Pharmacokinetics of potassium chloride in wax-based and syrup formulations

J. M. TONER & L. E. RAMSAY

University Department of Therapeutics, Royal Hallamshire Hospital, Sheffield, UK

1 The effect on plasma potassium of 64 mmol potassium chloride (KCl) in two oral formulations was compared against placebo in five healthy men, and their bioavailability was calculated from urinary data.

2 Mean plasma potassium varied between 4.0–4.6 mmol/l during the placebo phase and mean (s.d.) urinary potassium excretion was 84.4 (18.5) mmol over 36 h.

3 KCl syrup produced a significant change in plasma potassium over 24 h ($P < 0.02$) with a marked elevation in the first 3 h after dosing and a mean (s.d.) peak plasma potassium 1.72 (0.52) mmol/l higher than placebo ($P < 0.05$). By 36 h an excess of 55.9 (23.9) mmol potassium, equivalent to 87.3% of the stated dose, was excreted in the urine.

4 KCl in wax base had a less consistent effect on plasma potassium ($P > 0.5$) and its effect was no more prolonged. The mean peak increment in plasma potassium was 1.03 (0.42) mmol/l ($P < 0.01$) and the total potassium excretion was 50.5 (17.7) mmol higher than placebo values giving a bioavailability of 78.8% calculated from the stated dose.

Keywords potassium chloride pharmacokinetics

Introduction

The thiazide and loop diuretics invariably cause some disturbance of potassium homeostasis and it is common practice to prescribe potassium chloride simultaneously aiming to counteract this (Ramsay *et al.*, 1977). The usual daily dose averages 18 mmol potassium (Ramsay *et al.*, 1977) and it is generally given as a single daily dose (combined with diuretic), or twice daily. This pattern of prescribing is a carryover from the early years of diuretic use when it was thought that diuretics caused 'potassium depletion' and that potassium supplements would prevent or repair the 'deficit'. It is now known that whereas hypokalaemia is common, occurring for example in 19% of patients taking a thiazide diuretic (Toner & Ramsay, 1984), long-term diuretic treatment is not usually associated with an important deficit of total body potassium. This is true both in hypertension (Wilkinson *et al.*, 1975) and in heart failure (Davidson *et al.*, 1976).

Hypokalaemia is undoubtedly important in some patients, for example those taking digoxin or antiarrhythmic drugs, as it may predispose to cardiac arrhythmias (Steiness & Olesen, 1976), but it is a matter of debate whether mild or moderate diuretic-induced hypokalaemia presents a hazard to the uncomplicated patient (Poole-Wilson, 1983; Ramsay & Toner, 1984). Whatever the truth may be, potassium chloride supplements are widely prescribed primarily to prevent cardiac arrhythmias. In this context it is the ratio of extracellular potassium to intracellular potassium (K_e/K_i) which is thought important (Poole-Wilson, 1981). Therefore to abolish the supposed risk of cardiac arrhythmias the plasma potassium, and thus the K_e/K_i ratio, should presumably be maintained relatively constant. Potassium chloride supplements are relatively inefficient in correcting hypokalaemia, even at high doses (Ramsay *et al.*, 1980; Jackson *et al.*,

1982). Furthermore it is not known whether any change in plasma potassium is maintained throughout the usual dose interval of 12 or 24 h, as the time-course of changes in plasma potassium concentration after therapeutic doses of potassium chloride has not been reported, although the drug has been used in various formulations for many years.

We have examined the time-course of changes in plasma potassium concentration in healthy men after single doses of potassium chloride. The aims were firstly to determine whether measurable changes could be observed with an acceptable dose of potassium chloride, and secondly to compare two formulations of potassium chloride; a wax-based tablet (Slow-K, Ciba) and a syrup preparation (Kay-Cee-L, Geistlich).

Methods

Five healthy men aged 23–35 years were studied on four occasions, each of 36 h duration and separated by at least 1 week. In each phase the subjects fasted overnight and then drank 120 ml water hourly for 3 h before and for the first 12 h after treatment to ensure adequate urine flow. Coffee, tea and ethanol were prohibited during study periods. Subjects remained fasting until 2 h after treatment and then followed a diet which each selected himself and then reproduced on subsequent study days.

