

Report

Bioavailability and Pharmacokinetics of a New Sustained-Release Potassium Chloride Tablet

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The bioavailability of a new sustained-release potassium chloride (KCl) tablet, designed for once-a-day dosing, was compared to a KCl elixir using urinary excretion data. The study utilized 25 male volunteers dosed in a crossover design in a dietary/activity-controlled environment. The regimens consisted of a total of 80 mEq of potassium in three equally divided doses of elixir every 6 hr and a single 80-mEq dose using four 20-mEq sustained-release (SR) tablets. The mean time to maximum rate of potassium urinary excretion was 2.2 hr for the first elixir dose and 5.5 hr after the SR tablet ($P < 0.01$), thereby supporting the prolonged-release properties of this formulation. After correction for baseline urinary potassium excretion, the mean total 24-hr urinary potassium excretion was 42.18 mEq for the elixir and 40.41 mEq for the SR tablet. The results indicate that the absorption pattern from the SR tablet is equal to three doses of KCl elixir dosed 6 hr apart.

KEY WORDS: potassium chloride; sustained-release tablet; bioavailability; pharmacokinetics.

INTRODUCTION

Potassium chloride is indicated for patients with hypokalemia or severe potassium loss of various etiologies. The potassium chloride solutions, for many years the standard therapy, are notorious for their unpleasant taste. Therefore, patient compliance with a thrice-a-day dosage is expectedly poor. A once-daily potassium chloride replacement that is tasteless would certainly be expected to increase patient compliance.

Since potassium is an intracellular cation, an accurate determination of bioavailability is difficult. Plasma potassium concentrations are controlled by homeostatic mechanisms, thereby making it inaccurate to determine bioavailability by measuring blood levels. In order to determine the bioavailability of potassium preparations other investigators have measured urinary potassium concentration (1,2). This methodology is reasonable, since the major route of elimination for potassium is urinary excretion. To achieve successfully these goals, it is necessary to control the diet and physical activity of the subjects. Patients must receive menus of known potassium and sodium content and abstain from exercises that may cause excessive perspiration and thus electrolyte losses.

A study was undertaken to determine the bioavailability of a new 20-mEq sustained-release tablet. This product is a rapidly disintegrating tablet containing KCl crystals coated with a film which prolongs the release of drug from the crystal.

EXPERIMENTAL

Twenty-five healthy male volunteers, after an explanation of the protocol, agreed to participate in the study. The subject ranged from 19 to 43 years in age and from 52.0 to 97.9 kg in weight. Twenty-three volunteers completed the study, a two withdrew for personal reasons during the study. Subjects remained in the research center under the supervision of the nursing and medical staff for the entire 14 days. To avoid salt and water loss to perspiration, the subjects stayed indoors in a controlled-temperature environment and did not engage in strenuous activity.

The first 3 days, after patients checked into the research center, were diet adaptation days. Days 4 and 10 were control days for the treatments on days 5 and 11, respectively. On days 4 and 10 requirements with respect to fasting, menus, and meal times were exactly the same as for days 5 and 11 when the subjects were dosed. On day 13, the patients were discharged after their laboratory work and physical examinations were performed.

Eighty milliequivalents of the reference product (Kay Ciel elixir, Berlex Laboratories, Inc., Wayne, N.J.) and the test preparation (K-Dur 20, Key Pharmaceuticals, Inc., Miami, Fla.) was administered in a randomized two-way crossover design. The 80 mEq of elixir was divided into three equal doses (26.7 mEq) and given every 6 hr. Four of the 20-mEq sustained-release (SR) tablets were given as a single dose at the same time as the first dose of elixir. On the two dosing days (5 and 11) each volunteer received one of the two dosage forms after an 8-hr fast (7 AM). They continued to fast for 1 hr after ingesting the medication. The elixir was administered with 160 ml of water at 0, 6, and 12 hr. The sustained-release preparation was given with 180 ml of water to equal the total volume of liquid administered

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with the elixir dose. In addition, at 6 and 12 hr, this same volume of water was consumed to replicate the fluid intake at the time of the elixir doses. All urine voided on days 1 through 12 was collected. Throughout days 4, 5, 10, and 11 urine was collected hourly up to the 16th hour and pooled from 16 to 24 hr. The volume of each collection was recorded and a sample was analyzed for potassium and creatinine. Urine potassium was determined by flame photometry (3). The assay sensitivity was ± 0.1 mEq/liter. Creatinine was determined by the alkaline picrate method (4). Creatinine levels were used to confirm complete urine collection.

