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Renal Tubular Acidosis: Effects of Etacrynic Acid on Renal Acid and Calcium Excretion

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Summary. The fundamental disorder in renal tubular acidosis – the impaired excretion of hydrogen ions – can favourably be influenced by etacrynic acid (Hydromedin®). Net acid and calcium excretion was measured in eight patients with incomplete RTA I and five controls before and during treatment with the diuretic: urinary pH was lowered and net acid excretion increased ($p < 0.05$) with only slight rise in urinary calcium. Etacrynic acid appears to be particularly suitable for the long term treatment of patients with incomplete RTA I and calculous disease.

Key words: Renal tubular acidosis. Etacrynic acid, Treatment, Renal calculous disease, urine calcium.

Introduction

In complete renal tubular acidosis (RTA I) with stone formation and/or nephrocalcinosis, neutral or alkaline (infected) urine, low plasma bicarbonate and hypercalciuria treatment with buffers (Shohl's solution, Uralyt U®) aims at correcting the plasma acidosis and resorptive hypercalciuria [9]. In incomplete RTA without acidosis benefit from this regimen is limited and patients are often reluctant to follow the regimen for a reasonable length of time. Little clinical attention has been paid to the finding that etacrynic acid (Hydromedin®) enhances renal excretion of hydrogen ions [3]; this possibly fundamental treatment modality in renal tubular acidosis was investigated by Györi and Edwards (1971) [5] in 3 and by Heidbreder (1972) [7] in one patient. The encouraging results prompted us to investigate the effects of etacrynic acid in respect to renal hydrogen and calcium ion excretion in a larger number of patients with RTA I.

Material and Methods

The effects of etacrynic acid were investigated in eight patients with RTA I and five healthy volunteers (Table 1); the diagnosis of RTA was established by the oral acid loading test after Wrong and Davies [10]. No patient had a significant urinary infection (colony count $< 10^4$) during investigation.

After 1 week with a low-calcium diet a calcium-loading test (Broadus [2]) and the acid-loading test (see above) were performed: calcium/creatinine quotient, creatinine clearance and minimal urinary

Table 1. Data of eight patients with RTA I and five controls

	Age Sex	Creat. (ml/min)	Urine pH after NH_4Cl-load	Base excess (meq/l)	Urine culture (col. count)
I RTA I	45 m	117.9	5.67	+ 0.1	$<10^4$
	60 f	134.1	5.73	− 1.6	$<10^4$
	33 f	138.5	6.63	− 5.6	neg.
	40 f	31.6	7.0	− 9.8	10^4
	19 f	51.57	5.79	+ 0.6	$<10^4$
	40 f	78	5.79	+ 1.6	$<10^4$
	40 f	61.9	6.57	+ 3.2	neg.
	41 f	60.2	5.72	− 4.9	neg.
II controls $\bar{x}$	32	115.5	4.64	− 1.2	neg.
$n = 5$ s_{xi}		±26.3	± 0.25	± 1.5	

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Table 2. Data on urinary acid and calcium excretion in patients with RTA I and controls before and during etacrynic acid (EA) administration (50 mg/day p.o.)

				Before EA	During EA-administration
I	RTA I (n = 8)	pH		6.80 ± 0.51	6.53 ± 0.58
		Titrable acidity ($-HCO_3$)	meq/24^h	−5.8 ± 17.4	1.9 ± 20.0
		Ammonia	meq/24^h	23.8 ± 16.3	31.6 ± 21.5
		Net acid	meq/24^h	18.0 ± 11.4	33.5 ± 12.2
		Calcium (mg/24 h)		84 ± 33	102 ± 47
		Volume (ml)		1,760 ± 1.235	1,920 ± 1,100
II	Controls (n = 5)	pH		5.77 ± 0.34	5.91 ± 0.33
		Titrable acidity ($-HCO_3$)	meq/24^h	24.0 ± 12.5	21.0 ± 4.5
		Ammonia	meq/24^h	31.3 ± 7.3	34.0 ± 3.1
		Net acid	meq/24^h	55.3 ± 17.2	55.0 ± 4.2
		Calcium (mg/24 h)		72 ± 39	108 ± 58
		Volume (ml)		1,001 ± 333	1,839 ± 175

