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Renal Tubular Dysfunction-Chronic Alcohol Abuse - Impacts of Abstinence

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Abstract

Background: Alcohol abuse may be accompanied by a variety of disorders of electrolyte and acid-base metabolism. The role of the kidney in the pathogenesis sis of these disturbances is obscure. We sought to evaluate the alcohol-induced abnormalities of renal function and improvement during abstinence and to assess the relation between renal dysfunction and electrolyte and acid-base disorders.

Methods: We measured biochemical constituents of blood and renal function before and after four weeks of abstinence in 61 patients with chronic alcoholism who had little or no liver disease.

Results: On admission, 18 patients (30 percent) had hypophosphatemia and hypomagnesemia, 13 patients (21 percent) had hypocalcemia, and 8 patients (13 percent) had hypokalemia. Twenty-two patients (36 percent) had a variety of simple and mixed acid-base disorders. Twenty of these patients had metabolic acidosis, and among them, 80 percent had alcoholic acidosis. A wide range of defects in renal tubular function, with normal glomerular filtration rate, was detected in these patients. The defects included decreases in the threshold and maximal reabsorptive ability for glucose (38 percent of patients) and in the renal threshold for phosphate excretion (36 percent); increases in the fractional excretion of $\beta 2$-microglobulin (38 percent), uric acid (12 percent), calcium (23 percent), and magnesium (21 percent); and aminoaciduria (38 percent). Seventeen patients (28 percent) had a defect in tubular acidification, and five an impairment in urinary concentrating ability. Urinary excretion of N-acetyl-/3-0-glucosaminidase and alanine aminopeptidase was increased in 41 and 34 percent of patients, respectively. The abnormalities of blood chemistry and renal tubular function disappeared after four weeks of abstinence.

Conclusions. Transient defects in renal tubular function are common in patients with chronic alcoholism and may contribute to their abnormalities of serum electrolyte and blood acid-base profiles.

ALCOHOL abuse may result in a wide range of electrolyte and acid-base disorders, including hypophosphatemia, hypomagnesemia, hypocalcemia, hypokalemia, metabolic acidosis, and respiratory alkalosis. 1 The severity and clinical importance of these disorders depend largely on the quantity of alcohol ingested, the duration of drinking, and associated fac- tors, such as malnutrition, chronic liver disease, and intercurrent illness. Abnormalities of renal function are common in patients with advanced liver disease, the most common and severe clinical manifestation of chronic alcoholism. These abnormalities, which often have a central role in the clinical illness and may con- tribute to death, have been studied extensively.[2] The effects of alcohol abuse on renal function in the absence of chronic liver disease are not well defined, but alcohol abuse can induce excessive urinary excretion of calcium, magnesium, and phosphate.[3•4] Among patients with chronic alcohol abuse, a clear description of renal tubular dysfunction is lacking, however, the relation between electrolyte and acid-base disorders and renal tubular dysfunction is poorly understood. Over four weeks, we studied a group of patients with chronic alcoholism but little or no liver disease to evaluate the alcohol- induced abnormalities of renal tubular function and their improvement during abstinence and to assess the relation between tubular dysfunction and serum electrolyte and blood acid-base disturbances.

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Methods
Patients

We studied 61 patients with chronic alcoholism who volunteered for (and completed) four weeks of withdrawal therapy. To be eligible, the patients had to have had a large intake of alcohol for at least five years, weekly alcohol consumption of 600 g or more for the previous three months, and no histopathological evidence of cirrhosis or alcoholic hepatitis, no clinical or laboratory evidence of pancreatitis or malnutrition, no history of renal disease or exposure to lead or cadmium (from either occupational exposure or consumption of illicitly distilled spirits), and no laboratory evidence of excessi\'e body stores of lead (calcium-sodium-EDTA lead-mobilization test) or cadmium. We excluded patients admitted for alcohol-related diseases, such as alcoholic liver disease, pancreatitis, gastrointestinal bleeding, acute atrial fibrillation, cardiomyopathy, seizures, and rhabdomyolysis, as well as those with vomiting, diarrhea, or intercurrent illness that could influence acid-base and electrolyte homeostasis. Patients in whom severe symptoms of alcohol withdrawal developed were also excluded, as were those who required medications, such as phenobarbital, antihypertensive drugs, or fluid-replacement therapy. None of the patients had delirium tremens or alcoholic hallucinosis, and none were receiving medi- cations known to influence renal function or mineral and electrolyte metabolism. Each patient had been drinking until 24 hours before admission, although none were intoxicated at the time of entry into the study. We also studied 42 normal subjects who abstained from alcohol or consumed only small amounts (15 to 105 g of ethanol per week). All the subjects gave informed written consent for the study.

