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Relationship between plasma concentration, saliva concentration and urinary excretion rate of lithium in man

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Summary

The relationship between the plasma concentration, saliva concentration and urinary excretion rate of lithium was investigated and the possibility of using the saliva concentration or the urinary excretion rate for monitoring dosage was considered. The results in the present study support the idea that saliva concentration of lithium could be useful in monitoring dosage but, there are many difficulties to be overcome in using the urinary excretion rate of lithium due to inter-subject variation, intra-subject variation during the night and circadian variation in the renal excretion of lithium.

Introduction

For drugs that are partially secreted by the salivary glands, there is evidence that the concentration in the salivary fluids may reflect the plasma concentration (Borzelleca and Doyle, 1966; Glynn and Bastian, 1973; Graham and Rowland, 1972; Shopsin et al., 1969; Spring and Spirtes, 1969a). There have been several studies relating saliva to plasma concentration of lithium. The degree of correlation has been investigated as well as the saliva-to-plasma concentration ratio of lithium either in healthy or treated patients (Spring and Spirtes, 1969a; Groth et al., 1974; Shimizu and Smith, 1977; Shopsin et al., 1969; Lazarus et al., 1973; Sims and White, 1974; Neu et al., 1975; Singlas et al., 1976; Beresewicz et al., 1977; Verghese et al., 1977; Evrard et al., 1978; Ravenscroft et al., 1978; Sims et al., 1978; Preskorn et al., 1978; Man, 1979).

The flux of lithium from plasma to urine (via kidney) is treated as unidirectional because its fractional excretion (the ratio of lithium clearance to creatinine clearance) is constant over a wide lithium concentration range (Thomsen and Schou, 1968; Foulks et al., 1952). The constancy of this ratio demonstrates that the lithium excretion rate is directly proportional to the plasma lithium concentration. In addition, the urinary bladder has been shown to be highly impermeable to nearly all ions (Lewis and Diamond, 1976), and therefore any lithium that enters the bladder is expected to remain there until micturition.

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Because both the saliva concentration and the urinary excretion rate of lithium are directly proportional to the plasma concentration of lithium, the urinary excretion rate is expected to be proportional to the saliva concentration.

In the present study the relationships between the plasma concentration, the saliva concentration and the urinary excretion rate of lithium were investigated and the possibility of using the saliva concentration or the urinary excretion rate of lithium for monitoring dosage was considered.

Materials and Methods

Materials

Controlled-release pellets of lithium sulphate lots 10, 10A, 10.5, 11A and 11B were kindly supplied by Biovail S.A.; controlled-release tablets of lithium carbonate (Priadel lot 4289) were kindly supplied by Delandale Laboratories.

Subjects

The subjects participating in the study were healthy male or female informed volunteers, aged between 26 and 62 years (mean age 35 years).

In vivo experimental procedure

Lithium sulphate in the form of solution (500 mg) or controlled-release pellets (1 g) and lithium carbonate in the form of ordinary tablets (1 g) or controlled-release tablets (400 mg) were administered at different times to the subjects for a single dose bioavailability study. The dose was administered in the morning at about 08.00–10.00 h. Samples of biological fluids for lithium determination were collected at least for 24 h after administration. In two trials, plasma, saliva and urine samples were collected; in 24 trials only plasma and urine samples were collected; and in 30 trials only urine and saliva samples were collected. The samples were collected with sufficient frequency for a good estimation of the plasma concentration, saliva concentration and urinary excretion rate profiles.

Lithium determination

In the trials where plasma, saliva and urine (2 trials) or only saliva and urine (30 trials) samples were collected, the lithium in the biological samples was measured by Atomic Absorption Spectrometry (AAS). An Instrumentation Laboratory AA/AE Spectrophotometer Model 151 was employed for lithium determination using an air–acetylene flame and a wavelength of 670.7 nm. The final solutions for lithium determinations were in the concentration range from 0.5 to 2.5 ppm. To 1 ml of each urine sample, 1 ml of standard 50 ppm lithium solution was added and then distilled water was used to dilute to 100 ml. To 1 ml of each plasma or saliva sample, 1 ml of standard 5 ppm lithium solution was added and then distilled water was used to dilute to 10 ml. Concentrations of samples in the final solutions were obtained from the corresponding calibration curves.