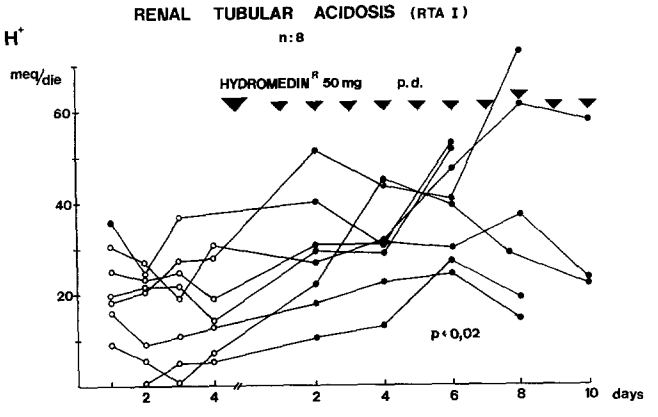

Fig. 1. Individual curves for net acid excretion in eight patients with RTA prior and during EA administration

pH (after acid loading) were determined. Three 24 h urine collections were analysed for volume, calcium and net acid excretion before and every other day for 5 days after daily treatment with 50 mg etacrynic acid (Hydromedin®, MSD Sharp + Dohme, München) by mouth. Urine collections were kept in the refrigerator with some thymol added.

Urine pH was measured electrometrically, titrable acidity (minus bicarbonate) after (Györy and Edwards [4] by autotitration (Dosimat, Metrohm), ammonia by ionsensitive electrodes (Ammoniak-Elektrode, Orion). Anaerobic handling of the urine specimens was unnecessary in our analyses because the sum of hydrogen ions is not influenced by exposure to air or infection [8]. Plasma acid base data were obtained from micro-Astrup measurements. Urine calcium was determined by complex binding (A-Gent-method; Abbott laboratories).

Statistical calculations were based on the mean of three premedication data and five data collections during etacrynic acid administration in RTA-patients and volunteers.

Results

1. Urinary Acid Exretion

In this study healthy volunteers (creatinine clearance: 115.5 ml/min) had a mean urine output of 1,001 ml/day, with a urinary pH of 5.77 and a net acid excretion of 55.3 meq/day. During the daily treatment with 50 mg etyacrynic acid urinary output was increased significantly ($p < 0{,}02$) with little change in urine pH or acid output (Tables 1 and 2).

In the eight patients with RTA I (one case with complete (mixed) RTA I) average creatinine clearance (88.9 ml/min) was lower than in the control group; urine volume increased by 9% during etacrynic acid treatment and urine pH was lowered from an average of 6.80 to 6.53 (Table 2). Increases in urinary titrable acid and ammonia added up to an increase in total net acid excretion ($p < 0.05$) from 18.0 to 33.5 meq/day. Individual acid excretion curves (Fig. 1) generally showed a tendency to an enhanced acid output during drug administration.

2. Calcium Excretion

Daily urinary calcium excretion in healthy controls was in the normal range; its increase to 108 mg/day after etacrynic acid was not significant. This was also true for the group of RTA-patients with an average increase of the urine calcium of 21% (Table 2). Despite normal calcium excretion in our patients with incomplete RTA the calcium loading test revealed a tendency for increased intestinal absorption: the calcium creatinine quotient (which averaged 0.02 in the control group and rose to 0.15 after calcium loading) went up to 0.23–0.28 (from 0.07) in four RTA-patients, indicating increased intestinal absorption.

Discussion

The basic functional disorder in renal tubular acidosis is the impaired excretion of hydrogen ions. In classical distal tubular acidosis (RTAI) associated with renal calculous disease, urinary infection and alkaline urine several factors contribute to stone formation. Treatment has so far been limited to the correction of plasma acidosis (when present and (re-

sorptive) hypercalciuria [1, 6]. In 1964 etacrynic acid was released for clinical trial [3] with its specific properties to increase renal excretion of hydrogen ions, calcium and water. The potential benefits of this diuretic in patients with RTA I were investigated in four cases [5, 7] with encouraging results. Surprisingly no further experience with this drug has been reported in RTA-treatment since 1972.

This study was designed to measure the effects of the diuretic in a number of RTA I-patients compared to normal controls and to balance the beneficial effects of an enhanced hydrogen ion excretion against the potential induction of hypercalciuria.

The present data confirm the findings of Györi and Edwards [5] and Heidbreder [7]: etacrynic acid induced a drop in urinary pH and a significant rise in net acid excretion in our patients with incomplete renal tubular acidosis during a 10 day oral administation of 50 mg. Ammonia formation and output of titrable acidity increased by a total of net acid of 15 meq/day. Though we found no case with hypercalciuria in the RTA group prior to the administration of the diuretic, increased intestinal absorption was detected in four cases by oral calcium loading test. This points to the possible pathogenetic theory in which hypercalciuria with tubular damage and subsequent disturbance of the acidifying mechanism is assumed to be the primary factor in RTA I [1, 6]. The increase in calcium excretion caused by etacrynic acid was slight and not significant in our study either in controls or in patients with RTA, so that the beneficial effects on acid-base balance seem to outweigh the tendency to an increased calcium output.

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