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EFFECTS OF INTRAVENOUS INFUSION OF POTASSIUM CHLORIDE ON POTASSIUM AND SODIUM EXCRETION AND ON THE RATE OF URINE FORMATION IN THE COW

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The normal diet of cattle, compared with that of man and the dog, is high in potassium and low in sodium content (Morrison, 1951). Spector (1956) quotes figures for daily urinary outputs which reflect these differences in dietary composition. Renal mechanisms promoting the excretion of potassium and the conservation of sodium are presumably more active in the cow than in man and the dog.

When potassium salts are infused intravenously into dogs, renal tubular secretion of potassium is demonstrated by the plasma clearance of potassium rising and exceeding the glomerular filtration rate (Mudge, Ames, Foulks & Gilman, 1950; Berliner, Kennedy & Hilton, 1950). These authors agree that this response occurs readily only after a supplement of a potassium salt has been fed over a period preceding the intravenous infusion, and this dietary supplementation is said to lead to the development of a state of potassium tolerance (Berliner *et al.* 1950). These authors also conclude that potassium secreted by the renal tubules probably reaches the urine by a process involving cation exchange with sodium.

The work to be described was undertaken to determine whether the renal response of the cow to intravenous infusion of a potassium salt resembles that reported for man and the dog, in view of the differences in the electrolyte content of the diet. A preliminary report has already been published (Anderson & Pickering, 1962).

METHODS

Experimental subjects. Urine samples for comparison of sodium and potassium concentrations were collected during micturition from male student volunteers and from cows of the dairy herd of the veterinary school farm. The animals were healthy and in various stages of pregnancy and/or lactation. They were under an indoor system of management, fed on turnips, silage and hay for maintenance requirements, with concentrates according to milk yield.

Clearance experiments were carried out repeatedly on three adult, non-pregnant, non-lactating, Ayrshire cows, fully conscious and confined in stocks. These animals were at grass for approximately half the period during which the work was carried out, but were kept indoors for the remainder. When housed these animals were fed on hay (20–30 lb., 9·1–13·6 kg, daily) and concentrates (7 lb., 3·2 kg, daily). All animals were allowed water *ad libitum*.

Clearance procedure. Under local anaesthesia produced by the subcutaneous injection of 6 ml. of 2 % procaine hydrochloride solution (May and Baker, Planocaine) a catheter 15–18 cm long (Portland Plastics, Ltd., no. 4 nylon tubing) was introduced into each jugular vein, 5–10 cm from the angle of the jaw. One catheter was used subsequently for the infusion of solutions and the other for blood sampling. Urine was collected continuously under epidural anaesthesia by means of an indwelling urethral catheter. A description of the urine-collection technique is given elsewhere (Anderson & Pickering, 1961).

The animals were fully accustomed to the experimental procedure. They stood quietly, ruminated frequently, and showed no sign of discomfort during infusion or sampling.

Before infusion was begun a blood sample was taken for plasma blank estimation of inulin. Inulin for infusion was dissolved in sterile NaCl solution, 0·9 g/100 ml., to a concentration of 5 g/100 ml. A priming dose of this solution (10 ml./100 lb.—45·4 kg—body wt.) was injected intravenously and infusion then begun, at 2·5 ml./min, by gravity feed from a 2 l. aspirator bottle fitted with an air inlet tube of constant height. The infusion was led through a Murphy drip tube, previously calibrated, and the rate regulated by adjustment of the outflow tap of the aspirator bottle. The rate of flow of drops was checked at regular intervals, but further adjustment of the outflow tap was rarely necessary.

In order to allow the plasma concentration and urinary excretion of inulin to stabilize, the first clearance period was not begun until 30 min after the start of inulin infusion. In these experiments plasma concentrations of inulin had stabilized within 15 min of the start of constant infusion, and it was assumed that inulin excretion had also stabilized 30 min after the start of the infusion. Poulsen (1957) suggests that the main portion of an excretory load following a single intravenous injection appears in the bladder after a delay of approximately twice the urinary appearance time of 2–3 min.

After one or two clearance periods when inulin was infused alone, intravenous infusion of potassium chloride was started and continued for up to 4 hr. Normal KCl, in solution in sterile water, was infused at a rate of 7–9 ml./min from an aspirator bottle, as described for the inulin infusion, and the rate was checked by measuring the residual volume at the end of the experiment. Clearance periods were of 15 min duration, blood samples being taken for estimation of plasma concentrations of inulin, sodium and potassium at the mid point of each period.