Study Design

The patients were allowed to move about freely in the hospital but not to leave it during the four-week study period. Renal func-tion, concentrations of serum electrolytes, and blood acid-base val- ues were determined immediately after admission and after four weeks of abstinence. Each patient\ nutritional state was evaluated on admission, and the patients were asked about their alcohol con-sumption. The renal tubular function was estimated based on a four-day protocol. Arterial blood gases and serum electrolyte concentrations were also measured on the fourth and seventh days of hospitalization, and the fractional urinary excretion of electrolytes was determined at the same time. A percutaneous liver biopsy was performed within two weeks after admission; the microscopical sec-tions were evaluated by a pathologist unaware of the patient's clini- cal status. During the study period, the patients were fed a standard diet that provided 140 mmol of sodium daily. Protein intake was not restricted. All the patients received vitamins and folic acid, but none received electrolyte supplements.

Assessment of Alcohol Consumption and Nutrltlonal State

Alcohol consumption was assessed with a structured questionnaire, and the results were corroborated by an in-depth interview performed by a trained interviewer. The total weekly alcohol con- sumption was calculated and expressed as grams of ethanol. In addition, biological markers of alcohol intake, such as mean corpus-cular volume and serum concentrations of gamma-glutamyltransferase, aspartate aminotransferase, and alanine aminotransferase were measured in all patients.[5] Nutritional state was estimated by anthropometric measurements and laboratory indexes (hemoglobin, blood lymphocytes, and serum concentrations of total protein, albumin, urea, and creatinine). Skin-fold thickness was measured at four sites with standard calipers, and estimates of body fat were obtained with appropriate equations based on age and sex.

Assessment of Plasma Hormone Concentrations

After the patient had been recumbent and fasting overnight, blood samples were collected on the first morning after admission for the estimation of plasma concentrations of aldosterone, par-athyroid hormone, cortisol, corticotropin, norepinephrine, and epinephrine and of plasma renin activity. Further blood sam-ples were obtained for plasma cortisol measurements at 4 p.m. and midnight that day. The hormone study was repeated after the patients had been abstinent for four weeks.

Assessment of Tubular Function

Renal function was estimated on the basis of a four-day protocol conducted immediately after admission and after four weeks of ab-stinence. On the first day we measured the glomerular filtration rate with tests of inulin clearance and endogenous creatinine clearance; the fractional urinary excretion of sodium, potassium, chloride, calcium, and magnesium; and the theoretical renal threshold for phosphate excretion. Fasting urine pH and osmolality were also meas-ured. A 24-hour urine specimen was collected for the determination of proteins, glucose, ammonium, titratable acidity, bicarbonate, and amino acids, as well as electrolytes, creatinine, N-acetyl-{3-o-glucosaminidase, a-glucosidase, and alanine aminopeptidase. On the second day, each patient was given 4 g of sodium bicarbonate with 250 ml of water, after which urine was collected for two hours and a blood sample was collected one hour after the administration of sodium bicarbonate for f3rmicroglobulin assay. Urine-concentrating ability was assessed on the third day by measurements of plasma and urinary osmolality during water deprivation. After 12 hours of water

deprivation, 5 units of vasopressin (desmopressin acetate [DDAVP, USV Pharmaceuticals)) was given subcutane-ously, after which hourly urine samples were collected for 4 hours for measurement of urinary osmolality. A maximal urinary osmolality of ;;,,750 mOsm per kilogram after vasopressin administration was considered a normal response.6 Patients whose fasting urinary osmolality exceeded 750 mOsm per kilogram were considered to have normal concentrating ability and did not undergo the water- deprivation and vasopressin tests. The acidification ability of the distal renal tubules was tested by a short acid-loading test on the fourth day. Calcium chloride (2 mmol per kilogram of body weight) was administered orally over a 60-minute period, and urine and blood pH were measured every 2 hours for 6 hours.7 If the fasting urine pH was less than 5.5, regardless of the blood pH, the patient was considered to have normal acidification ability, and the acid- loading test was not performed. Finally, a glucose-titration study was performed8 to determine the threshold and the maximal reab-sorptive ability for glucose.

Assessment of Plasma Hormone Concentrations

After the patient had been recumbent and fasting overnight, blood samples were collected on the first morning after admission for the estimation of plasma concentrations of aldosterone, par-athyroid hormone, cortisol, corticotropin, norepinephrine, and epinephrine and of plasma renin activity. Further blood sam-ples were obtained for plasma cortisol measurements at 4 p.m. and midnight that day. The hormone study was repeated after the patients had been abstinent for four weeks.