In the trials where only plasma and urine samples were collected (24 trials) the lithium in the biological samples was measured by Flame-photometry. An IL 543 Flame Photometer fitted with a second dilutor was used. The dilutor automatically performed a 1 : 40 dilution of any aspirated solution and therefore lithium determination could be performed automatically. Samples containing less than 2.5 mmol/l lithium were aspirated undiluted and the lithium concentration recorded from the display.

Results and Discussion

The relationship between the saliva and plasma concentration of lithium was investigated in two subjects. Fig. 1 shows that there was a very good correlation between plasma and saliva concentration profiles; Table 1 shows the ratios of their areas under the curves, calculated by using the trapezoidal method. The mean ratios (from 10.00 to 10.00 h) of saliva-to-plasma concentrations found in the present study are very close to those obtained by others in healthy subjects (Spring and Spirtes, 1969a; Groth et al., 1974; Shimizu and Smith, 1977). In all samples the saliva concentration was found to be higher than the plasma concentration measured at the same time. This may be due to active secretion of lithium into the saliva as indicated by stop-flow studies performed

TABLE 1

Ratios of areas under the curves of urinary excretion rates, saliva concentrations and plasma concentrations of lithium after administration of 1 g lithium carbonate conventional tablets to subjects RD and SMc; analysis by AAS

Period of time	Subject RD			Subject SMc		
	Ru/p *	*Ru/s* **	*Rs/p* ***	*Ru/p* *	*Ru/s* **	*Rs/p* ***
10.00–13.00 h	33.1	11.7	2.89	32.5	14.9	2.18
13.00–16.00 h	29.0	8.4	3.45	20.9	8.0	2.62
16.00–19.00 h	32.6	10.1	3.24	29.2	10.6	2.76
19.00–22.00 h	35.2	10.2	3.46	25.5	10.0	2.55
22.00–01.00 h	29.5	8.2	3.10	25.0	9.9	2.53
01.00–04.00 h	26.3	8.5	3.08	20.7	8.2	2.51
04.00–07.00 h	25.0	8.2	3.07	19.1	7.7	2.50
07.00–10.00 h	34.5	11.3	3.06	22.1	8.9	2.50
10.00–22.00 h	33.4	10.1	3.31	26.7	10.6	2.53
22.00–07.00 h	27.2	8.8	3.08	21.9	8.7	2.51
10.00–10.00 h	31.6	9.8	3.22	25.1	10.0	2.52
10.00–16.00 h	30.1	9.3	3.28	26.0	10.7	2.43

* *Ru/p* = Ratio of *AUC*s of urinary excretion rate to plasma concentration.
** *Ru/s* = Ratio of *AUC*s of urinary excretion rate to saliva concentration.
*** *Rs/p* = Ratio of *AUC*s of saliva to plasma concentrations.

in submaxillary glands of cats (Spring and Spirtes, 1969b). If lithium is excreted into human saliva by a similar active process, this may indicate that the mechanism is not saturated at the concentration range studied (from 1.69 to 5.96 μg/ml). However, red blood cell flux measurements in vitro show that the Li^+ ratio is set mainly by the balance of Li^+ movements into the cell via a leak and out of the cell via Na^+–Li^+ countertransport. From the transport parameters measured in red blood cells, a cell-to-plasma lithium concentration ratio of about 3 was predicted (Ehrlich and Diamond, 1980) for a cell with intracellular potentials of 90 mV, inside negative. Since the potential difference across the lumen of the salivary duct ranges between −80 and −90 mV (Young, 1973) the saliva-to-plasma ratio measured in the present study was the expected one.

Table 1 also shows that during the phase of absorption (from 10.00 to 13.00 h) the ratios of saliva-to-plasma concentrations were significantly lower than those after the third hour. This indicates that a certain time is required for establishing equilibrium between plasma and saliva concentrations.

