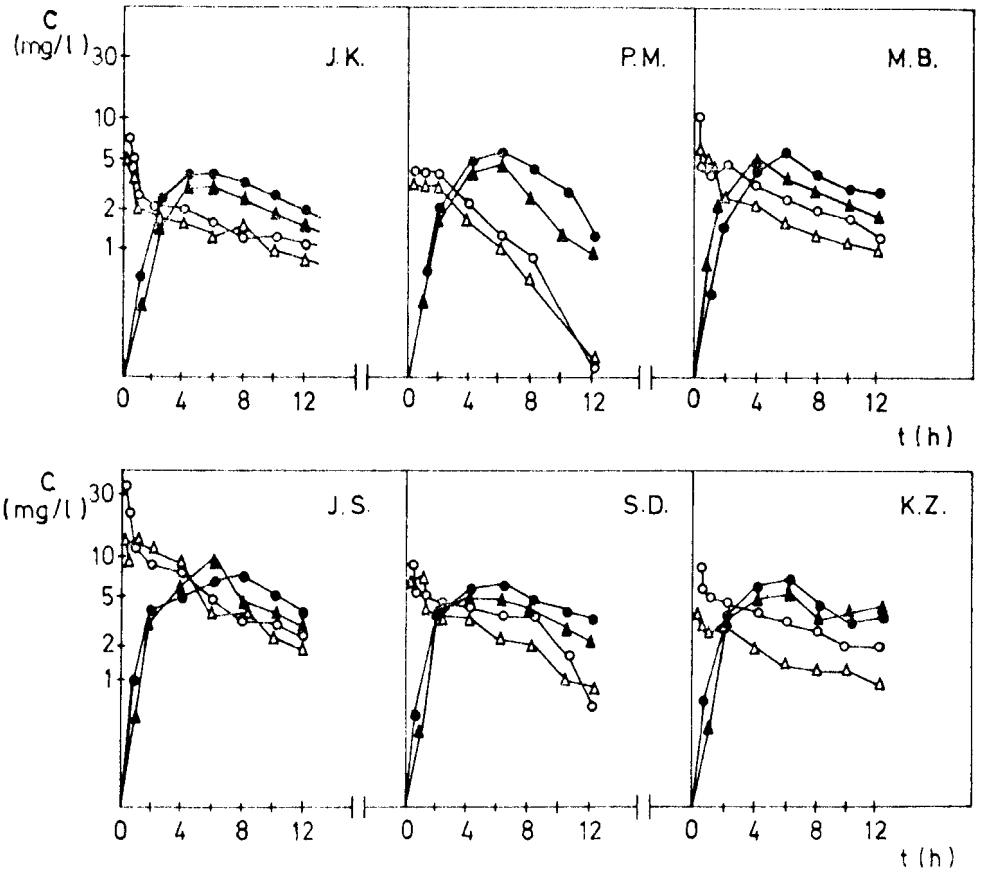

FIGURE 1.

Concentrations of theophylline against time in plasma (o) and saliva (△) after intravenous, and in plasma (●) and saliva (▲) after oral administration of the SRP of the drug.

TABLE 1.

The AUC values in saliva and plasma after both intravenous and oral administration of a SRP of Th.

Subject	AUC_{iv} (mgh/l) plasma	saliva	AUC_{or} (mgh/l) plasma	saliva
J.K.	45.2o	38.2o	56.9o	36.9o
R.Z.	44.5o	37.35	51.oo	38.85
P.M.	19.2o	18.9o	41.3o	34.oo
M.B.	57.3o	39.1o	73.9o	6o.3o
B.D.	37.7o	32.2o	149.9o	156.2o
J.S.	85.4o	8o.45	71.oo	71.7o
S.D.	49.4o	44.4o	78.9o	85.6o
K.Z.	49.8o	31.oo	66.7o	102.16

TABLE 2.

Individual values of elimination rate constants and of extent of the bioavailability for 8 subjects

Subject	β(1/h)	k_{el}(1/h)	$F_{pl.}$(%)	$F_{sal.}$(%)
J.K.	o.165	o.136	87.87	67.38
R.Z.	o.o59	o.117	76.78	69.35
P.M.	o.245	o.211	1o3.5o	85.68
M.B.	o.o91	o.o76	61.78	74.1o
B.D.	o.1o9	o.o4o	98.53	99.92
J.S.	o.147	o.158	55.41	59.41
S.D.	o.116	o.o97	8o.56	92.29
K.Z.	o.o84	o.o56	11o.29	1o6.11

slope of terminal part of log of concentration versus time plot after oral administration of the drug (k_{el}). The values of the constants and of the extent of bioavailability (F) are shown in Table 2.

The mean F for 8 subjects on the basis of plasma data was 84.34 $\pm$ 19.54%, and from saliva was 81.78 $\pm$ 16.76%. There was no significant difference between these values ($p > o.o5$). Maximum Th concentrations in plasma

and saliva,respectively, after administration of a single dose of a SRP of Th were 5.4 ± 1.7 mg/l and 4.2 ± 1.8 mg/l (mean ± S.E.), while at steady state these values were lo.38 ± 1.74 mg/l and 7.92 ± 1.28mg/l. The time to reach the peak was 6hr in both plasma and saliva.

DISCUSSION

Plasma, or serum is generally preferred in bioavailability studies. In spite of some errors which are obtainable when saliva is used for predicting of Th concentrations in plasma (19), it is considered that this can be overcomed if sufficient number of saliva samples for AUC assessment is obtained (20). Uden et al., (3) found that with frequent sampling saliva can reliably be used in assessment of extent of absorption, and further in bioavailability assessment in young children.

In this work, correlation of Th concentrations in plasma and saliva resulted in very high intraindividual correlation coefficients (r) after intravenous administration, with the highest value of r of o.991, and the lowest one of o.829. After administration of a single dose of a SRP of Th, coefficient of correlation in 5 out of 8 subjects was higher than o.9. Interindividual coefficient of correlation for 62 samples after intravenous administration was o.859, for 45 samples after a single dose of a SRP of a Th was o.75o, and at steady state was o.9oo (16). Correlation of Th concentrations in plsama and saliva at each sampling time was also very high.Coefficient of correlation 1 hr after intravenous administration was o.92o, while

in elimination phase, after 4 and 6 hr was o.9oo.Similar to this, 1 hr after a single dose of a SRP of Th coefficient of correlation was o.93o (absorption phase), and 1o hr after the administration r was o.86o (elimination phase). This is also an explanation more for consistency of P/S values with the $AUC_{pl.}$ / $AUC_{sal.}$ ratio. The $AUC_{iv.pl.}/AUC_{iv.sal.}$ ratio was 1.22 ± o.12 (mean±SD) (range from 1.61 to 1.o1), while $AUC_{pl.or.}/AUC_{sal.or.}$ ratio was 1.13 ± o.27 (range from 1.54 to o.65), and there was no significant difference between these and values of the mean P/S ratio of Th after intravenous: 1.28 ± o.2 (range from 1.78 to o.92), and oral dose of Th: 1.28 ± o.27 (range from 1.78 to 1.o3).

Kaskya et al., (21) suggested a new method for bioavailability testing of a sustained release Th products, taking into account nonlinear Th kinetics in metabolites forming, as well as intraindividual differences in drug clearance after intravenous and oral dose of a SRP of Th, which is more exact testing procedure compared to the other ones used so far. As the aim of this work was to compare plasma and saliva in bioavailability testing, that was documented with necessary data. On the basis of the results obtained, it can be concluded that saliva can reliably be used in bioavailability assessment of a SRP of Th.

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