Laboratory Measurements

Routine biochemical determinations were performed in serum and urine by standard automated methods. Inulin was determined photometrically with indoleacetic acid after hydrolyzation to fruc-tose. The unmeasured-anion concentration was calculated as the sodium concentration minus the sum of the chloride and bicarbon-ate concentrations. Standard formulas were used to calculate the fractional urinary excretion of substances. Plasma and urinary os-molality was determined by freezing-point depression. Arterial-blood pH and partial pressure of carbon dioxide ($PaCO_2$) and urine pH were measured with a digital acid-base analyzer. Urinary am-monium, titratable acidity, and total carbon dioxide content were measured by standard techniques. Serum and urine f3rmicroglobu- lin was measured with Phadebas /32 micro-test kits (Pharmacia Di- agnostics). Urinary excretion of N-acetyl-{3-o-glucosaminidase, alanine aminopeptidase, and a-glucosidase was determined by colorimetric methods (Far Diagnostic). Urinary amino acids were measured by high-performance liquid chromatography. Serum /3-hydroxybutyrate was assayed with a procedure based on the method of Williamson et al.9 Serum acetoacetate was measured semiquantitatively by the nitroprusside reaction, and urine ketones by dipstick. Lead and cadmium were measured in plasma and urine by electrothermal atomic absorption spectrometry. Plasma concen- trations of norepinephrine and epinephrine were determined by a modification of the radioenzymatic method of Da Prada and Ziircher.10 Plasma concentrations of aldosterone, cortisol, and corticotropin and plasma renin activity were measured by radioimmunoassay. Plasma parathyroid hormone was measured with a two- site immunoradiometric assay.

Statistical Analysis

The results are expressed as means ±SD. Comparisons within and between groups were analyzed by analysis of variance, the Wilcoxon rank-sum test, and Student's t-test, as appropriate. Cor- relation was assessed with simple and multiple linear regression and Spearman's rank test. P values less than 0.05 were considered to indicate statistical significance.

Results
Drinking Habits, Laboratory Markers of Alcoholism, and Liver Damage

Some characteristics of the patients with chronic alcoholism and the normal subjects are shown in Ta- ble l. The values for the biological markers of alcohol

Table 1. Characteristics of the Alcoholic Pa-tients and Normal Subjects.*

CHARACTERISTIC	ALCOHOLIC PATIENTS (N = 61)	NORMAL SUBJECTS (N = 42)
Sex (M/F)	47/14	30/12
Age (yr)	46±8	48±11
Years of alcohol abuse	11±7	—
Alcohol intake (g/wk)†	980±280	—
Body-mass index‡	25±3	23±2
Body fat (% of body weight)	27±5	25±4

*Plus−minus values are means ±SD. No significant differ-ences were found between the groups in any variables.

†Values shown are means for the preceding three months.

‡Calculated by dividing the weight in kilograms by the square of the height in meters.

Table 2. Biochemical and Hematologic Markers of Alcohol Intake, Laboratory Indexes of Nutrition, and Other Measures of Serum Chemistry in the Alcoholic Patients on Admission and after Four Weeks of Abstinence and in the Normal Subjects.*

INDEX	ALCOHOLIC PATIENTS (N = 61) ADMISSION	ALCOHOLIC PATIENTS (N = 61) ABSTINENCE	NORMAL SUBJECTS (N = 42)
Hemoglobin (g/dl)	14.0±1.4	13.5±1.4	14.2±1.2
Mean corpuscular volume (μm^3)	94±6.3†	91±4.2	90±2.4
Serum gamma-glutamyltransfer-ase (U/liter)	150±182†	45±49	29±6
Serum aspartate aminotransfer-ase (U/liter)	44±35†	25±14	24±12
Serum alanine aminotransferase (U/liter)	33±21†	23±14	23±12
Serum bilirubin (mg/dl)	1.3±0.7†	0.6±0.3	0.5±0.3
Prothrombin-time ratio	0.92±0.21	0.92±0.21	0.93±0.12
Blood lymphocytes (cells/mm³)	1800±350†	2100±420	2200±300
Serum total protein (g/dl)	7.4±0.7	7.2±0.7	7.3±0.6
Serum albumin (g/dl)	3.8±0.4	3.7±0.6	3.9±0.5
Serum glucose (mg/dl)	89±14	91±14	89±12
Serum creatinine (mg/dl)	1.05±0.21	1.07±0.21	1.04±0.36
Serum urea nitrogen (mg/dl)	13.1±4.2	13.7±4.2	13.7±3.0

*Values are means ±SD. To convert values for bilirubin to micromoles per liter, multiply by 17.1; to convert values for glucose to millimoles per liter, multiply by 0.05551; to convert values for creatinine to micromoles per liter, multiply by 88.4; and to convert values for urea nitrogen to millimoles per liter, multiply by 0.357.

†P<0.001 for the comparison of the values obtained in the alcoholic patients at admission with those obtained after four weeks of abstinence and with the values in the normal subjects.

intake in the alcoholic patients are shown in Table 2. The liver-biopsy specimens were normal or showed only minor, nonspecific changes in 45 patients. They showed moderate steatosis in 6 patients, with and without fibrosis (3 patients each), and showed mild- ly fatty liver in IO patients. The values for the bio- logic markers were similar in the 45 patients with no or minor histologic abnormalities and in all 61 patients.