At 10.00 h subjects were given placebo (water alone); 64 mmol potassium chloride as a sugar-free syrup (1 mmol/ml, Kay-Cee-L, Geistlich); or 64 mmol potassium chloride in sugar-coated wax-based tablets (8 mmol/tablet, Slow-K, Ciba); in random order in three study phases. A second, non-random placebo phase was included to assess the reproducibility of the study conditions. Venous blood was drawn without forearm exercise and whenever possible without using a tourniquet, at intervals over 24 h (Figure 1) and all urine was collected for 36 h, in four 2 h fractions, a 4 h fraction and then a 24 h fraction.

The protocol was approved by the hospital ethics committee and all subjects gave their informed consent

Plasma and urinary potassium were measured by flame photometry against an internal lithium standard. Inter-assay and intra-assay coefficients of variation were together less than 4%.

Six plasma samples were not obtained for technical reasons and the missing values were estimated by taking the mean of the results of the two adjacent sampling points. Area under the curve (AUC) was calculated by linear summation of trapezoids. Results were analysed by Friedman two-way analysis of variance (Siegel, 1956) with paired comparisons by Student's *t*-test because of the small number of subjects.

Results

Plasma and urinary potassium after placebo

The plasma potassium concentration varied significantly and unpredictably over time after placebo treatment ($\chi^2_r = 22.8$, $P < 0.05$, Figure 1) with mean (and standard deviation) values ranging from 4.55 (0.23) mmol/l at 1 h, to 3.97 (0.29) mmol/l at 10 h. The time course of changes in plasma potassium in the second, non-random, placebo phase was not significantly different ($\chi^2_r = 16.7$, $P > 0.2$). Urinary potassium also varied with time ($\chi^2_r = 12.1$, $P < 0.05$, Figure 3), the hourly rate ranging from 7.60 (2.63) mmol between 0 and 2 h, to 1.95 (0.35) mmol from 12 to 36 h. The total 36 h potassium excretion was 84.4 (18.5) mmol in the random placebo phase and 93.9 (24.9) mmol in the non-random placebo phase ($P > 0.05$).

Potassium chloride syrup

Compared to the placebo phase, the mean plasma potassium concentration was higher at every time point until 10 h, and the overall pattern differed significantly ($\chi^2_r = 27.3$, $P < 0.02$,

Figure 1 Mean (and s.d.) plasma potassium concentration during placebo phase:

Figure 2). The mean peak plasma potassium was 1.72 (0.52) mmol/l higher than placebo ($P < 0.05$) at 5.79 (0.52) mmol/l. The pattern of urinary potassium excretion over time also differed from placebo ($\chi^2 = 18.8$, $P < 0.01$, Figure 3), with peak excretion rates 0–4 h after dosing. The total potassium excretion over 36 h was 55.9 (23.9) mmol higher than the placebo values, giving a bioavailability of 87.3% calculated from the stated dose of 64 mmol.

Wax-based potassium chloride

Changes in plasma potassium from placebo values were less consistent than after the syrup (Figure 2) and the overall difference from placebo was not significant ($\chi^2 = 14.3$, $P > 0.5$). However the mean peak plasma potassium was significantly higher than placebo, by 1.03 (0.42) mmol/l, and urinary potassium excretion was increased significantly between 2–4 and 6–36 h

(Figure 3). Over 36 h, an excess of 50.5 (17.7) mmol of potassium, equivalent to 78.8% of the stated dose, had been excreted in the urine.

Comparison of syrup and wax-based formulations

The pattern of the plasma potassium concentration-time curves differed for the two formulations (Figure 2) and this approached significance ($\chi^2 = 22.3$, $P < 0.1$). In the first three hours after treatment the average plasma potassium was higher after the syrup than after the wax-based tablets ($P < 0.05$), but beyond this there was little difference between the formulations. The peak increase in plasma potassium and the AUC to 24 h were higher for the syrup and the time to peak was shorter, but these differences were not significant (Table 1). The time-course of urinary potassium excretion was also significantly different (Figure 4, $\chi^2 = 19.3$, $P < 0.01$) with higher excretion after the syrup between 0–4 h

Figure 2 Mean (and s.d.) change in plasma potassium from placebo after 64 mmol KCl as syrup (Δ) and in wax base ($\blacksquare$).

Figure 3 Mean (and s.d.) 2 hourly urinary potassium excretion during placebo phase and after 64 mmol KCl as syrup and in wax base. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$ vs placebo.

