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Urinary acidification assessed by simultaneous furosemide and fludrocortisone treatment: an alternative to ammonium chloride

SB Walsh[1], DG Shirley[1], OM Wrong[1] and RJ Unwin[1]

[1]*Department of Physiology and Centre for Nephrology, Royal Free and University College Medical School, London, UK*

Distal renal tubular acidosis (RTA) can lead to rickets in children or osteomalacia in adults if undetected. This disorder is normally diagnosed by means of an oral ammonium chloride-loading test; however, the procedure often leads to vomiting and abandonment of the test. In this study, we assess an alternative, more palatable approach to test urinary acidification. This was achieved by the simultaneous oral administration of the diuretic furosemide and the mineralocorticoid fludrocortisone to increase distal tubular sodium delivery, principal cell sodium reabsorption, and α-intercalated cell proton secretion. We evaluated 11 control subjects and 10 patients with known distal RTA by giving oral ammonium chloride or furosemide/fludrocortisone in random order on separate days. One control and two patients were unable to complete the study owing to vomiting after NH_4Cl; however, there were no adverse effects with the furosemide/fludrocortisone treatment. The urine pH decreased to less than 5.3 in the controls with both tests, whereas none of the patients was able to lower the urine pH below 5.3 with either test. We conclude that the simultaneous administration of furosemide and fludrocortisone provides an easy, effective, and well-tolerated alternative to the standard ammonium chloride urinary acidification test for the diagnosis of distal RTA.

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Correspondence: *SB Walsh, Department of Physiology and Centre for Nephrology, Royal Free and University College Medical School, Rowland Hill Street, London NW3 2PF, UK. E-mail: s.walsh@medsch.ucl.ac.uk*

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The renal tubular acidosis (RTA) syndromes are a disparate group of disorders united by impaired urinary acidification that is unrelated to the glomerular filtration rate.[1] The classic and commonest form of RTA, type I or distal RTA (dRTA), is characterized by a hyperchloremic, normal anion gap metabolic acidosis with reduced net acid excretion and an inability to lower urine pH to <5.3. Patients with type I RTA are often also hypokalemic,[2] and hypercalciuric, and many develop nephrocalcinosis.[3] If distal RTA is undiagnosed or untreated, chronic acidosis with increased urinary losses of calcium and phosphate may lead to bone demineralization and (in severe cases) to rickets in children and osteomalacia in adults.[2–4]

dRTA results from failure of the collecting tubule α-intercalated cell to secrete H^+ and has a number of causes. Primary dRTA can occur as an inherited defect due to mutations, both dominant and recessive, of the basolateral anion exchanger-1[5,6] or of the apical proton pump (v-H^+-adenosine triphosphatase).[7] Secondary dRTA can occur in almost any autoimmune disorder, but has been most commonly described in Sjögren's syndrome. It is also found in association with disorders that damage the renal medulla, such as chronic pyelonephritis and obstructive uropathy,[1] including nephrocalcinosis itself, as in medullary sponge kidney. Regardless of etiology, the clinical features of dRTA can vary, ranging from an asymptomatic urinary acidification defect without systemic acidosis (so-called 'incomplete' dRTA), with or without the incidental finding of renal tract calcification, to major effects in childhood with acidosis, growth retardation, rickets, and extensive medullary nephrocalcinosis, sometimes progressing to renal failure. Detection and diagnosis are worthwhile, even in those with asymptomatic or incomplete dRTA, so as to minimize future skeletal and renal complications,[8] and in familial cases to assist genetic counseling.

In those patients with a metabolic acidosis and near-normal glomerular filtration rate, a diagnosis of dRTA can be made when urine pH is consistently >5.3;[9] but if there is no systemic acidosis and plasma bicarbonate concentration is within the normal range, a test of urinary acidification is required. This was originally done by acid loading to induce a

mild systemic acidosis and was attempted in various ways. In 1959, Wrong and Davies[4] described the short ammonium chloride test, which involved the oral ingestion of a quantity of ammonium chloride and serial measurements of urine pH. The authors demonstrated consistent lowering of plasma pH and total CO_2 with this protocol, which has subsequently been adopted internationally as the 'gold standard' diagnostic test for dRTA. However, although the test lasts only 8 h and does not require blood testing, it can be unpleasant for some patients, because gastric irritation, nausea, and vomiting are common.