The possibility of using saliva concentration of lithium for monitoring dosage has been investigated quite extensively since it was first suggested as a convenient alternative to plasma concentration (Sims and White, 1974). Most opinions recommend caution in the use of saliva lithium at present (Sims et al., 1978; Beresewicz et al., 1977; Johnson, 1980), but it is possible that it might be used safely in patients with normal renal function when the saliva-to-plasma ratio has been calculated for the individual patient (Neu et al., 1975; Ravenscroft et al., 1978; Davis et al., 1978). The results in the present study (low intra-subject variability, e.g. from 2.50 to 2.76 in subject SMc and 3.06 to 3.46 in subject RD) support the idea that the saliva concentration of lithium could be useful in monitoring therapy in the individual case but that the saliva-to-plasma ratio is variable between subjects.

The relationship between urinary excretion rate and plasma concentration of lithium was investigated in the present study in 10 subjects (26 trials). In two trials the samples were analysed by Atomic Absorption Spectrometry and in the rest by Flame-photometry. A good correlation be-

TABLE 2

Ratios (Ru / p) of areas under the curves of urinary excretion rate profiles to plasma concentration profiles of lithium

Subject	Dosage form	Period of Time of the day (from....to....)											
		09.00–12.00	12.00–15.00	15.00–18.00	18.00–21.00	21.00–24.00	24.00–03.00	03.00–06.00	06.00–09.00	09.00–24.00	24.00–09.00	00.00–24.00	09.00–15.00
RD	Tablets	32.4	24.4	35.1	44.6	43.0	26.4	25.7	32.6	34.8	28.0	32.9	27.8
RD	10A	37.6	21.6	39.2	32.7	30.2	25.5	24.7	22.3	31.7	24.1	28.6	27.8
RD	10.5	39.9	45.4	35.2	54.8	70.8	50.3	40.9	39.2	50.9	42.9	46.7	44.0
TVDM	Tablets	34.1	23.1	27.6	31.6	31.9	29.5	32.3	28.4	29.4	30.1	29.6	29.0
TVDM	10A	42.5	36.5	36.3	31.1	25.9	17.1	10.1	10.5	32.6	12.9	24.9	38.9
TVDM	10.5	49.5	45.1	39.1	34.7	23.4	16.5	10.5	12.0	36.0	13.1	27.2	46.5
PC	Tablets	43.0	49.4	54.6	47.9	33.0	23.7	17.3	12.1	46.5	15.5	38.7	46.4
PC	10A	72.1	52.1	35.9	39.6	34.6	30.6	22.2	12.4	47.2	22.0	40.0	59.6
PC	10.5	65.7	48.0	49.5	58.0	33.9	21.9	17.5	11.0	49.3	17.1	39.9	51.8
PG	Tablets	30.4	26.2	29.1	36.8	24.5	27.9	15.3	13.5	29.2	19.3	26.7	30.6
PG	10A	63.7	52.6	66.7	53.5	16.8	16.7	17.7	17.4	52.7	17.3	42.8	58.3
PG	10.5	70.2	33.2	45.0	52.7	52.6	34.4	16.0	14.6	46.2	22.2	38.2	38.3
MC	10A	25.7	27.0	24.1	26.0	26.5	21.2	32.9	38.1	26.9	30.2	27.9	26.4
MC	10.5	47.9	26.9	34.8	33.1	24.0	18.9	20.6	23.0	31.0	20.7	27.7	30.2
MC	11A	45.9	38.2	38.0	24.4	25.0	17.5	16.3	15.4	31.1	16.4	25.0	39.6
JB	10A	36.2	47.8	45.1	44.0	60.4	44.0	41.8	45.5	46.1	43.9	45.4	42.3
JB	10.5	38.1	29.1	28.8	36.9	38.0	23.6	17.4	17.2	33.1	19.4	28.1	31.5
JB	11A	28.0	26.5	28.1	41.0	33.2	24.6	27.5	25.6	32.9	25.9	29.7	26.8
JN	10A	23.2	26.3	17.2	12.1	15.0	39.5	44.3	32.7	18.7	39.1	24.9	24.9
JN	10.5	61.4	13.1	10.5	15.3	30.1	23.9	26.1	24.6	18.0	24.9	20.2	20.2
JN	11A	28.7	8.5	6.8	15.7	16.0	15.4	17.1	18.5	11.8	16.9	13.6	10.9
TVR	10A	45.1	30.4	37.6	13.0	11.8	13.7	16.9	21.7	25.5	17.3	22.4	35.5
TVR	10.5	30.9	36.4	31.9	18.6	20.5	17.8	16.9	17.8	26.5	17.5	22.4	34.7
GM	10.5	52.1	20.0	26.7	51.6	32.2	7.8	8.4	9.1	32.5	8.4	24.8	24.7
Mean		43.5	32.8	34.3	35.4	31.4	24.5	22.3	21.5	34.1	22.7	30.3	35.3
±S.D.		14.1	12.1	12.8	13.7	13.7	9.7	9.7	9.9	10.7	9.0	8.3	11.6

