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Bioavailability and Pharmacokinetics of a New, Slow-Release Potassium Chloride Capsule

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Abstract □ The bioavailability of a new, slow-release potassium chloride product consisting of coated beads in a hard gelatin capsule was compared with the bioavailability of two marketed products, an elixir and a slow-release tablet, by determining the urinary excretion of potassium. Twelve healthy male volunteers were dosed with a total of 80 mEq of potassium, in a single dose for the capsule and tablet and in three 26.6-mEq doses at 6-hr intervals for the elixir. Mean recoveries in 24-hr urine potassium levels from all three dosage forms after subtracting normal urine potassium excretion levels were 50.8% from the capsule, 53.9% from the elixir, and 63.1% from the tablet. Maximum excretion rates were reached at 2.0 hr for the elixir, 6.8 hr for the capsule, and 4.0 hr for the tablet. Fewer side effects were reported with the capsule than with the elixir and tablet.

Keyphrases □ Potassium chloride—bioavailability and pharmacokinetics of slow-release capsule □ Bioavailability—potassium chloride in slow-release capsule □ Pharmacokinetics—potassium chloride in slow-release capsule

Potassium chloride is indicated for the treatment of hypokalemic alkalosis associated with various cardiovascular disorders. Aqueous solutions of potassium chloride are effective potassium supplements when taken as prescribed; however, because of an unpleasant taste due to the chloride ion, patient compliance during long-term therapy has been a problem. More palatable forms of potassium salts, such as the gluconate or mixtures of bicarbonate, citrate, and acetate, are available, but the chloride ion has been shown to be a prerequisite for effective treatment (1).

BACKGROUND

A new, slow-release potassium chloride preparation containing 600 mg (8 mEq) of potassium chloride[1] in the form of small, nearly spherical beads enclosed in a hard gelatin capsule was developed to avoid or minimize a high localized concentration of potassium within the GI tract. The potassium chloride crystals are specially coated to permit a uniform, controlled *in vivo* release over 8–10 hr. Extensive toxicity testing in animals was carried out to compare the new capsule preparation with a marketed wax-matrix tablet[2]. The results indicated a marked difference in the ulcerogenic potential of the tablet and capsule dosage forms (2). Based on the animal toxicity data, it was concluded that the new capsule dosage form is not likely to cause local irritation of the GI mucosa.

Certain pharmacokinetic characteristics of potassium make accurate determination of bioavailability difficult. Up to 98% of the physiological potassium in humans is distributed within the intracellular space. The major elimination pathway of potassium is *via* urinary excretion; the secondary elimination pathway is *via* the feces and perspiration. Bioavailability estimates derived from serum potassium levels are inaccurate because of the homeostatic mechanisms that maintain serum potassium levels within a relatively narrow range (3).

Attempts to determine the bioavailability of potassium preparations by measuring urinary potassium levels have been reported (4–6). To achieve any success, the bioavailability study must be conducted where there can be careful control of the diet, fluid intake, physical activity, and urine collection. Fixed menus with a known potassium content should be given throughout the study. Strenuous exercises that might cause

Table I—Cumulative Potassium Recovery from 12 Subjects after 24 hr

Subject	Mean[a] Control Potassium Level, mEq	Net Increase in Urine Potassium in 24 hr, mEq		
		Elixir	Capsule	Tablet
1	51.0 ± 7.3	46.6	22.0	49.1
2	47.9 ± 6.1	48.4	38.3	55.4
3	52.9 ± 8.2	43.3	40.1	53.8
4	61.7 ± 5.6	51.0	37.2	61.6
5	66.7 ± 6.3	42.1	31.0	65.1
6	52.9 ± 4.1	52.5	39.0	52.1
7	45.8 ± 10.1	56.0	42.4	45.3
8	41.6 ± 12.0	50.6	61.0	41.6
9	64.2 ± 1.3	12.3	38.7	42.9
10	48.8 ± 3.2	37.3	32.9	42.6
11	52.2 ± 12.8	37.6	62.5	44.8
12	54.1 ± 5.9	39.2	42.2	51.9
Mean ± *SD*	53.3 ± 7.5	43.1 ± 11.4	40.6 ± 11.4	50.5 ± 7.6

[a] Average of 3 control days (Days 0, 4, and 8).