Nutritional State

In the alcoholic patients the mean values for body- mass index and body fat were slightly, but not significantly, higher than those in the normal subjects (Ta- ble I). Conversely, there was no significant difference in any of the laboratory indexes of nutritional status (Table 2).

Electrolyte and Acid-Base Disorders

Several patients had symptoms and signs attribut- able to serum electrolyte or blood acid-base disturbances. Generalized muscular weakness was a common finding and could have resulted from hypophosphate- mia, hypocalcemia, or hypomagnesemia. Tachypnea and hyperpnea were present in the patients with severe metabolic acidosis. The serum electrolyte and blood acid-base values are shown in Table 3. As com- pared with the normal subjects, the alcoholic patients had lower serum concentrations of phosphate, potassium, magnesium, and ionized calcium on admission, lower values for blood pH and $PaCO_2$, and lower plasma bicarbonate concentrations, whereas there was no significant difference between the groups in serum sodium and chloride concentrations. Among the alcoholic patients, 18 (30 percent) had hypophosphatemia, 18 (30 percent) had hypomagnesemia, 13 (21 percent) had hypocalcemia, and 8 (13 percent) had hypokalemia. The serum uric acid concentrations of these patients were similar to those of the normal subjects. Six patients (IO percent) had hyperuri- cemia (serum uric acid concentration, >7.0 mg per deciliter [420 µ,mo! per liter] in men and 6.2 mg per deciliter [370 µ,mo! per liter] in women), and seven patients (II percent) had decreased serum uric acid concentrations (<3.2 mg per deciliter [I90 µ,mol per liter]).

The mean blood pH and plasma bicarbonate con- centration were lower in the alcoholic patients than in the normal subjects. Two patients (3 percent) had primary respiratory alkalosis and actually had alkalemia (pH >7.45). Twenty patients (33 percent) had metabolic acidosis. The mean (±SD) arterial-blood pH and plasma bicarbonate concentration in these 20 patients were 7.32±0.03 and 18.3±3.0 mmol per liter, respectively. Ten patients had pH values ranging from 7.31 to 7.36, and seven had values less than 7.30. Eight patients (13 percent) had wide-anion-gap metabolic acidosis, and four (7 percent) had normal-anion-gap hyperchloremic acidosis. Four of these patients with acidosis had coexisting primary respiratory alkalosis as defined by a $PaCO_2$ value below the value predicted by the formula of Albert et al.[11]: expected $PaCO_2$ = 1.5 (serum bicarbonate) + 8±2. Another two patients (3 percent) had wide-anion-gap metabol- ic acidosis combined with normal-anion-gap hyper- chloremic acidosis, defined by a reduction in the plasma bicarbonate concentration that exceeded the increase in the anion gap in the absence of respiratory alkalosis. Four patients (7 percent) had wide-anion- gap metabolic acidosis combined with primary metabolic alkalosis, defined by a decrease in plasma bicarbonate that was substantially less than the increase in the anion gap. Finally, two patients (3 percent) had a triple acid-base disorder, with primary wide-anion- gap acidosis, primary metabolic alkalosis, and pri- mary respiratory alkalosis. All 16 patients with wide- anion-gap metabolic acidosis had increased serum /3-hydroxybutyrate

Table 3. Measures of Blood Chemistry in the Alcoholic Patients on Admission and after Four Weeks of Abstinence and in the Normal Subjects.*

MEASURE	ALCOHOLIC PATIENTS (N = 61)		NORMAL SUBJECTS (N = 42)
	ADMISSION	ABSTINENCE	
Blood pH	7.37±0.05	7.40±0.03†	7.40±0.05†
Plasma bicarbonate (mmol/liter)	21.5±2.8 (33)‡	24.5±2.1§ (3)‡	24.9±3.0§
$PaCO_2$ (mm Hg)	36.7±4.8	39.0±4.6§	39.7±4.3†
Anion gap (mmol/liter)	19.0±5.2 (26)	15.1±2.1§ (0)	14.1±1.2†
Serum sodium (mmol/liter)	139±2.8 (7)	140±1.4 (0)	140±1.9
Serum chloride (mmol/liter)	100±2.8	100±2.2	100±2.5
Serum potassium (mmol/liter)	3.8±0.4 (13)	4.4±0.5§ (2)	4.5±0.4§
Serum phosphate (mg/dl)	3.0±0.6 (30)	3.7±0.6§ (5)	3.7±0.9§
Serum ionized calcium (meq/liter)	2.04±0.15 (21)	2.24±0.16† (7)	2.24±0.13†
Serum magnesium (meq/liter)	1.40±0.15 (30)	1.70±0.15† (5)	1.80±0.38†
Serum uric acid (mg/dl)	5.0±1.2 (11)¶	5.4±1.2‖ (2)¶	5.4±1.8
Plasma osmolality (mOsm/kg)	294±10	295±10	295±9

