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Dissolution and saliva concentrations of some lithium dosage forms

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Dissolution and bioavailability studies of lithium preparations have been carried out on both the conventional and sustained release products (Coppen et al 1969; Caldwell et al 1971; Crammer et al 1974; Shaw et al 1974; Tyrer et al 1976), and deficiencies were observed for both dosage forms (Shepherd et al 1972; Sugita et al 1973; Persson 1974).

We have investigated four conventional (I–IV) and two sustained release (V, VI)‡ forms of lithium carbonate and a sustained release form of the sulphate (VII) in vitro and for some of these products, in vivo, for the rate of release and saliva concentrations of the drug.

The products were examined in simulated gastric fluid U.S.P. (1975) (SGF) without addition of pepsin and in simulated intestinal fluid U.S.P. (1975) (SIF) without addition of pancreatin. Other materials were of reagent grade.

For dissolution rate testing six tablets of each product were individually assessed in SGF and in SIF using a U.S.P. (1975) dissolution apparatus operated at 60 rev min^{-1} with 900 ml of dissolution media. 10 ml samples were removed at specified time intervals and total release was found after >24 h. The samples were assayed using a Perkin Elmer 403 Atomic Absorption Spectrophotometer in the emission mode. The standard conditions used were: air 383 ml s^{-1}, acetylene adjusted to peak intensity (~100 ml s^{-1}), wavelength 670·1 nm, spectral band width 0·4 nm. For in vivo determinations single doses of the products, I–III, V, were given in a latin square design as described by Wall et al (1978) to eight volunteers.

Approximately 7–10 ml of saliva was collected at specified time intervals over 96 h. Samples were stored at −17 °C until required for assay, which was the method used by Wall et al (1978) to obtain the urine results.

The dissolution data at each sampling time in SGF and SIF were compared using Student's *t*-test for unpaired comparisons. Analysis of the salivary concentrations was by split plot analysis of variance over the first 24 h. Peak salivary concentration and the time to reach the peak was subjected to analysis of variance as described by Westlake (1973). For specific products a significant F-statistic was assessed by the Tukey test (Keppel 1973) and paired formulations by the methods of Westlake (1973). Data from V were adjusted by dividing by 1·6 before analysis.

A representative dissolution profile from the conventional tablets tested and the profiles from each sustained release product are shown in Fig. 1. Comparisons of the time taken to release 4 mmol of lithium from all dosage forms tested are listed in Table 1. Batch assays of all conventional tablets by the BP (1973) method were within specification. The amounts of lithium released at equilibrium in dissolution studies correlated with these results.

After the administration of tablets of I–III, V, the amounts of lithium recovered over 96 h from urine by Wall et al (1978) were not significantly different between preparations, typically only 1 to 3% of the total remaining to be excreted.

The mean salivary concentrations obtained at each sampling time for the first 14 h are shown in Fig. 2. The variation of these data about the mean was similar to that reported for urine (Wall et al 1978). Analysis of variance on the peak salivary concentrations and times taken to reach the peak showed no significant difference between formulations with respect to the peak values. The differences in the time taken to reach the peak was significant at $P < 0.01$. Analysis of variance of the salivary concentrations data showed the times vs formulations interaction to be significant at $P < 0.001$. Logarithmic transformation did not alter the results of these analyses.

The dissolution profiles of the conventional products

Table 1. Mean time for the release of lithium into simulated gastric fluid (SGF) and simulated intestinal fluid (SIF) from conventional and sustained release tablets.

	Time to release 4 mmol Li (min)		Nominal Li content (mmol)
Brand product	SGF	SIF	
I	17	25	6·77
II	4	3	6·77
III	19	22	6·77
IV	13	11	6·77
V*	25	50	10·83
VI*	>360	330	8·04
VII*	112	130	6·00

* Sustained release product.

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‡ I Camcolit 250 mg, batch 078X25 (Norgine); II Lithicarb 250 mg, batch 50722X3, (Protea); III Manialith 250 mg batch 124–99 (Muir and Neil); IV Drug Houses of Australia 250 mg batch 62024. V Priadel 400 mg, batch 5404, (Delandale Laboratories); VI Phasal 300 mg, batch 6003, (Pharmax Ltd). VII Lithionit 6 mmol, batch ZB41, (A. B. Hassle).