None of the animals used over a period of 6 months showed any ill effects from this repeated intravenous infusion of up to 2 l. of N-KCl. Electrocardiography during the early experiments did not show any cardiac abnormalities, as described by Bergman & Sellers (1954) in calves; but the rate of intravenous infusion of the potassium to these calves was, on a unit weight basis, considerably in excess of that used here.

Chemical estimations. All blood samples were taken into heparinized syringes, transferred immediately to 12·5 ml. centrifuge tubes and centrifuged at once, and the plasma separated.

Inulin estimations were carried out by the method described by Roe, Epstein & Goldstein (1949), with a Unicam 'S.P. 600' spectrophotometer. Urinary inulin estimations were made on samples of the collected volumes diluted to lie within the range of the reference standards. Sodium and potassium were estimated with an EEL flame photometer, mains coal gas and air being used. It was found necessary to maintain gas pressure constant at 3 in. (7·6 cm) of water by means of a Jeavons 'J 55' gas governor, and air pressure was maintained at 12 Lb./sq. in. (0·83 kg/cm^2). Analyses of freeze-dried serum of known composition (C. Davis Keeler), and recovery of known increments of potassium and sodium added to different urine samples with preservation of their millimolar ratio, indicated an average accuracy for these estimations of ± 1 %.

RESULTS

Comparison of potassium and sodium concentrations in bovine and human urine

Mean values of the potassium to sodium millimolar ratio in urine samples collected at midday from twenty male students and from twenty dairy cows were $0{\cdot}43 \pm 0{\cdot}21$ (S.D.; range 0·12–0·87) and $5{\cdot}39 \pm 4{\cdot}75$ (S.D.; range 1·65–20·8), respectively. This difference is statistically significant ($P < 0{\cdot}001$).

Responses of the cow to intravenous KCl

Plasma clearance of potassium. In eleven experiments plasma potassium concentrations rose 1–2 m-equiv/l. as a result of the infusion, but progressive increase in plasma potassium did not occur. The individual animals showed some variation but, in general, the increase in plasma concentration occurred within 2 hr of the onset of infusion and was sustained around this level for the duration of the experiment, as is shown in Fig. 1. At the same time the rate of excretion of potassium increased and within 2 hr of the onset of infusion the rate of excretion had risen to equal, approximately, the rate of administration (Fig. 2).

In all experiments potassium clearances rose to exceed inulin clearance values, giving ratios of potassium clearance to inulin clearance greater than unity and ranging as high as 2·0 towards the end of the infusion period (Fig. 3). Inulin clearance values were not affected by the infusion (Fig. 4).

Rate of urine flow and sodium excretion. The mean rate of urine flow before infusion in eleven experiments was $13{\cdot}26 \pm 5{\cdot}64$ (S.D.) ml./min. After starting infusion a marked increase in urine flow was noted in all experiments, but this diuresis was not sustained. In most experiments urine flow followed a distinct pattern, with a three- to sevenfold increase over the immediate pre-infusion rate occurring 1–2 hr after the onset of infusion (Fig. 5). The diuresis then declined gradually, but had not returned to pre-infusion values 4 hr after starting the infusion. Peak diuresis ranged from 312 to 777 % of the pre-infusion rate, with a mean peak diuresis for all experiments of 456 %.

In eleven experiments the mean rate of excretion of sodium in twenty clearance periods before potassium infusion was $1{\cdot}16 \pm 1{\cdot}41$ (S.D.; range 0·03–4·20) m-equiv/min. During infusion sodium excretion in every experiment increased, and reached peak values 1–2 hr after the start of infusion. Like the concomitant diuresis, these values then fell progressively but persisted above pre-infusion levels during 4 hr of infusion (Fig. 6). During this time no changes were noted in the plasma sodium concentration.