The subjects were required to drink 1500 ml of fluid each day. They received a uniform daily diet containing an average 50 mEq of potassium, 100 mEq of sodium, and 2400 kcal. No additional food or snacks were permitted. Meals were served at 8:00 AM, 12:30 PM, and 5:00 PM, and a snack at 10:00 PM. The effects of the treatments were monitored by the attending staff physician. All subjects received the constant attention of the nursing staff and were encouraged to report any adverse effects, however trivial it might appear to them.

Urine potassium was examined by looking at the cumulative amount (mEq) of potassium excreted in the urine over a 24-hr period; the cumulative urinary potassium grouped into intervals of 0–6, 6–12, and 12–24 hr; and the urinary potassium excretion rate (mEq/hr) over a 24-hr period. All potassium data have been corrected for the mean control potassium from control days 4 and 10. An analysis-of-variance model was used to evaluate statistically data from this two-treatment crossover.

RESULTS AND DISCUSSION

In spite of fluid intake in amounts thought to be adequate (1500 ml) and intensive monitoring by the staff to ensure subject compliance with hourly voiding requirements, there was a high incidence of collection intervals in which subjects were unable to provide a urine specimen. For the study as a whole, 148 of 1472 (10.1%) hourly urine spec-

imens were not provided at the time required. These events could have reflected either retention of urine in the bladder with subsequent voiding in a following collection interval or true loss of urine.

To answer the question of whether missing specimens represented true loss of urine, daily urinary creatinine excretion was examined as a measure of adequacy or completeness of quantitative urine collection. In only two instances was the daily amount of creatinine excreted less than 1.15 g, suggesting incomplete urine collection. Thus, there was reasonable confidence that any missing specimens reflected retention of urine in the bladder rather than true loss of urine. Twenty-four-hour comparative potassium bioavailability results should have, therefore, remained virtually unaffected by the incidence of apparently missing specimens.

The cumulative amount (mEq) of potassium excreted in the urine over 24 hr for the two products is illustrated in Fig. 1. The mean cumulative 24-hr urinary potassium values corrected for the control were 42.18 ± 12.49 and 40.41 ± 16.51 mEq for the elixir and the SR tablet, respectively, and were not significantly different. These values are presented in Table I.

The 24-hr urine collection data were divided into three time segments to determine the potassium elimination patterns of the tablet in relation to the elixir doses. These intervals were 0–6, 6–12, and 12–24 hr, since the elixir was dosed at 0, 6, and 12 hr. The results from this data analysis can be found in Table I. The ratio of the tablet to the elixir was close to unity for the 0- to 6-hr group, indicating slow release of the potassium from the SR tablet. More potassium was excreted in the urine after the tablet during the 6- to 12-hr time period. A total of only 53.4 mEq of the elixir had been dosed by the 12th hour and 80 mEq of sustained-release potassium had been given by this time. More potassium was excreted in the urine after the elixir during the 12- to 24-hr period. This reflects a decreased release of potassium from the SR tablet. It is interesting to note that a similar study (1) performed at the same study site during the

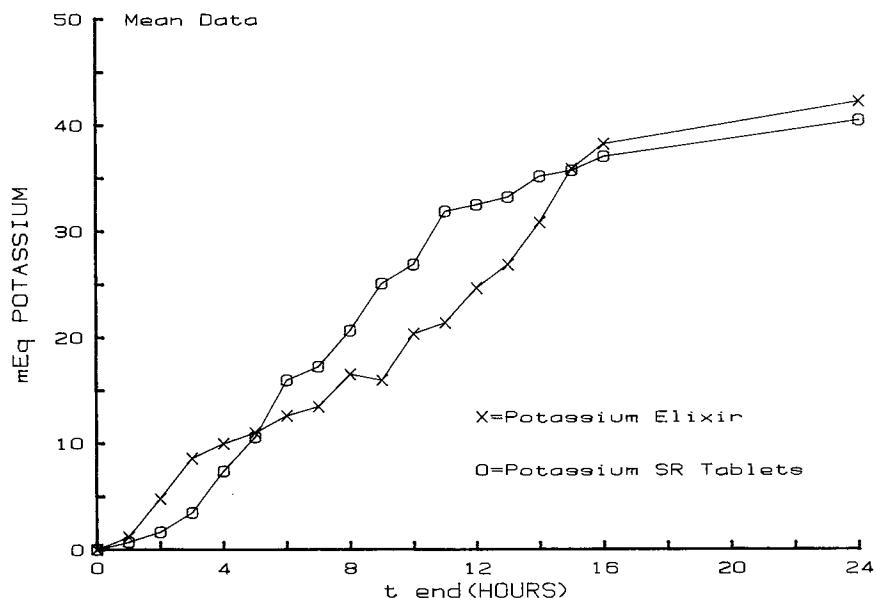


Fig. 1. Cumulative amount (mEq) of potassium excreted in the urine corrected for the background, "t end" refers to the end point of the urine collection interval.