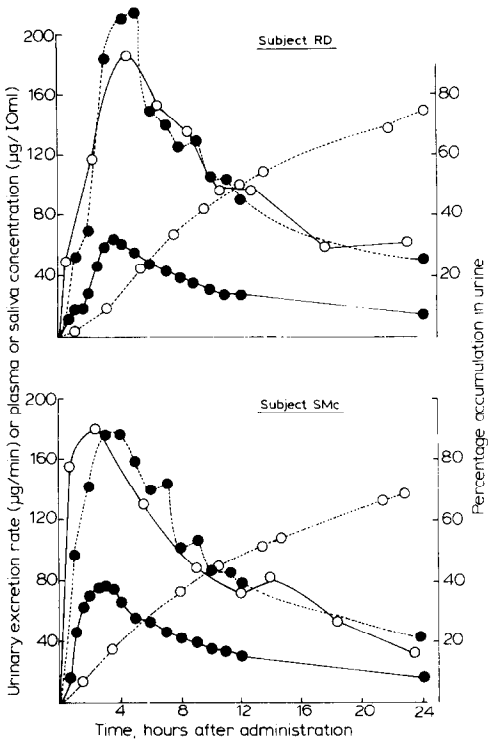

Fig. 1. Excretory profiles and plasma concentration of lithium after administration of 1 g lithium carbonate conventional tablets. O——O, Urinary excretion rate; ●------●, saliva concentration; ●——●, plasma concentration; O------O, % accumulation in urine.

tween urinary excretion rate and plasma concentration profiles was obtained as is shown in Fig. 1 (2 examples). Further investigation of the relationship between urinary excretion rate and plasma concentration was made by means of renal clearance calculated as the ratio of the areas under the curves (AUC). Tables 1 and 2 show the ratios of the AUCs of urinary excretion rate to plasma concentration profiles for subjects where samples were analysed by Atomic Absorption Spectroscopy and Flame-photometry, respectively.

The mean renal clearance values of lithium (from 00.00 to 24.00 h) ranging from 13.6 to 46.7 (Tables 1 and 2) are in agreement with those obtained by others (Groth et al., 1974) and may indicate tubular reabsorption of lithium.

There is a fluctuation in the renal clearance values of lithium during the day. In 8 out of 9 subjects the mean renal clearance values of lithium during the day were significantly higher than those during the night (see Tables 1 and 2). The opposite was true only for subject JN (Table 2) and this may have been due to the sleep–wake pattern of this subject, since in rats, where the sleep–wake pattern is opposite to that of man, the renal clearance values of lithium during the day were found to be lower than during the night (Smith, 1973). This fluctuation in the renal clearance may reflect the circadian variation in lithium excretion which has been observed in rats (Smith, 1973) and in humans (Ehrlich et al., 1980).

The highest mean renal clearance value of lithium was found during the first 3 h after administration when absorption predominates (Table 2). This may be due to the fact that renal excretion is related to the plasma concentration of arterial blood which during the period of higher absorption rates may be higher than that of venous blood from which samples were collected for lithium determination.

Formulation factors do not significantly affect the variation of the values of lithium renal clearance, since inter-subject variation remains the same regardless of the formulation administered. For example, in experiment C (Table 3) two lots of controlled-release pellets (lots 10A and 10.5) with completely different release characteristics were administered to the same 8 subjects; the coefficient of variation of the lithium renal clearance did not differ significantly for these two formulations. The same can be said for the other two experiments A and B (Table 3), but the small number of subjects combined with the intra-subject variation makes it less clear.