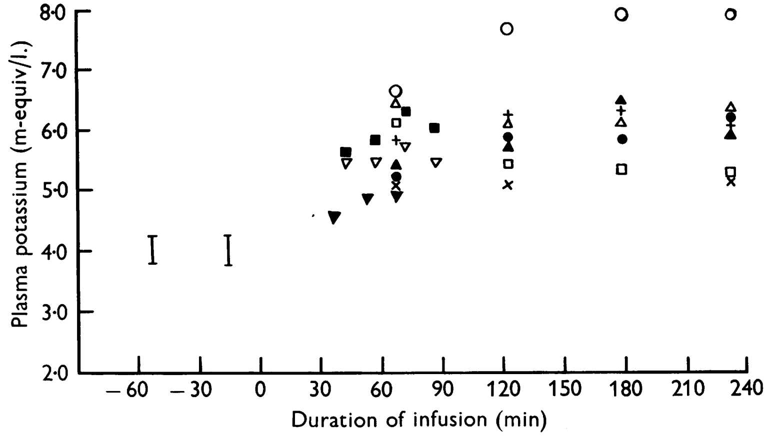

Fig. 1. The effect of intravenous infusion of N-KCl at rates of 7·0–9·0 ml./min on plasma potassium concentration. In all figures different symbols are plotted to distinguish individual experiments. Pre-infusion values in all experiments lie within the indicated range.

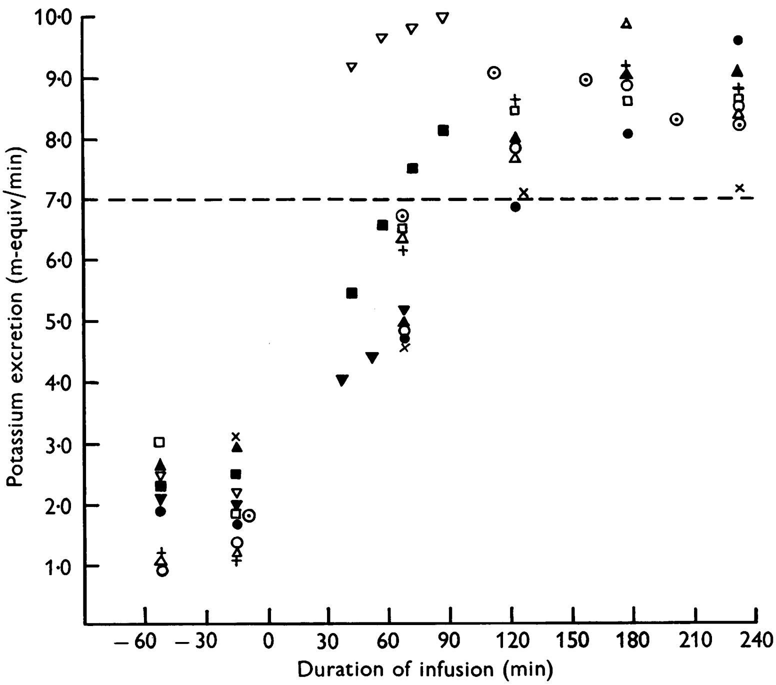

Fig. 2. The effect of intravenous infusion of N-KCl at rates of 7·0–9·0 ml./min on the rate of excretion of potassium. The horizontal interrupted line indicates a rate of excretion equal to the lowest rate of infusion.

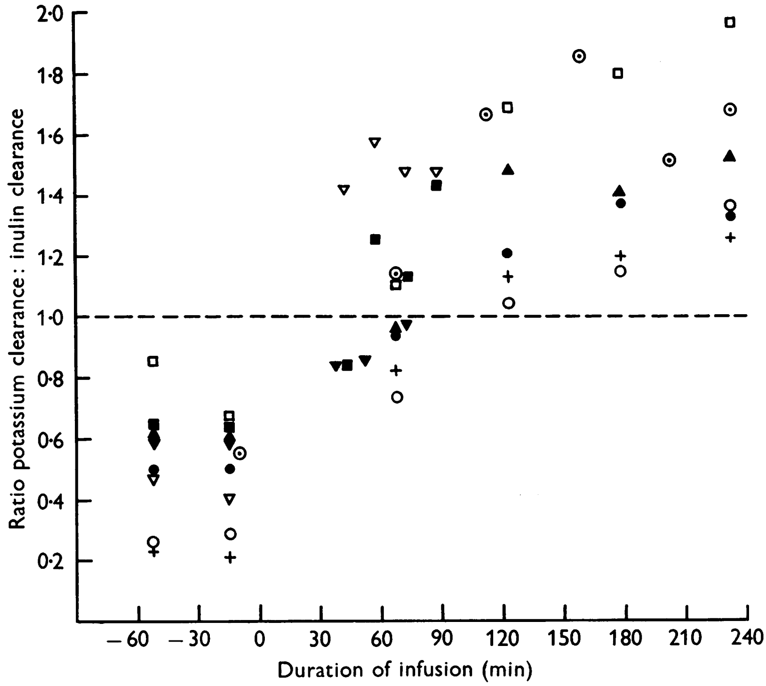

Fig. 3. The effect of intravenous infusion of N-KCl at rates of 7·0–9·0 ml./min on the ratio of potassium clearance to inulin clearance.