[1] Berlex Laboratories Inc., Cedar Knolls, N.J.

[2] Slow-K, Ciba Pharmaceutical Co., Summit, N.J.

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Table II—Cumulative Potassium Excretion (Milliequivalents) per Time Period for Each of 12 Subjects [a]

Interval, hr	Subject 1	2	3	4	5	6	7	8	9	10	11	12	Mean ± *SD*
Elixir													
0–6	9.7	17.8	11.2	7.9	12.1	11.3	9.2	21.0	2.9	14.6	2.3	13.2	11.1 ± 5.4
6–12	16.7	10.3	14.2	9.1	16.0	17.5	12.0	11.2	7.8	10.7	19.8	6.3	12.6 ± 4.2
12–24	20.1	20.3	17.9	34.0	13.9	23.7	34.8	18.4	1.6	12.0	15.5	19.7	19.3 ± 9.0
Total	46.5	48.4	43.3	51.0	42.0	52.5	56.0	50.6	12.3	37.3	37.6	39.2	43.0 ± 11.4
Capsule													
0–6	8.2	25.5	16.0	6.3	9.1	12.4	0.2	28.5	13.0	11.5	19.3	12.2	13.6 ± 7.9
6–12	7.5	9.7	11.1	19.8	12.9	21.6	32.2	32.5	17.7	11.3	26.6	16.3	18.3 ± 8.2
12–24	3.9	3.1	13.0	11.1	9.0	5.3	10.8	0.0	8.0	10.1	16.0	13.7	8.7 ± 4.8
Total	19.6	38.3	40.1	37.2	31.0	39.3	43.2	61.0	38.7	32.9	61.9	42.2	40.6 ± 11.4
Tablet													
0–6	25.0	37.2	33.8	41.3	29.5	28.9	30.5	24.9	19.4	21.3	29.3	39.8	30.1 ± 7.0
6–12	13.8	7.8	13.2	11.9	18.9	16.1	12.5	16.7	11.8	11.9	15.5	8.4	13.2 ± 3.3
12–24	10.3	10.4	6.8	8.4	16.7	7.1	2.3	0.0	11.7	9.4	0.0	3.7	7.2 ± 5.0
Total	49.1	55.4	53.8	61.6	65.1	52.1	45.3	41.6	42.9	42.6	44.8	51.9	50.5 ± 7.6

[a] After correcting for control values for each urine collection period.

excessive perspiration, and thus loss of electrolytes, should be avoided.

The following three-way crossover study was designed to determine the bioavailability and pharmacokinetics of potassium chloride sustained-release capsules by urinary potassium excretion in volunteers maintained in a cloistered environment.

EXPERIMENTAL

Twelve healthy male volunteers, 19–55 years (mean 31 years) and weighing within ±10% of the ideal weight for their height and frame (7), participated in the study. Informed consent was obtained. The subjects were examined and found to have no hepatic, renal, or cardiovascular disease or history of GI disorders due to peptic or duodenal ulcer. Routine laboratory determinations, 12-lead ECGs, and physical examinations were conducted before admission to the study center[3].

The subjects remained in the study center under the supervision of the medical and nursing staff throughout the 15-day study. To avoid salt and water loss through perspiration, the subjects stayed indoors in air-conditioned rooms from 9:00 am to 4:30 pm every day and did not engage in strenuous exercise.

The first 3 days after admission (Days −3, −2, and −1) were diet-adaptation days. Day 0 was the control day for the treatment on Day 1. After two rest days (Days 2 and 3), a second control day (Day 4) was observed and then was followed by the second treatment on Day 5. Days 6 and 7 were rest days, followed by the third control day (Day 8) and the final treatment on Day 9. On Day 12, 3 days after the final treatment, the subjects were released from the center.

The three potassium chloride products, capsules[4], elixir[5], and tablets[6], were administered in a randomly assigned fashion in an open-label, three-way crossover treatment. The total dose of elixir, equivalent to 80 mEq of potassium, was divided into three 26.6-mEq doses administered at 6-hr intervals. The capsules and tablets were administered as single doses, each consisting of 80 mEq of potassium (10 capsules and 10 tablets, respectively). On the three treatment days (Days 1, 5, and 9), each subject received one of the three treatments after an 8-hr fast.