Inter-subject variation regarding renal clearance of lithium was greater than intra-subject variation during the day, but not during the night. For example, the coefficients of variation in Table 3 (inter-subject variation) range from 12.7 to 37.7 and 10.8 to 48.2 for day- and night-time, respectively, while the corresponding coefficients of variation in Table 4 (intra-subject variation) range from 2.5 to 23.2 and 10.3 to 43.1, respectively. This may be connected to changes in the sleep–wake pattern of each subject during the night (see above).

TABLE 3

Ratios (Ru/p) of areas under the curves of urinary excretion rate to plasma concentration profiles for each formulation

Analysis by Flamephotometer.

Experiment	Dosage form	No. of subjects	Time of the day								
			09.00–24.00 h			24.00–09.00 h			00.00–24.00 h		
			$\overline{Ru/p}$	±S.D.	CV	$\overline{Ru/p}$	±S.D.	CV	$\overline{Ru/p}$	±S.D.	CV
A	Tablets	4	35.0	7.0	20.0	23.2	6.0	26.0	32.0	4.5	13.9
	Lot 10A	4	41.0	9.1	22.2	19.1	4.3	22.4	34.1	7.5	22.0
	Lot 10.5	4	45.6	5.8	12.7	23.8	11.5	48.2	38.0	7.0	18.4
B	Lot 10A	3	30.6	11.5	37.5	37.7	5.7	15.0	32.7	9.0	27.5
	Lot 10.5	3	27.4	6.7	24.4	21.7	2.3	10.8	25.3	3.6	14.4
	Lot 11A	3	25.3	9.6	37.7	19.7	4.4	22.2	22.8	8.3	36.3
C	Lot 10A	8	35.2	11.3	32.1	25.8	10.3	40.0	32.1	8.5	26.6
	Lot 10.5	8	36.4	10.9	29.9	22.2	8.5	38.2	31.3	8.7	27.7

There are many difficulties to be overcome in using the urinary excretion rate of lithium for monitoring dosage and these are due to inter-subject variation, intra-subject variation during the night and circadian variation in the renal excretion of lithium. The results in the present study suggest that the urinary excretion rate could be useful in monitoring therapy in the individual case provided that intra-subject and circadian variations are taken into consideration.

The relationship between urinary excretion rate and saliva concentration of lithium was investigated in the present study in 5 subjects (32 trials). In all trials the samples were analysed by Atomic Absorption Spectroscopy. A good correlation between urinary excretion rate and saliva concentration profiles was obtained as is shown in Fig. 1 (2 examples). Further investigations were made by means of the ratio (Ru/s) of the areas under the curves (AUC) of the two profiles calculated by using the trapezoidal method. Tables 5, 6 and 7 show the ratios of the AUCs of urinary excretion rate-to-saliva concentration profiles. There is no significant difference in the Ru/s values of lithium during the day and night; some trials gave higher values during the day and others higher during the night (see Tables 5 and 6). Intra-subject variations regarding the Ru/s were not significant, since the coefficient of variation for the subjects AK, SM and AA ranged from 9.2 to 27.6 (see Tables 5 and 6). Inter-subject variation regarding the mean Ru/s were also not significant since the coeffi-

TABLE 4

Ratios (Ru/p) of areas under the curves of urinary excretion rate to plasma concentration profiles for each subject

Subject	No. of trials	Time of the day from....to....								
		09.00–24.00 h			24.00–09.00 h			00.00–24.00 h		
		$\overline{Ru/p}$	±S.D.	CV	$\overline{Ru/p}$	±S.D.	CV	$\overline{Ru/p}$	±S.D.	CV
RD	3	39.1	8.4	21.5	31.7	8.1	25.6	36.1	7.7	21.4
TVDM	3	32.7	2.7	8.2	18.7	8.1	43.1	27.2	1.9	7.0
PC	3	47.7	1.2	2.5	18.2	2.8	15.2	39.5	5.9	1.5
PG	3	42.7	9.9	23.2	19.6	2.0	10.3	35.9	6.8	18.9
MC	3	29.7	2.0	6.6	22.4	5.8	25.7	26.9	1.3	4.9
JB	3	37.4	6.2	16.5	29.7	10.4	34.9	34.4	7.8	22.7
JN	3	16.2	3.1	19.1	27.0	9.2	34.0	19.6	4.6	23.6

TABLE 5

Ratios (Ru/s) of areas under the curves of urinary excretion rate profiles to saliva concentration profiles of lithium in subject AK

S.D. = standard deviation; CV = coefficient of variation.