*Numbers in parentheses are the percentages of patients with abnormal results. Abnormali- ties of serum electrolytes or acid–base metabolism were defined as follows: hyponatremia, by a serum sodium concentration <135 mmol per liter; hypokalemia, by a serum potassium concen- tration <3.5 mmol per liter; hypophosphatemia, by a serum phosphate concentration <2.8 mg per deciliter; hypocalcemia, by a serum ionized calcium concentration <2.08 meq per liter; hypomagnesemia, by a serum magnesium concentration <1.30 meq per liter; hypouricemia, by a serum uric acid concentration <3.2 mg per deciliter; and metabolic acidosis, by a blood pH <7.36 and a plasma bicarbonate concentration <20.5 mmol per liter. Plus–minus values are means ±SD. To convert values for $PaCO_2$ to kilopascals, multiply by 0.1333; to convert values for phosphate to millimoles per liter, multiply by 0.3229; to convert values for magnesium and ionized calcium to millimoles per liter, multiply by 0.5; and to convert values for uric acid to micromoles per liter, multiply by 59.48.

†P<0.01 for the comparison with the value obtained in the alcoholic patients on admission.

‡Indicates the percentage of patients with metabolic acidosis.

§P<0.001 for the comparison with the value obtained in the alcoholic patients on admission.

¶Indicates the percentage of patients with hypouricemia.

‖P<0.05 for the comparison with the value obtained in the alcoholic patients on admission.

concentrations (3540±270 µ,mol per liter; normal, < 100). The nitroprusside reaction was positive in 13 of these patients, and 12 patients had ketone bodies in their urine.

Renal Tubular Dysfunction

The mean glomerular filtration rate in the alcoholic patients, as estimated from the inulin clearance, did not differ from that of the normal subjects (Table 4). The mean values for creatinine clearance were also similar. None of the patients had a 24-hour uri- nary protein excretion exceeding 0.15 g. The alco- holic patients had a variety of transport abnormali- ties of renal tubules on admission (Table 4). Their mean fractional excretion of /32-microglobulin was higher than that of the normal subjects, and in 23 of the 61 alcoholic patients it exceeded the mean value in the normal subjects by more than 2 SD. The patients' serum concentrations of /32-microglobulin ranged from 0.9 to 2.6 mg per liter (mean, 1.8±0.5), as compared with 2.2±0.5 mg per liter in the normal subjects (P = 0.004). The mean values for the excretion threshold and the maximal reabsorptive ability for glucose were lower than those of the normal sub- jects, and 23 patients had values for these measures that were more than 2 SD below the mean in the normal subjects. Twelve of these 23 patients had glycosuria, with glucose levels ranging from

1.5 to 11.5 g in a 24-hour urine sample. All the patients with renal glycosuria had increased urinary excretion of amino acids. The pattern of excretion was generalized, m- cluding neutral, acidic, and basic amino acids.

Table 4. Studies of Renal Function in the Alcoholic Patients on Admission and after Four Weeks of Abstinence and in the Normal Subjects.*

INDEX	ALCOHOLIC PATIENTS (N = 61)				NORMAL SUBJECTS (N = 42)
	ADMISSION		ABSTINENCE		
Renal-function studies					
GFR (ml/min/1.73 m^2)	95±21		97±33		98±24
TmG (mg/min/1.73 m^2)	260±35	(38)	299±40†	(10)	332±36‡
TmPO$_4$/GFR (mg/dl)	3.1±0.7	(36)	3.8±0.7‡	(13)	3.7±0.6‡
Fractional excretion (%)					
β_2-Microglobulin	78±68	(38)	30±25‡	(10)	24±18‡
Uric acid	8.8±4.0	(12)	8.3±2.1	(0)	8.5±3.1
Sodium	0.7±0.4		0.8±0.3		0.8±0.4
Calcium	2.5±1.1	(23)	2.0±0.5§	(13)	1.6±1.0†
Magnesium	3.3±1.8	(21)	2.2±1.3§	(10)	1.9±1.2§
Potassium	9.1±4.0	(16)	7.2±2.8§	(3)	7.8±1.8
Urinalysis					
Volume (ml/24 hr)	1417±672		1747±595§		1602±610
Osmolality (mOsm/kg)	641±220		620±266		682±174
Fasting pH	6.6±0.6		6.0±0.6‡		5.5±0.6‡
Minimal pH¶	5.4±0.7	(28)	4.8±0.6‡	(5)	4.8±0.4‡
Enzymes (mU/mg of creatinine)					
NAG	13.0±12	(41)	7.5±6.3‡	(10)	5.1±1.7‡
Alanine aminopeptidase	13.0±7.1	(34)	9.1±5.6‡	(8)	8.5±2.0‡
α-Glucosidase	1.9±0.7	(18)	1.4±1.2‡	(5)	1.3±0.5‡