In 1955, Schwartz *et al.*[10] had described urinary acidification in response to intravenous infusion of pH-neutral sodium sulfate. The mechanism was believed to be indirect and crucially different from the provocation of a systemic acidosis by NH_4Cl, as it involved an increase in the delivery of a non-reabsorbed anion to the distal nephron, where it was thought to increase the lumen-negative electrical gradient favoring increased proton (H^+) secretion. In 1986, Batlle[11] described a variation of this test using oral furosemide to increase distal nephron sodium delivery and enhance sodium reabsorption, again increasing lumen negativity and stimulating H^+ secretion. Urine pH changes in response to an increased distal delivery of sodium have been reported to be greater in normal subjects when they are sodium depleted[12] or following previous administration of a mineralocorticoid.[13] Although our own initial observations suggested that this modification led to a more consistent effect than furosemide alone,[14] the timing of the mineralocorticoid seemed to be important. This may be because the relevant action of mineralocorticoids like aldosterone is, in part, non-genomic and can occur more rapidly than was originally supposed. Aldosterone increases epithelial sodium channel density on the apical surface of principal cells within 30 min of administration via mobilization of endocytic stores of preformed epithelial sodium channel.[15] Basolateral Na^+,K^+-adenosine triphosphatase activity is also increased acutely following mineralocorticoid administration,[16] as is α-intercalated cell vH^+-adenosine triphosphatase activity; the latter has been shown to occur within 15 min of exposure.[17–19]

With these observations in mind, we hypothesized that simultaneous dosing of furosemide (to increase distal tubular sodium delivery) and fludrocortisone (to enhance principal cell sodium reabsorption and α-intercalated cell H^+ secretion) should provide a sufficient and consistent stimulus to unmask an acidification defect in dRTA, without the need for NH_4Cl. To test this, we examined urinary acidification in response to the standard short NH_4Cl test and compared it with the response to the furosemide/fludrocortisone test in healthy subjects and in a group of patients with known dRTA.

RESULTS

Three subjects (two from the dRTA group and one from the control group) had to withdraw from the study because of vomiting after taking NH_4Cl. Eight subjects remained in the dRTA group and 10 in the control group. Six subjects (three in each group) reported nausea following NH_4Cl, whereas one subject in the dRTA group had difficulty swallowing the required number of NH_4Cl-containing capsules. No subjects reported any difficulties with the furosemide/fludrocortisone test.

Urinary acidification

All subjects in the control group acidified their urine to a pH <5.3 when given the NH_4Cl test and also when given the furosemide/fludrocortisone test (Figures 1 and 2). The minimum pH values were 4.87 ± 0.07 after NH_4Cl and 4.92 ± 0.10 after furosemide/fludrocortisone (not significant).

Urinary acidification appeared to be more rapid after the furosemide/fludrocortisone test than after NH_4Cl, although it should be noted that the complete dose of NH_4Cl took an hour to ingest, unlike the dosing of furosemide plus fludrocortisone. All control subjects acidified their urine to a pH <5.3 by 3–4 h after furosemide/fludrocortisone, whereas this was achieved 5–6 h after NH_4Cl (Figure 3), that is, 4–5 h following the end of NH_4Cl ingestion. In the dRTA group, all patients failed to acidify their urine to pH <5.3 with either test. Minimum pH values were 6.83 ± 0.10 after NH_4Cl and 6.59 ± 0.13 after furosemide/fludrocortisone (not significant).

Ammonium excretion

In the control group, ammonium excretion increased during both tests. For the NH_4Cl test, ammonium excretion increased from a baseline of 26 ± 9 μmol/min to a maximum of 64 ± 17 μmol/min (at 6 h). For the furosemide/fludrocortisone test, baseline ammonium excretion was 33 ± 8 μmol/min, increasing to a transient peak of 85 ± 23 μmol/min at 2 h (Figure 4a).

In the dRTA group, changes in ammonium excretion were less striking. After NH_4Cl, ammonium excretion was variable, but increased significantly at 4 and 7 h; no significant increase in ammonium excretion was seen with the furosemide/fludrocortisone test.

Titratable acidity

In the control group, titratable acidity (TA) increased during both tests (Figure 4b). With NH_4Cl, TA increased from a baseline of 11 ± 3 μmol/min to a maximum of 48 ± 9 μmol/min (at 6 h). With furosemide/fludrocortisone, TA increased from a baseline of 10 ± 3 μmol/min to a maximum of 42 ± 5 μmol/min (at 3 h).

In the dRTA group, there were much smaller, but significant, increases in TA during both tests.

Urine flow rate and electrolyte excretion

Baseline urine flow rates were higher in dRTA patients than in control subjects. Urine flow rates were generally raised following NH_4Cl, reflecting the usually higher fluid intake at the time of NH_4Cl ingestion. As expected, diuresis, natriuresis, and kaliuresis followed furosemide/fludrocortisone administration in control subjects and dRTA patients, reaching a peak at 2 h (Figure 5). The natriuretic response was similar in the dRTA group to that described previously[11]