All urine voided on Days −3–+11 was collected. On the control days (Days 0, 4, and 8) and treatment days (Days 1, 5, and 9), urine was collected hourly for 16 hr beginning at 6:00 am. On the other days, urine was collected every 4 hr for 16 hr. A 16–24-hr collection was made on the control days as well as on the treatment days. The volume of each collection was recorded, and a sample was analyzed for its potassium and creatinine concentration. Urine potassium was determined by flame photometry (8). The assay sensitivity was ±0.1 mEq/liter. Creatinine was determined by the alkaline picrate method (9). Stool guaiac tests were performed on all feces to determine any loss of blood.

The subjects were required to drink 5200 ml of fluid each day. They received a uniform diet containing an average of 100 mEq of potassium, 340 mEq of sodium, and 4920 cal/day. No additional food or snacks were permitted. Meals were served at 7:00 am, 12:30 pm, 5:00 pm, and 10:00 pm. Drugs were administered, and 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 untoward effect, however trivial it might appear to them. During morning, afternoon, and evening rounds, drug effects and general health problems were discussed with every subject.

[3] Quincy Research Center, Kansas City, Mo.
[4] Potassium Chloride SR Capsules (lot L-7717), Berlex Laboratories Inc.
[5] Kay Ciel Elixir (lot w60920), Berlex Laboratories Inc., Cedar Knolls, N.J.
[6] Slow-K (lot 1670), Ciba Pharmaceutical Co., Summit, N.J.

RESULTS AND DISCUSSION

Changes in the urine potassium levels for each collection were determined by first averaging the urine potassium levels for the three predosing control days for each subject and then subtracting these values from the corresponding urine potassium levels of the treatment day. Each subject's cumulative urine levels for 24 hr on the control days and treatment days are listed in Table I. The mean control value for 12 subjects was 59.0 mEq. The mean increase in the 24-hr potassium level was 43.1 mEq for the elixir, 40.6 mEq for the capsule, and 50.5 mEq for the tablet. These values correspond to 53.9% recovery from the 80-mEq dose administered for the elixir, 50.8% for the potassium chloride sustained-release capsule, and 63.1% for the tablet.

The 24-hr urine collection data were divided into three fractions to determine the potassium elimination patterns of the capsule and tablet in comparison to the elixir. The results (Table II) indicate that the elixir, which was administered every 6 hr, showed eliminations of 11.1 mEq in 0–6 hr, 12.6 mEq from 6 to 12 hr, and 19.3 mEq from 12 to 24 hr. The corresponding figures for the capsule were 13.6, 18.3, and 8.7 mEq, respectively, indicating slow and sustained release of potassium. In contrast, the tablet showed eliminations of 30.1 mEq in 0–6 hr, 13.2 mEq from 6 to 12 hr, and 7.2 mEq from 12 to 24 hr. Sixty percent of the total potassium eliminated from the tablet was eliminated in the first 6 hr, compared to 33.5% for the capsule.

The mean maximum excretion rate and the time for the maximum excretion rate were calculated for each dosage form. The excretion rate maximum was 6.1 mEq/hr (average of three doses) for the elixir, 8.1 mEq/hr for the capsule, and 10.1 mEq/hr for the tablet (Table III). The mean time for the maximum excretion rate was 2.0 hr for the elixir (average of three doses), 6.8 hr for the capsule, and 4.0 hr for the tablet. The capsule showed a slow excretion rate, characteristic for a sustained-release

Table III—Potassium Excretion Kinetics

	Elixir First Dose	Elixir Second Dose	Elixir Third Dose	Capsule	Tablet
Mean maximum excretion rate ± *SD*, mEq/hr	6.2 ± 2.9	5.1 ± 1.9	6.9 ± 3.1	8.1 ± 4.0	10.1 ± 3.0
Mean time of maximum excretion rate ± *SD*, hr	1.8 ± 1.1	1.9 ± 1.1	2.3 ± 0.8	6.8 ± 3.0	4.0 ± 2.5

[a] Excretion rate (mEq/hr) = [urine potassium (mEq) − mean control urine potassium (mEq) for urine collection period]/urine collection period (hr).