Dosage form	Period of time after administration (h)										
	0–3	3–6	6–9	9–12	12–15	15–18	18–21	21–24	0–15	15–24	0–24
Solution	12.2	10.3	11.9	9.9	7.5	6.3	6.4	12.8	10.7	7.9	10.2
Solution	9.9	9.5	12.1	9.8	12.4	13.1	14.5	7.1	10.3	11.8	10.6
Lot 10	9.5	10.9	9.9	12.6	12.1	12.5	11.6	9.9	10.8	11.4	10.9
Lot 10	9.4	11.5	11.6	12.6	10.9	9.4	7.1	8.0	11.1	8.3	10.4
Lot 10A	15.1	15.1	12.8	15.4	11.9	12.4	8.8	9.7	14.1	10.5	13.2
Lot 10A	15.0	13.8	12.8	14.2	12.0	11.5	9.7	5.3	13.4	9.1	12.4
Lot 10A	14.6	10.7	11.2	12.5	13.0	11.9	10.7	12.2	12.2	11.5	12.0
Lot 10A	19.4	13.5	10.4	11.0	10.5	10.4	10.4	13.6	11.3	11.2	11.3
Lot 10.5	17.5	8.5	19.1	21.3	13.4	16.6	19.0	13.1	14.8	16.4	15.2
Lot 10.5	6.4	11.5	10.6	10.8	10.9	13.6	12.2	10.3	10.6	12.3	11.0
Lot 10.5	10.2	8.4	8.2	7.3	7.3	7.8	8.1	9.5	8.1	8.3	8.2
Lot 10.5	10.9	7.8	10.2	9.1	7.0	9.1	10.5	10.8	8.5	10.2	9.3
Lot 11A	11.2	10.7	14.9	14.8	9.7	12.1	13.2	10.0	12.3	11.9	12.2
Lot 11B	10.3	9.0	14.9	8.7	9.8	10.3	12.0	10.1	10.9	10.8	10.9
C.R. Tablet	12.2	8.5	9.7	11.5	11.1	10.0	9.0	9.0	10.1	9.4	9.9
C.R. Tablet	13.0	10.5	10.2	9.9	10.8	11.3	9.2	13.3	10.8	11.2	10.9
Mean	12.3	10.6	11.9	12.0	10.6	11.1	10.8	10.3	10.4	10.8	11.2
($n = 16$) ± S.D.	3.2	2.0	2.5	3.2	1.9	2.4	3.0	2.3	2.8	2.0	1.6
CV	26.2	19.1	21.4	27.1	17.8	21.3	27.6	21.9	26.8	18.4	14.0

TABLE 6

Ratios (Ru/s) of areas under the curves of urinary excretion rate profiles to saliva concentration profiles of lithium in different subjects

S.D. = standard deviation; CV = coefficient of variation.