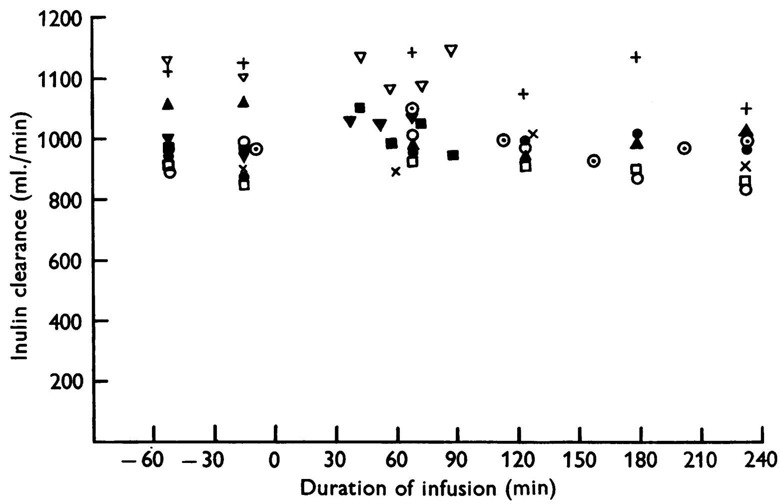

Fig. 4. Collected results showing inulin clearance values measured during intravenous infusion of N-KCl at rates of 7·0–9·0 ml./min.

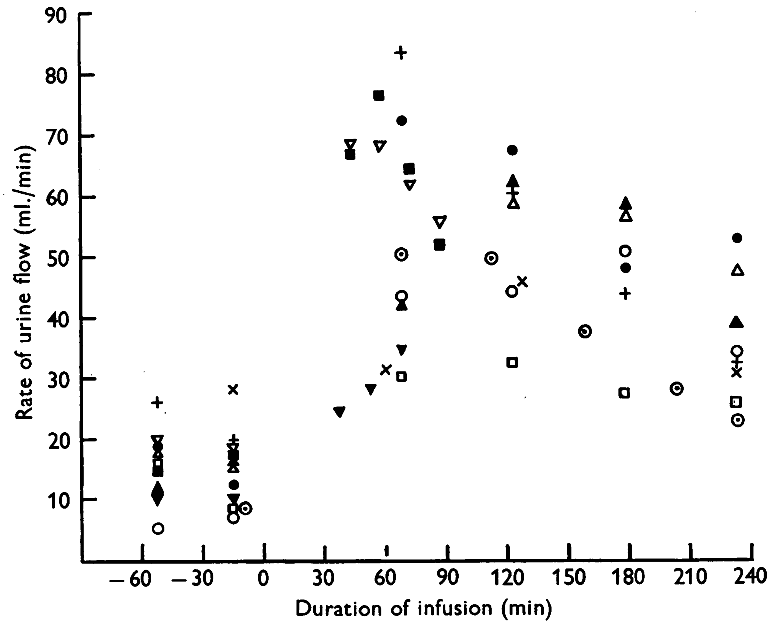

Fig. 5. The effect of intravenous infusion of N-KCl at rates of 7·0–9·0 ml./min on the rate of urine flow.

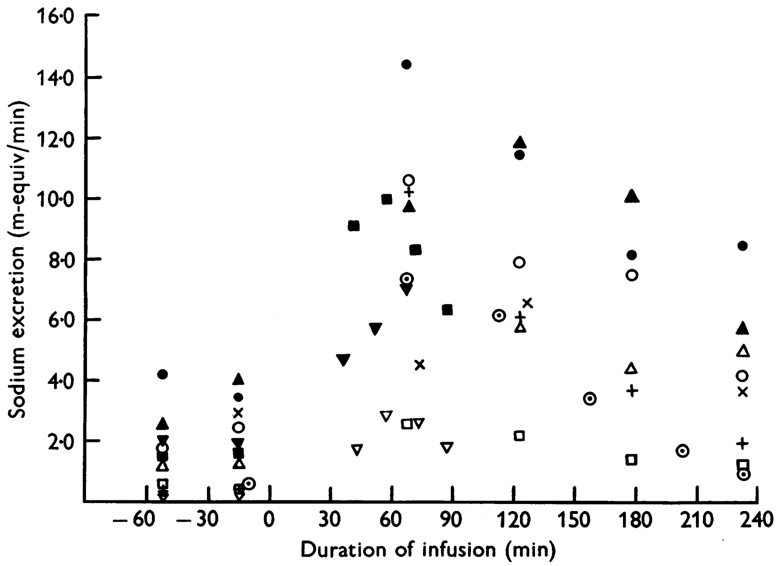

Fig. 6. The effect of intravenous infusion of N-KCl at rates of 7·0–9·0 ml./min on the rate of excretion of sodium.