*GFR denotes glomerular filtration rate, TmG maximal reabsorptive ability for glucose, TmPO$_4$/GFR renal threshold for phosphate excretion, and NAG N-acetyl-β-D-glucosaminidase. Plus−minus values are means ±SD. Numbers in parentheses are the percentages of patients with abnormal results. The criteria for an abnormal result were as follows: TmG <260 mg per minute per 1.73 m^2, TmPO$_4$/GFR <2.7 mg per deciliter, fractional excretion of β_2-microglobulin >60 percent, fractional excretion of uric acid >15 percent, fractional excretion of calcium >3 percent, fractional excretion of magnesium >2.5 percent, fractional excretion of potassium >13 percent, NAG >8.5 mU per milligram of creatinine, alanine aminopeptidase >12.5 mU per milligram of creatinine, and α-glucosidase >2.3 mU per milligram of creatinine. Failure to produce a urine with a pH below 5.5 after calcium chloride acid loading indicated abnormal acidification. To convert values for TmPO$_4$/GFR to millimoles per liter, multiply by 0.3229.

†P<0.01 for the comparison with the value obtained in the alcoholic patients on admission.

‡P<0.001 for the comparison with the value obtained in the alcoholic patients on admission.

§P = 0.02 for the comparison with the value obtained in the alcoholic patients on admission.

¶Measured during the calcium chloride acid-loading test.

The alcoholic patients had a lower renal threshold for phosphate excretion and higher values for the frac- tional excretion of calcium and magnesium than the normal subjects. The fractional excretion of sodium, potassium, and uric acid was similar in the two groups, although seven patients had increased frac- tional excretion of uric acid (> IS percent). The alco- holic patients had higher values than the normal sub- jects for fasting urine pH and urinary excretion of bicarbonate and lower values for titratable acidity (26± II vs. 38± 10 mmol per 24 hours; P<0.001), ammonium (25± IO vs. 39±9 mmol per 24 hours; P<0.001), and net acid excretion (42± I 7 vs. 74± 13 mmol per 24 hours; P<0.00 I). Seventeen of the 61 patients (28 percent) did not have normal urinary acidification (pH <5.5) after calcium chloride load- ing. Acid ingestion actually lowered the venous-plas- ma bicarbonate concentration in all these patients (from 22.1 ±0.8 to 20.1 ±0.5 mmol per liter). In this subgroup the mean values for net acid excretion, ti-titratable acidity, and ammonium were lower than those in the patients with normal urinary acidification

(Table 5). Furthermore, the patients whose urine pH was not decreased had greater excretion of bicarbon- ate and less excretion

of phosphate. In the entire group of alcoholic patients, titratablc acidity correlat- ed positively with urinary excretion of phosphate (P<0.001).

Twenty-six of the 61 patients had values for fastingurinary osmolality exceeding 750 mOsm per kilogram and were consequently excluded from the urine-con- centration study. Among the remaining 35 patients,5 had impaired responses to water deprivation. In these patients, despite plasma osmolality values simi- lar to those of the other 26 patients (296± 14 vs. 295± 15 mOsm per kilogram), the maximal urinary osmolality after 12 hours of dehydration was more than 2 SD below the mean in the normal subjects (mean values, 674±71 vs. 892±73 mOsm per kilo- gram; P = 0.004). In these five patients, the administration of vasopressin induced an increase in urinary osmolality of less than 3 percent, indicating that the abnormality in urine concentration was due to decreased renal sensitivity to vasopressin. In the alcoholic patients, the urinary excretion of N-acetyl-/3-0-glucosaminidasc, alanine aminopepti- dasc, and a-glucosidase was higher than that in the normal subjects (Table 4).

Relation between Tubular Dysfunction and Blood Chemistry

Tubular dysfunction appeared to contribute to the abnormalities of scrum electrolyte and blood acid- base profiles in the alcoholic patients. There was a positive correlation (P<0.00I) between the serum phosphate concentration and the renal threshold for phosphate excretion, and there were inverse correlations between the serum concentrations of ionized calcium (**P** = 0.002), magnesium (**P** = 0.008), and uric acid (P<0.00 I) and their fractional urinary excretion, measured simultaneously. The defects in tubular function were more common in patients with corresponding abnormalities of serum electrolytes. Specifically, 78 percent of the patients **with** hypo- phosphatemia had a low renal threshold for phosphate excretion, and 62 percent of the patients with hypocalccmia, 50 percent of those with hypomagnesemia, and 50 percent of those with hypokalemia had in- creased fractional urinary excretion of the respective substance. The percentages of patients with normal scrum electrolyte concentrations who had these abnormalities were 9, 10, 9, and 8 percent, respectively. Six of seven patients with hypouricemia (86 percent) had increased fractional excretion of uric acid. Eleven patients with metabolic acidosis (55 percent) had impaired renal acidification ability and reduced net acid excretion. Six of IO patients in whom metabolic acidosis was not accompanied by respiratory alkalosis, metabolic alkalosis, or both had abnormally low net acid excretion despite systemic acidcmia. Finally, of the six patients with renal tubular acidosis, two (33 percent) had hypokalemia and three (50 percent) had hypophosphatemia.