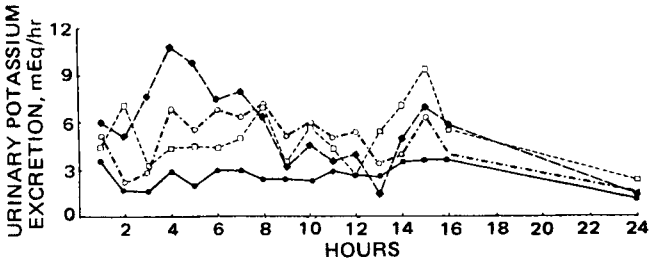

Figure 1—*Mean urinary potassium excretion rate before and after administration of 80-mEq oral doses of potassium chloride as slow-release capsules, elixir, and tablets in 12 subjects. Data for dosage forms were corrected for the mean potassium excretion during each collection period on the control days. Key: – • – O • –, capsules; - - □ - -, elixir; – – ■ – –, tablets; and —●—, control (mean of 3 control days).*

product, and reached a maximum much later than the immediately available elixir dosage form. The tablet also showed delayed release; however, the time for the maximum excretion rate was considerably shorter than for the capsule. The excretion rate curve of each product is shown in Fig. 1. Urine creatinine values for all subjects were within the normal range. Stool guaiac tests were negative for all subjects.

A Friedman two-way analysis of variance nonparametric, K-sample, related-measures test was significant at the 0.05 level, and differences in potassium excretion between the various formulations for each time interval were analyzed further using Wilcoxon's matched-pairs signed-ranks procedure (one tailed) (Table IV). For the mean 24-hr cumulative potassium recovery, both the elixir and the capsule were significantly lower than the tablet but were not significantly different from each other. This also was true for the early period of potassium excretion (0–6 hr), where the mean potassium level from the tablet was almost triple that of the other two formulations. During the 6–12-hr period, both the elixir and tablet means were significantly lower than the capsule mean; in the 12–24-hr period, both the capsule and the tablet gave significantly lower values than the elixir.

There also were significant differences between the mean potassium excretion between the time intervals for each formulation. For tablets, the greatest excretion occurred during the first 6 hr, and each succeeding interval featured significantly less excretion than its predecessor. For capsules and the elixir, the 12–24-hr period was significantly different from the two earlier periods.

Because of the complexity of potassium distribution and elimination kinetics in humans, the comparatively low recoveries seen in this study are not surprising. In another well-controlled crossover study with strict management of the diet, exercise, and fluid intake, only 27.4% of the potassium was recovered from the tablet[2] compared to 59.7% from a 10% solution of potassium chloride (4).

In a study of subjects receiving an effervescent tablet form of potassium chloride, only 46.4% of the potassium was recovered from the urine (5). Higher recoveries of potassium from urine have been reported (10, 11). However, these results are questionable because the controls seemed to be inadequate.

Despite the fact that 10 potassium chloride sustained-release capsules were administered as a single dose, there were no serious adverse reactions in any of the 12 subjects. Subject 1 complained of diarrhea from 2 to 10 hr after receiving the dose. A similar dose of the tablets elicited complaints of stomach pains starting 20 min after the dose and lasting for ~1 hr in Subjects 1, 3, and 9. Abdominal cramps and nausea lasting ~1 hr were reported by Subject 7 who received the tablets. The elixir produced nausea in Subject 10 30 min after the second dose of 26.6 mEq, and Subject 1 vomited 45 min after the second dose. Thus, of the seven complaints, four were related to the tablet, two to the elixir, and one to the capsule.

Table IV—Differences in Cumulative Potassium Excretion for Three Formulations

Formulation	Interval			
	0–6 hr	6–12 hr	12–24 hr	0–24 hr
Elixir – capsule	NS[a]	0.05	0.05	NS
Elixir – tablet	0.05	NS	0.05	0.05
Capsule – tablet	0.05	0.05	NS	0.05

[a] Not significant.

CONCLUSION

The results of this study show that the new potassium chloride slow-release capsule dosage form is equal in bioavailability to a 10% solution of potassium chloride. When tested in a three-way crossover study in 12 normal, healthy male volunteers, the rate of elimination, and thereby the rate of absorption, of potassium chloride sustained-release capsules were slower and more uniform than for the tablets or the elixir. The two slow-release products produced prolonged potassium levels after administration of a single dose. The potassium chloride sustained-release capsule was well tolerated, even though the subjects were given an unusually high single dose of 10 capsules, equivalent to 80 mEq of potassium.

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