Subject	Dosage Form	Period of time after administration (h)										
		0–3	3–6	6–9	9–12	12–15	15–18	18–21	21–24	0–15	15–24	0–24
SM	Solution	8.8	7.3	12.0	8.5	9.0	7.1	6.6	5.1	8.9	6.2	8.3
SM	Lot 10A	9.3	8.3	9.6	9.6	9.6	9.6	9.3	8.0	9.3	9.1	9.2
SM	Lot 10A	6.0	7.4	7.6	7.1	7.1	7.4	7.8	7.9	7.2	7.6	7.3
SM	Lot 10.5	6.6	10.6	9.9	6.5	11.0	10.8	10.9	6.2	9.4	9.5	9.3
SM	Lot 10.5	6.7	7.7	7.6	7.0	7.5	7.7	8.5	7.3	7.2	7.9	7.4
SM	Lot 10.5	9.0	7.3	8.6	6.9	8.9	10.8	10.8	8.8	8.0	10.3	8.8
SM	C.R. Tablets	7.6	6.8	6.5	8.2	8.7	9.0	9.1	9.4	7.3	9.2	7.7
SM	C.R. Tablets	9.1	8.5	6.9	6.5	6.3	6.7	7.3	7.8	7.9	7.2	7.7
Mean		7.9	8.0	8.6	7.5	8.5	8.6	8.8	7.6	8.2	8.4	8.2
($n = 8$) ± S.D.		1.2	1.1	1.8	1.0	1.4	1.5	1.5	1.3	0.9	1.3	0.8
CV		15.6	13.9	20.5	14.8	16.5	17.9	16.5	16.9	10.6	15.2	9.2
AA	Lot 10A	7.6	8.2	11.5	11.8	6.2	6.6	7.7	10.0	9.3	7.7	8.9
AA	Lot 10A	11.9	10.6	7.9	9.7	8.2	6.3	8.5	10.2	9.2	8.2	8.9
AA	Lot 10.5	13.5	11.6	6.5	6.1	7.4	9.3	7.8	6.3	8.3	8.0	8.2
AA	Lot 10.5	7.7	9.5	7.9	6.7	7.4	8.7	12.9	10.7	7.7	10.7	8.5
AA	C.R. Tablets	7.8	5.6	6.5	11.0	6.0	6.8	6.9	7.1	7.3	6.9	7.2
AA	C.R. Tablets	9.7	12.5	11.2	7.5	8.5	12.0	12.8	10.7	10.4	11.9	10.7
Mean		9.7	9.7	8.6	8.8	7.3	8.3	9.4	9.2	8.7	8.9	8.7
($n = 6$) ± SD		2.3	2.3	2.0	2.2	0.9	2.0	2.5	1.8	1.1	1.8	1.0
CV		23.5	23.5	23.7	24.5	12.7	24.0	26.2	19.3	12.0	20.0	12.0

TABLE 7

Mean ratios (Ru/s) of areas under the curves of urinary excretion rate profiles to saliva concentration profiles of lithium in various subjects

S.D. = standard deviation; CV = coefficient of variation.

Subject	No of Trials	Period of time after administration (h)										
		0–3	3–6	6–9	9–12	12–15	15–18	18–21	21–24	0–15	15–24	0–24
AK	16	12.0	10.6	11.9	12.0	10.6	11.1	10.8	10.3	10.4	10.8	11.2
SM	8	7.9	8.0	8.6	7.5	8.5	8.6	8.8	7.6	8.2	8.4	8.2
AA	6	9.7	9.7	8.6	8.8	7.3	8.3	9.4	9.2	8.7	8.9	8.7
RD	1	11.7	8.4	10.1	10.2	8.2	8.5	8.2	11.3	10.0	9.2	9.8
SMc	1	14.9	8.0	10.6	10.0	9.9	8.2	7.7	8.9	10.5	8.2	10.0
Mean		11.3	8.9	10.0	9.7	8.9	8.9	9.0	9.5	9.6	9.1	9.6
±S.D.		2.37	1.04	1.25	1.50	1.19	1.08	1.07	1.29	0.94	0.92	1.05
CV		21.0	11.7	12.5	15.5	13.4	12.2	11.9	13.2	9.7	10.1	10.9

cients of variation ranged from 9.7 to 21.0 (see Table 7).

The mean ratio ($Ru/p = 30.3$) of urinary excretion rate-to-plasma concentration of lithium (see Table 2) divided by the mean ratio ($Ru/s = 9.6$) of urinary excretion rate-to-saliva concentration of lithium (see Table 7) gives a value of 3.15 which closely approximates to the value of the ratio (Rs/p) of saliva to plasma concentration (see Table 1) obtained in the present study. This suggests that the equation $Ru/p = Ru/s \times Rs/p$ describes the relationship between the 3 ratios. It is of great interest that this equation applies to the results of the present study where the 3 mean ratios were calculated from different subjects and the samples were analysed by different methods.

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