Table I. Cumulative and Grouped Potassium Excretion (mEq) Corrected for Control

Hours	Elixir	P	Tablet	Tablet/elixir
0-6	12.63 (60) ^a	NS	15.98 (64)	1.01 (152)
6-12	10.70 (44)	<0.05	16.67 (40)	1.69 (54)
12-24	19.43 (30)	<0.05	10.16 (84)	0.58 (84)
0-24	42.18 (30)	NS	40.41 (41)	1.01 (39)

^a Arithmetic mean (coefficient of variation).

late 1970s produced a nearly identical grouped cumulative potassium excretion for the elixir as was seen with this study.

The excretion rate of potassium depicted in Fig. 2 and expressed as units of milliequivalents per hour was calculated by dividing the amount of potassium excreted in the urine during a collection interval by the time elapsed during the interval and by subtracting the control potassium excretion rate. Excretion rate data of this type are very variable, but they do provide a useful method of evaluating potassium absorption in that a "rate plot" is analogous to a plasma concentration-time profile. Even though the peak potassium level for the second elixir dose is considerably flatter than the peak levels from the other two doses, the amounts of potassium accumulated in the 0- to 6-hr and 6- to 12-hr intervals were not significantly different. The difference in the shape of the excretion rate plot after the second elixir dose may be the result of a slowing down of potassium absorption by food. The second elixir dose was administered 0.5 hr after lunch. Possibly the absorption rate of potassium from the elixir was delayed by an increase in the gastric emptying time. The mean time to reach the maximum rate of potassium urinary excretion was 2.2 ± 1.7 hr for the first elixir dose and was significantly faster than the 5.5 ± 1.7 hr after the tablet dose ($P < 0.01$). The prolonged-release character of this tablet, therefore, was verified by these results. The maximum urinary elimination rates of potassium were 3.48 ± 3.42 mEq/hr after the first elixir dose and 4.50 ± 2.64 mEq/hr for the tablet. These maximum rate values were not significantly different, thus lending credibility to the sustained release of potassium from the tablet. If the tablet had released KCl in a nonprolonged fashion, the maximum rate from the tablet would have been greater, since the tablet dose consisted of 80 mEq, while the first elixir dose was only 26.7 mEq. There was no evidence of dose dumping in any of the subjects and adverse effects were minimal, with one case of flatulence and two cases of mild stomachache.

The results of this controlled study demonstrated that a single dose of a new sustained-release potassium chloride tablet delivered the same amount of potassium as a 10% po-

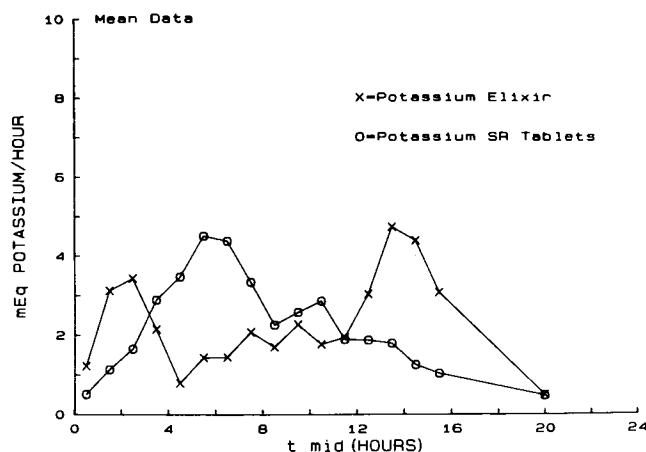


Fig. 2. Mean plot of urinary potassium excretion rate (mEq/hr) corrected for the background versus the midpoint of the collection interval.

tassium chloride elixir dosed three times a day. The time to maximum urinary potassium excretion rate was significantly longer with the tablet than with the elixir, illustrating the sustained-release properties of the tablet. The maximum urinary potassium excretion rates were approximately the same, indicating that a once-daily dose of the tablets (80 mEq) safely provided potassium similarly to three 26.7-mEq doses of an elixir over 24 hr. Finally, the total amount of potassium excreted after dosing with the sustained-release tablet was not statistically different from the amount excreted after the elixir doses. The extent of absorption from the tablet relative to the elixir, therefore, was complete.

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