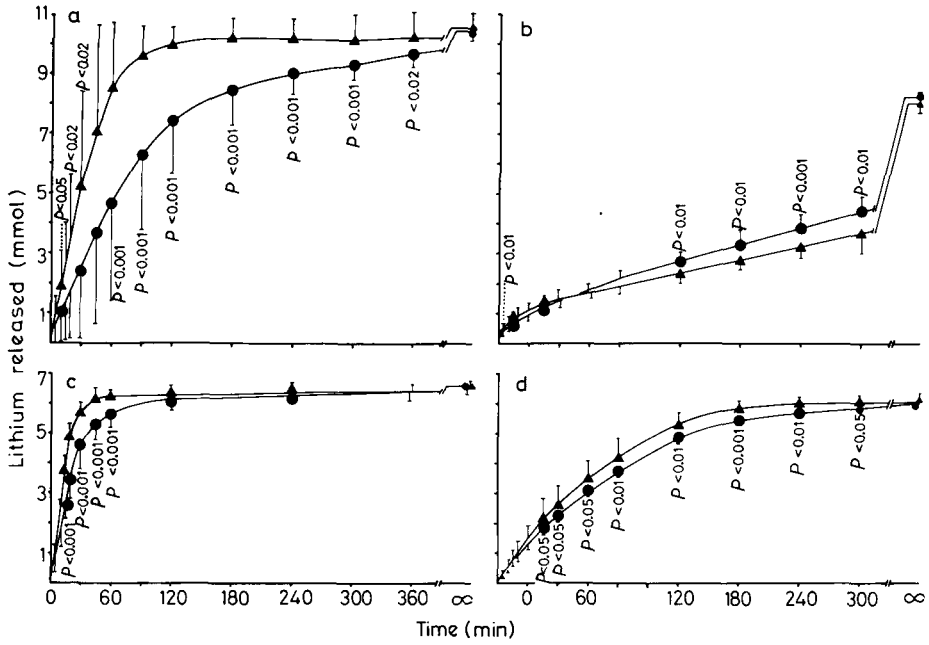

FIG. 1. Mean dissolution profiles of lithium tablets—V a; VI b; I c and VII d in SGF (▲) and SIF (●) with 2 s.d. Significant differences $P \leq 0{\cdot}05$ are shown at the appropriate time intervals.

(Table 1 and Fig. 1c) showed some statistically significant differences between the amount of drug dissolved with time in SGF or SIF. These profiles however, do not provide any evidence of the greatly prolonged dissolution times reported by Shepherd et al (1972) and Sugita et al (1973). It was with the sustained release product V (Fig. 1a), that large differences in the amount of lithium released into SGF and SIF occurred. This product also exhibited a large inter-tablet variation and a rapid rate of release of lithium only slightly less than conventional tablets. Since it contains 1·6 times more lithium, higher peak plasma concentrations would be predicted on the basis of its dissolution profile. Product VI had released only approximately 50% of its stated content into either medium after 6 h. Release from this formulation has previously been reported as being unreliable (Tyrer et al 1976). The lithium sulphate formulation VII released at a rate between V and VI, giving almost total release in 5–6 h with little inter-tablet variation.

The saliva/plasma lithium concentration ratio is constant and reproducible for an individual (Groth et al 1974; Neu et al 1975), salivary lithium concentrations were therefore used to compare the in vivo performance of formulations I–III and V. The conventional forms behaved as predicted by the in vitro study and when the salivary data for V is divided by 1·6 (see Fig. 2) it can be seen to perform similarly to the conventional products but the larger dose of lithium could produce plasma concentrations associated with toxicity. There is a statistically significant delay in the time to reach the peak, but we believe this to have no clinical significance. The statistically significant 'time vs formulations' interaction shows V to have a different salivary profile inadequate for this formulation to be classified as a true sustained release product.