Effects of Abstinence on Serum Electrolyte and Blood Acid-Base Disorders

During hospitalization and the period of abstinence the mean serum concentrations of potassium, magnesium, phosphate, and ionized calcium increased, be- ing significantly higher after four and seven days and four weeks than on day I (Table 6). There was parallel improvement of acid-base abnormalities (Table 3). On day 7 all the patients with wide-anion-gap metabolic acidosis and coexisting respiratory or metabolic alkalosis had recovered, but three patients still had normal-anion-gap hyperchloremic acidosis.

Effects of Abstinence on Tubular Function

The abnormalities of renal tubular function improved with abstinence, and after four weeks the frequency of abnormal findings was

markedly decreased (Table 4). The fractional excretion of potassium de- creased quickly, with significantly lower values on values on days 4 and 7 than on day I

Table 5. Urinary Values in Alcoholic Patients with Impaired or Normal Renal Acidification on Admission and after Four Weeks of Abstinence.*

URINARY MEASURE	IMPAIRED ACIDIFICATION (N = 17)		NORMAL ACIDIFICATION (N = 44)	
	ADMISSION	ABSTINENCE	ADMISSION	ABSTINENCE
Fasting pH	7.0±0.4†	5.9±0.4	6.3±0.3	6.1±0.4
Minimal pH‡	5.7±0.4†	5.0±0.4	5.1±0.2	4.6±0.4
Bicarbonate (mmol/24 hr)	11.2±4.8†	3.6±1.2	3.8±1.2	2.6±0.6
Titratable acidity (mmol/24 hr)	18±4.8†	43±20	30±9	44±7
Ammonium (mmol/24 hr)	18±5.2†	36±10	31±13	35±7
Net total acid (mmol/24 hr)§	24±7.6†	75±12	56±16	76±17
Phosphate (g/24 hr)	0.37±0.1¶	0.53±0.1	0.59±0.12	0.68±0.13
Creatinine (g/24 hr)	1.37±0.3	1.40±0.4	1.36±0.7	1.43±0.4
Sodium (mmol/ 24 hr)	132±29	141±25	133±37	138±33

*Values are means ±SD. To convert values for phosphate to millimoles per 24 hours, multiply by 32.29; to convert values for creatinine to millimoles per 24 hours, multiply by 8.8.

†P<0.001 for the comparison with the value obtained in the same patients after four weeks of abstinence.

‡Measured during the calcium chloride acid-loading test.

§Calculated by subtracting the value for bicarbonate from the sum of the values for titratable acidity and ammonium.

¶P<0.01 for the comparison with the value obtained in the same patients after four weeks of abstinence.

(Table 7); at these times, the values were clearly subnormal (P<0.001). There was a parallel increase in the renal threshold for phosphate excretion during the first days of hospitalization. The fractional excretion of calcium and magnesium decreased more slowly. After four weeks of abstinence, six patients had decreases in the threshold and the maximal reabsorptive ability for glucose. Uri- nalysis revealed generalized aminoaciduria in five of these patients. The disturbances in renal acidification disappeared almost completely (Table 5), and only three patients did not have normal urinary acidifica- tion after calcium chloride loading. The abnormal responses to water deprivation and vasopressin persist- ed in two patients.

Table 6. Changes in Serum Concentrations of Phosphate, Ion-ized Calcium, Magnesium, and Potassium in 61 Alcoholic Pa-tients during Four Weeks of Abstinence in the Hospital.*

DAY	PHOSPHATE	IONIZED CALCIUM	MAGNESIUM	POTASSIUM
	mg/dl	meq/liter		mmol/liter
1	3.0±0.6	2.04±0.15	1.40±0.15	3.8±0.4
4	3.6±0.7†	2.12±0.14‡	1.57±0.15‡	4.0±0.5‡
7	3.5±0.8†	2.20±0.13§	1.60±0.16§	4.2±0.5†
28	3.7±0.6†	2.24±0.16§	1.70±0.15§	4.4±0.5†

*Values are means ±SD. To convert values for phosphate to millimoles per liter, multiply by 0.3229; to convert values for magnesium and ionized calcium to millimoles per liter, multiply by 0.5.

†P<0.001 for the comparison with the value obtained on day 1.

‡P<0.02 for the comparison with the value obtained on day 1.

§P<0.01 for the comparison with the value obtained on day 1.

Effects of Abstinence on Plasma Hormone Concentrations

On admission, the alcoholic patients had higher mean plasma

renin activity and higher plasma concentrations of aldosterone, norepinephrine, epineph- rine, and cortisol than did the normal subjects (Table 8). The mean plasma concentration of parathyroid hormone in the alcoholic patients was lower than that in the normal subjects, and all the patients with hypo- calcemia or hypomagnesemia had low plasma concentrations of parathyroid hormone. After four weeks of abstinence, their values were similar to those in the normal subjects, except that the mean plasma concen-tration of parathyroid hormone was still lower than that in the normal subjects.