Table 1 Comparison of potassium chloride formulations in five healthy subjects

<i>Plasma potassium</i>	<i>Syrup</i>	<i>Wax-base</i>
Mean (s.d.) peak increment (mmol/l)	1.72 (0.52)	1.03 (0.42)
Median (range) time to peak (min)	60 (30–120)	120 (30–1440)
Mean (s.d.) AUC (mmol ⁻¹ min)	161 (248)	103 (276)
<i>Urine potassium</i>		
Mean (s.d.) increment (36 h, mmol)	55.9 (23.9)	50.5 (17.7)
Mean (range) bioavailability* (%)	99.3 (35.0–132.8)	88.3 (29.9–95.5)

(* – calculated from dose; 64 mmol)

Figure 4 Mean (and s.d.) change in potassium excretion from placebo after 64 mmol KCl as syrup (□) and in wax base (▨) **P* < 0.02, ***P* < 0.01 vs wax base.

from dosing. Beyond this urinary potassium was higher with the wax-based preparation so that total 36 h excretions were similar for the two formulations (Table 1).

Side-effects

The placebo and wax based phases were associated with minor headache, but were generally well tolerated. Potassium chloride syrup was found unpalatable and caused some nausea, epigastric burning and looseness of motion, bordering on diarrhoea.

Discussion

Previous studies of the bioavailability of potassium chloride have generally only examined urinary

potassium excretion and have shown complete absorption from solution (Ben-Ishay & Engleman, 1973) and from a wax base (Wynn, 1965; Ben-Ishay & Engleman, 1973), with a difference in the time course of potassium excretion following the two formulations (Ben-Ishay & Engleman, 1973; Levine, 1973). Our results are similar with bioavailabilities, calculated from the stated dose, of 87% and 79% respectively for the syrup and wax-based formulations and an earlier peak potassium excretion after the syrup.

Such studies would be sufficient if potassium chloride was prescribed simply to prevent or correct potassium depletion. However as discussed in the introduction, the aim of treatment is to maintain a normal plasma potassium and K_e/K_o ratio throughout the 24 h period. Otherwise some patients, for example those taking digoxin,

will presumably remain at risk of serious arrhythmias. It follows that the time-course of changes in plasma potassium after treatment with potassium chloride needs to be examined.

Brown *et al.* (1951) gave 200 mmol potassium in solution as chloride and citrate to six subjects, and reported a peak rise in serum potassium of 1.28 mmol/l. Gonick *et al.* (1971) gave potassium chloride in solution at a dose of 0.75 mmol/kg to 19 volunteers and showed a peak rise in plasma potassium of 1.0 (0.3) mmol/l. However in both studies the changes in potassium concentration were measured from baseline values, thus ignoring the possibility of spontaneous variation over time. The placebo phases of the present study show that there is indeed considerable variability of plasma potassium, with the mean values ranging from 4.0 to 4.6 mmol/l. These fluctuations presumably result from potassium intake at meals, physical activity and circadian potassium fluxes (Moore Ede *et al.*, 1975). By including a second non-random placebo phase in the present study we were able to show that the pattern of change was acceptably reproducible. In view of this variability it is evidently necessary to compare changes in plasma potassium after potassium chloride with those after placebo treatment, and to our knowledge this has never been done. It is also necessary to use rather a high dose of potassium chloride (64 mmol), and unfortunately this proved unpalatable in the syrup formulation. We had in fact planned to study a larger sample of subjects but additional volunteers proved rather elusive.

After potassium chloride in syrup form the plasma potassium was clearly and significantly different from placebo values. However elevation of the plasma potassium was largely confined to the first 3 h after dosing and the major part of the dose was excreted in the urine within 4 h. This formulation of potassium chloride is thus unlikely to maintain a reasonably constant plasma potassium unless it is given at short dosing intervals.

Wax-based potassium chloride formulations are by far the most widely used and are generally

prescribed to be taken once or twice daily. In this study the effect of a single dose of 64 mmol on plasma potassium was erratic, although there was a significant effect, as shown by a peak concentration higher than that during the placebo phase. It is surprising to note that there was little discernible effect on plasma potassium beyond 3 h after dosing (Figure 2) despite the delay in urinary potassium excretion when compared to the syrup (Figure 4). When the effect of a single large dose is so small and inconsistent it is difficult to envisage how the much smaller doses used in ordinary practice (8–16 mmol per day) can have any useful effect on the plasma potassium.