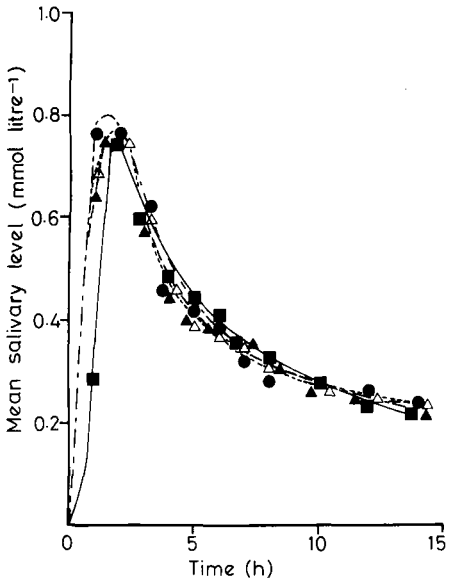

FIG. 2. Mean salivary lithium level of eight volunteers for I - - △ - - - △ -; II —●— - —●—; III—▲——▲— and V (corrected to the 250 mg dose of other products used in the study) —■——■—.

The salivary results correlate closely with urinary data reported by Wall et al (1978), when V was indicated as not being a true sustained release product.

Because of the unsatisfactory dissolution profile for VI, saliva concentrations were measured after a volunteer had taken a 250 mg dose. This gave a total urinary recovery of 52·1%, a peak urinary excretion rate and a peak salivary concentration only one-third those of conventional tablets with a marked delay. The dissolution rate thus reflected the in vivo situation with all the products tested.

Our results contrast with the conclusions of Coppen et al (1969), Shaw et al (1974), and Bennie et al (1977) who found peak values for V occurring later than we did. Jeppsson & Sjogren (1975) have shown that the presence of food can delay lithium absorption. Recently, Johnson et al (1979) showed a statistically significantly delayed peak for V over a conventional product in fasted subjects, however, they too do not consider this product to be a true sustained release preparation. Tyrer et al (1976), as we did, administered tablets on an empty stomach and found the rates of absorption of V and I to be almost identical and release from V too fast to prevent potentially toxic blood concentrations of drug. It is clear that the administration of the tablet in relation to food may significantly affect the rate of lithium absorption, but overall there appears to be no real therapeutic advantage in using V as a sustained action product over conventional tablet formulations.

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The influence of indomethacin on the acute toxicity of some anticholinesterases in mice

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Recently we have reported that prostaglandins E_2 and $F_{2\alpha}$ (PGE_2, $PGF_{2\alpha}$) enhance the toxicity of carbachol, physostigmine and pilocarpine (Radmanović & Grbović 1979; Radmanović 1980). We have also found that relatively small doses of PGE_2 and $PGF_{2\alpha}$, injected intracerebroventricularly 15 min before cholinomimetic drugs, potentiated their stimulant action on the central nervous system. In the same doses, which exceeded several-fold the physiological concentrations of PGs in the brain, PGE_2 and $PGF_{2\alpha}$ inhibited acetylcholinesterase activity in various regions of the brain in cats both after in vivo i.c.v. injection and in vitro experiments (Grbović & Radmanović 1981). It is therefore possible that the potentiation of cholinomimetic drugs by PGE_2 and $PGF_{2\alpha}$ occurs, at least partly, as a result of the accumulation of acetylcholine in the central nervous system. In view of presented data we have investigated the influence of indomethacin, an inhibitor of prostaglandin biosynthesis, on the toxicity of some anticholinesterases.

Acute toxicities of physostigmine salicylate, neostigmine (Prostigmine Roche), Dyflos (DFP) and paraoxon given alone and when combined with drug treatment were determined in albino mice of either sex, 20–24 g. Drugs were dissolved in 0·9% NaCl and injected subcutaneously, with the exception of atropine sulphate which was injected intraperitoneally, in a volume of 0·1 ml per 10 g body weight. LD50 values, based on 24 h mortalities, were calculated by the method of Litchfield & Wilcoxon (1949); each group of animals consisted of 18 to 24 mice. In pilot experiments it was found that the used dose of indomethacin (10 mg kg^{-1} s.c.) did not produce toxic signs by itself and that

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