In vivo Evaluation of Two Controlled Release Lithium Carbonate Tablets

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Abstract—A lithium carbonate controlled release tablet was evaluated in vivo and compared with a conventional lithium carbonate tablet. Changes in the first formulation were made in order to achieve a better performance. The modified formulation showed a sustained release pattern and did not show differences in the amount of lithium absorbed in comparison to the conventional tablet.

Introduction

The lithium ion is readily absorbed from the gastrointestinal tract. It is not bound to plasma proteins. It penetrates into tissues at varying rates and its apparent volume of distribution corresponds to about 70% of body weight. Elimination takes place almost exclusively through the kidneys, with a half life of 15 to 30 h.[1,2]

Conventional lithium dosage forms make the drug immediately available for absorption, producing rapid and relatively high blood levels. In order to avoid this, controlled-release lithium preparations have been developed.

In previous reports from our laboratory, we have shown the in vivo performance of a controlled-release lithium carbonate tablet in a hydrophilic matrix.[3,4] In the present study, we examined the in vivo behaviour of a new lithium carbonate controlled release tablet in an acrylic matrix and compared it with a marketed conventional tablet.

Materials and methods

The study was carried out in two steps: in the first, we evaluated the performance of Formulation 1 (Table 1) in comparison with the conventional marketed tablet in ten young normal adult volunteers, six females and four males, in a cross-over fashion. In the second part of the study, we modified the formulation (Formulation 2; Table 1) and evaluated it in 12 young normal adult male volunteers.

Medical history, physical examination and laboratory tests were carried out prior to beginning the study; the results were within normal limits for all the volunteers. All subjects gave their informed written consent. They were instructed to abstain

Table 1 Composition (mg) of the two formulations.

	Formulation	
	1	*2*
Lithium carbonate	300	300
Avicel pH 101	20	20
Lactose spray-dried	20	20
Eudragit S 100	18.6	18.6
Eudragit RSPM	80	60
Magnesium stearate	2.1	2
Aerosil	0.5	0.5

from taking any medication and alcohol 1 week prior to starting and during the study.

On the day of the experiment they arrived having fasted overnight; two 300 mg lithium carbonate tablets of the selected formulation were swallowed with 150 ml of water. The volunteers remained for 14 h in the place where the experiment was performed. They were under medical supervision and were instructed to inform the investigators of any adverse reaction. They were ambulatory but were not permitted to engage in strenuous physical exercise. No food was allowed for 3 h after the ingestion of the dose; after this time, a light standard breakfast was served and a full standard lunch was served 6 h after dosing.

Urine was collected before dosage and at 1, 2, 4, 6, 8, 12, 24, 36, 48, 60 and 72 h after dosing. The urine volume was measured for each sample and an aliquot was frozen until its analysis by atomic absorption spectrophotometry using a GBC instrument.

Pharmacokinetic analysis

The urinary data were analysed by the excretion rate method in order to obtain the slow disposition rate constant, β. The total amount of drug excreted in the urine Xu_∞ was obtained using the equation:[3,5]

$$(Xu)_i = Xu_\infty - [1/(1-e^{-B\Delta t})][(Xu)_{i+1} - (Xu)_i]$$

$Xu_{\frac{1}{4}}$ is obtained as the intercept of the graph of the amount of drug excreted at time t and the amount excreted in the following equal interval. This equation applies when the urine is collected at equal intervals and after the absorption has ceased. Since lithium is excreted near 100% in the urine, Xu_∞ was considered as the fraction of the dose absorbed, F.

Statistical analysis

Analysis of variance and Tukey's method were employed to assess the differences between the various parameters calculated.[6]

Results and discussion

Mean urinary excretion rates for the conventional tablet and Formulation 1 are shown in Figure 1.

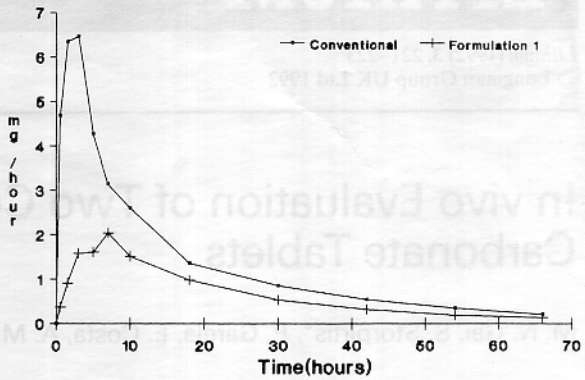

Figure 1 Mean urinary excretion rates following the administration of a Conventional tablet and Formulation 1.

The controlled-release tablet produced a smoother curve than the conventional tablet. The maximum excretion rate was 6.46 ± 2.43 mg/h in the interval 2–4 h for the conventional tablet. With the sustained-release formulation this value was 2.04 ± 0.9 mg/h in the interval 6–8 h, indicating a delay in the release of the drug. The slow disposition rate constant β was 0.03933 ± 0.0065 h^{-1} for the conventional tablet and 0.04376 ± 0.0076 h^{-1} for the controlled-release preparation, corresponding to half-life values of 18.08 ± 3.14 h and 16.13 ± 2.97 h respectively. These values are similar to the half-lives reported in the literature for lithium.[1–4]

The values obtained for Xu_∞, considered as a measure of the amount of lithium absorbed, were $81.22 \pm 9.33\%$ for the conventional tablet and $40.38 \pm 22.68\%$ for the controlled-release formulation. These results indicate a too-long delay in the release of the drug.

As Eudragit RSPM controls the liberation of the drug, we modified Formulation 1, lowering the amount of the acrylic resin Eudragit RSPM whilst keeping constant the rest of the formulation. Formulation 2 was evaluated in 12 volunteers.

Figure 2 shows the mean urinary excretion rates obtained with Formulation 2. The maximum urinary excretion rate was 3.10 ± 1.00 mg/h in the interval 4–6 h, in between the values obtained for the conventional tablet and Formulation 1. The slow disposition rate constant β and half-life did not show a significant difference from those obtained in the first step of the study ($p > 0.05$).

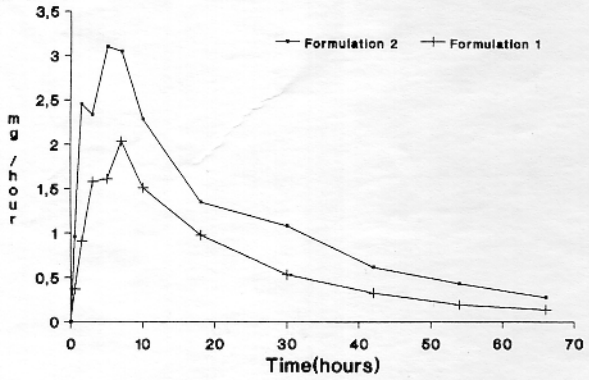

Figure 2 Mean urinary excretion rates following the administration of Formulations 1 and 2.

Bioavailability of Formulation 2 was 75.52± 17.91%, which is significantly higher than that of Formulation 1 but shows no statistical difference from the conventional one ($p > 0.05$).

These results demonstrate that the acrylic resins Eudragit S 100 and Eudragit RSPM in combination may be a suitable method for controlling the release of lithium carbonate and that the rate of absorption may be controlled by modifying the amount of Eudragit RSPM.

Acknowledgements

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