This type of study clearly needs to be performed in patients taking diuretics and long-term potassium chloride treatment. However, it is of interest that patients taking a thiazide diuretic, and given 64 mmol potassium chloride daily, had increases in plasma potassium averaging 0.44 mmol/l (Ramsay *et al.*, 1980) and 0.28 mmol/l (Jackson *et al.*, 1982). These responses are of the same order as those observed in the present study and we believe that our single-dose findings are likely to be relevant to long term treatment.

It might be argued that potassium chloride treatment may increase the intracellular potassium during chronic therapy. This is unlikely, as there does not appear to be a deficit of total body potassium (and therefore intracellular potassium) during long term treatment of hypertension (Wilkinson *et al.*, 1975) or heart failure (Davidson *et al.*, 1976). Even if the intracellular potassium did increase the response would be unsatisfactory. Elevation of the intracellular potassium without correction of the plasma (extracellular) potassium would result in a low K_e/K_i ratio and might leave susceptible patients at risk of arrhythmias (Poole-Wilson, 1981).

G. D. Searle Pharmaceuticals provided financial support to J. M. T.

References

- Ben-Ishay, M. D. & Engleman, K. (1973). Bioavailability of potassium from a slow-release tablet. *Clin. Pharmac. Ther.*, **14**, 250–258.
- Davidson, C., Burkinshaw, L., McLachlan, M. S. F. & Morgan, D. B. (1976). Effect of long term diuretic treatment on body potassium in heart disease. *Lancet*, **ii**, 1044–1048.
- Gonick, H. C., Kleeman, C. R., Rubini, M. E. & Maxwell, M. H. (1971). Functional impairment in chronic renal disease. III Studies of potassium excretion. *Am. J. med. Sci.*, **261**, 281–290.
- Jackson, P. R., Ramsay, L. E. & Wakefield, V. (1982). Relative potency of spironolactone, triamterene and potassium chloride in thiazide-induced

- hypokalaemia. *Br. J. clin. Pharmac.*, **14**, 257–263.
- Levine, D. L. (1973). The absorption of potassium chloride – liquid vs tablet. *Can. med. Ass. J.*, **108**, 1480–1481.
- Moore Ede, M. C., Brennan, M. F. & Ball, M. R. (1975). Circadian variation of intercompartmental potassium fluxes in man. *J. appl. Physiol.*, **38**, 163–170.
- Poole-Wilson, P. A. (1981). The myocardial cell membrane; the effects of diuretics In *Arrhythmias and myocardial infarction, the role of potassium*, eds. Wood, C. & Sommerville, W. R., pp 9–16. Roy. Soc. Med. Congr. symp. Series Number 44. London: Royal Society of Medicine.
- Poole-Wilson, P. A. (1983). Hypokalaemia induced by thiazide diuretics in the treatment of hypertension: a cause for concern, not nihilism. *Postgrad. med. J.*, **59**, suppl 3, 137–139.
- Ramsay, L. E., Boyle, P. & Ramsay, M. H. (1977). Factors influencing serum potassium in treated hypertension, *Quart. J. Med.*, **46**, 401–410.
- Ramsay, L. E., Hettiarachichi, J., Fraser, R. & Morton, J. J. (1980). Amiloride, spironolactone and potassium chloride in thiazide treated hypertensive patients *Clin. Pharmac. Ther.*, **27**, 533–543.
- Ramsay, L. E. & Toner, J. M. (1984). Is diuretic-induced hypokalaemia dangerous? – the case against. Roy. Soc. Med. Congr. symp. (in press). London: Royal Society of Medicine.
- Siegel, S. (1956). In *Non-parametric Statistics for the behavioral sciences* New York: McGraw-Hill.
- Steiness, E. & Olesen, K. H. (1976). Cardiac arrhythmias induced by hypokalaemia and potassium loss during maintenance digoxin therapy *Br. Heart J.*, **38**, 167–172.
- Toner, J. M. & Ramsay, L. E. (1984). Thiazide-induced hypokalaemia; prevalence higher in women *Br. J. clin. Pharmac.*, **18**, 449–452.
- Wilkinson, P. R., Issler, H., Hesp, R. & Raftery, E. B. (1975). Total body and serum potassium during prolonged thiazide therapy for essential hypertension. *Lancet*, **i**, 759–762.
- Wynn, V. (1965). Potassium chloride and intestinal ulceration. *Lancet*, **ii**, 1241.

(Received October 1, 1984,
accepted December 9, 1984)