Maximum increases in the rate of sodium excretion ranged from two to fifty times the pre-infusion figure, the larger percentage increases being noted for the lower pre-infusion rates of excretion.

DISCUSSION

The present work has shown that slow intravenous infusion of potassium chloride in the cow causes some rise in plasma concentration of potassium but no progressive rise with continuing infusion. In addition, the rate of potassium excretion rose rapidly to equal the rate of administration, and clearance measurements indicated an excess of potassium excreted over that filtered. The ability to tolerate intravenous loading with potassium seems to result from adaptation to high dietary intake of this element, and to involve an enhanced excretory capacity rather than tolerance of high potassium levels in plasma. Berliner *et al.* (1950) have shown that the dog reacts differently to potassium loading, in that potassium levels in plasma rise progressively unless this animal has been made 'tolerant' by addition of potassium salts to its diet for 2 weeks before infusion.

There is good evidence that urinary excretion of potassium is mainly the result of secretion by the renal tubules (Black & Emery, 1957; Davidson, Levinsky & Berliner, 1958), and the technique of stop-flow analysis indicates that secretion occurs in a distal tubular site (Pitts, Gurd, Kessler & Hierholzer, 1958). Thus the ability of animals with a large dietary turnover of potassium to tolerate intravenous loading appears to involve the secretory capacity of the distal tubules. However, the physiological mechanism initiating and maintaining the tolerant state is not clear. So far no evidence has been reported which indicates that adrenocortical activity is increased, although there is good evidence that aldosterone and other mineralocorticoids stimulate tubular exchange of potassium and sodium (Giebisch, 1961) and Vander, Wilde & Malvin (1961) argue from analysis of stop–flow data that aldosterone may act by increasing the number of distal tubular carrier sites.

The diuresis observed in the present work may be due in part to an increased solute load in the glomerular filtrate as a result of the infusion of hypertonic potassium chloride. The decline in the diuresis which occurred after 1–2 hr of infusion may largely be due to increased secretion of antidiuretic hormone, because of the hypertonicity of the infusion and the water lost during the initial marked diuresis. Nevertheless, urine flow persisted above the pre-infusion level throughout the infusion period and competition between hydrogen ions and potassium for secretion by the distal tubules probably contributes to the diuresis. Competition of this type has been shown in dogs by the infusion of acetazolamide, which caused an increased urinary excretion of potassium considerably less than the concomitant decrease in hydrogen ion excretion (Berliner, Kennedy & Orloff, 1951). It is suggested that during potassium loading a greater suppression of hydrogen-ion excretion occurs than increase in potassium, giving rise to a net reduction in sodium-ion reabsorption, with consequent increased restriction of the tubular reabsorption of water. Similarly, chlorthiazide has been shown to increase the urinary excretion in cattle of both potassium and sodium (Knudsen, 1960).

Our experiments also showed a rise and subsequent decline of sodium excretion during potassium infusion, with a time course similar to the diuretic response. Like urine-flow values, sodium excretion remained elevated above pre-infusion rates for the duration of the infusion period. This is explicable by the osmotic diuresis already mentioned sweeping sodium out of the proximal convoluted tubules more rapidly than it can be reabsorbed distally (Smith, 1951) and by the suggested shift in the secretory activity of the distal tubules during potassium infusion.

SUMMARY

1. The capacity of the bovine kidney to sustain high excretory rates of potassium has been investigated by clearance studies carried out on three conscious cows before and during intravenous infusion of potassium chloride.

2. During infusion plasma potassium concentrations increased by 1–2 m-equiv/l. and then were maintained around this level. The rate of excretion of potassium rose to equal approximately the rate of infusion, and in all cases the clearance of potassium rose to exceed that of inulin. At the same time sodium excretion and the rate of urine flow showed a parallel increase, which declined as infusion continued but persisted above pre-infusion rates.

3. The possible renal mechanisms involved in these responses are discussed.

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