In vivo Evaluation of Two Controlled Release Lithium Carbonate Tablets

M. N. Gai, S. Storpirtis*, P. Garcia, E. Costa, A. M. Thielemann and A. Arancibia

Departamento de Ciencias y Tecnología Farmacéuticas, Facultad de Ciencias Químicas y Farmacéuticas, Universidad de Chile, Santiago, Chile and *Faculdade de Ciencias Farmacêuticas, Universidade de São Paulo, Brazil

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>
<thead>
<tr>
<th>Table 1 Composition (mg) of the two formulations.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Formulation</strong></td>
</tr>
<tr>
<td>Lithium carbonate</td>
</tr>
<tr>
<td>Avicel pH 101</td>
</tr>
<tr>
<td>Lactose spray-dried</td>
</tr>
<tr>
<td>Eudragit S 100</td>
</tr>
<tr>
<td>Eudragit RSPM</td>
</tr>
<tr>
<td>Magnesium stearate</td>
</tr>
<tr>
<td>Aerosil</td>
</tr>
</tbody>
</table>
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 per-
formed. 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 disposi-
tion rate constant, \( \beta \). The total amount of drug excreted
in the urine \( \text{Xu}_\infty \) was obtained using the
equation: \(^3,5\)

\[
\text{Xu}_1 = \text{Xu}_\infty - \left[ \frac{1}{1 - \beta} \right] \left[ \text{Xu}_1 - \text{Xu}_0 \right]
\]

\( \text{Xu}_1 \) 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, \( \text{Xu}_\infty \) was considered as the fraction of the
dose absorbed, \( \text{F} \).

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

The values obtained for \( \text{Xu}_\infty \), 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 formu-
lation. 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. For-
mulation 2 was evaluated in 12 volunteers.
Figure 2 shows the mean urinary excretion rates
obtained with Formulation 2. The maximum ur-
inary excretion rate was \( 3.10 \pm 1.00 \text{ mg/h} \) in the
interval 4–6 h, in between the values obtained for
the conventional tablet and Formulation 1. The
slow disposition rate constant \( \beta \) and half-life did
not show a significant difference from those
obtained in the first step of the study (\( p > 0.05 \)).
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

This work was supported by grant M 3117/9013 from DTI, University of Chile, Chile.

References