DISCUSSION

We found that patients with chronic alcoholism have a variety of renal tubular abnormalities that are independent of chronic liver disease, pancreatitis, and rhabdomyolysis and that occur in the presence of nor- mal glomerular filtration. The abnormalities were reversible,

Table 7. Changes in Renal Tubular Function in 61 Alcoholic Pa-tients during Four Weeks of Abstinence in the Hospital.*

DAY	RENAL THRESHOLD FOR PHOSPHATE EXCRETION	FRACTIONAL EXCRETION OF CALCIUM	FRACTIONAL EXCRETION OF MAGNESIUM	FRACTIONAL EXCRETION OF POTASSIUM
	mg/dl	percent		
1	3.1±0.7	2.5±1.1	3.3±1.8	9.1±4.0
4	4.2±1.4†	2.2±0.9	3.1±1.3	4.9±2.3†
7	4.2±0.8†	2.2±0.9	2.9±1.2	4.5±2.1†
28	3.8±0.7†	2.0±0.5‡	2.2±1.3‡	7.2±2.8‡

*Values are means ±SD. To convert values for renal threshold for phosphate excretion to millimoles per liter, multiply by 0.3229.

†P<0.001 for the comparison with the value obtained on day 1.

‡P = 0.02 for the comparison with the value obtained on day 1.

in most instances disappearing after four weeks of abstinence, despite many years of alcohol abuse. The fact that alcoholism is associated with multiple abnormalities of renal tubules, involving differ- ent segments of the nephron, leads to the conclusion that exposure to ethanol may cause generalized tubu- lar dysfunction. The presence of glycosuria, aminoaciduria, and a decreased renal threshold for phosphate excretion suggests that ethanol abuse may result in a generalized reduction in the reabsorptive ability of the proximal tubular cells. This hypothesis is supported by recent studies indicating that ethanol interferes with the carrier functions of these cells by decreasing Na^+/K^+-ATPase activity.[12,14] Thirty-eight percent of the patients with chronic alcoholism had increased fractional excretion of .Brmicroglobulin, another dis- turbance indicating abnormal proximal tubular function.[15] The increases in the urinary excretion of N-acetyl-,8-o-glucosaminidase, a lysosomal enzyme from the proximal tubules, and of alanine aminopepti- dase, a brush-border enzyme, also suggested the presence of proximal tubular defects.[16] Rat-kidney tissue contains alcohol dehydrogenase activity that appears to be similar or identical to that of the class I alcohol dehydrogenase in liver.[17,19]

The oxidation of ethanol by alcohol dehydrogenase generates acetalde- hyde, which may inhibit the activity of several enzymes, causing the cells to become less efficient.[14,20] In addition, the oxidation of acetaldehyde, especially by the acetaldehyde dehydrogenase, that has a low- er Michaclis-Menten constant, generates species of free radical oxygen that are capable of damaging cell membranes.[21,n] In patients with chronic alcoholism these mechanisms may result in increased urinary excretion of enzymes and proximal tubular dysfunction.

Fractional calcium excretion was increased in one fourth of our patients, in whom serum concentrations of ionized calcium were slightly reduced. The effect of ethanol in decreasing the Na+/K +- ATPase activity in the proximal tubular cells12 may result in a decrease in the tubular reabsorption of calcium. The suppressed secretion of parathyroid hormone would further con- tribute to the decreased tubular reabsorption of calci- um. The reduced secretion of parathyroid hormone may also have caused the enhanced fractional excretion of magnesium23 found in 21 percent of the alco- holic patients, to which the increased plasma con-centrations of cortisol and aldosterone may have contributed.2•1

During the first days of hospitalization, the frac- tional excretion of potassium decreased to subnormal values, suggesting the possibility of a transport in the distal nephron. The fact that nearly 30 percent of the patients had an inability to acidify their urine indicates impairment in the function of the collecting duct. Our results are coincident with recent studies of the effects of prenatal exposure to ethanol on postnatal renal function. Rats exposed to ethanol during fetal life had defects in potassium excretion when given a

Table 8. Plasma Hormone Concentrations in the Alcoholic Patients on Admission and after Four Weeks of Abstinence and in the Normal Subjects.*

PLASMA HORMONE	ALCOHOLIC PATIENTS (N = 61)		NORMAL SUBJECTS (N = 42)
	ADMISSION	ABSTINENCE	
Parathyroid hormone (pg/ml)	10.2±2.8	11.3±4.2	23.5±6.5†
Renin activity (ng/ml/hr)	1.9±1.8	1.1±1.0‡	1.4±1.1‡
Aldosterone (ng/dl)	11.0±9.0	7.4±4.2‡	8.0±6.6‡
Catecholamines (pg/ml)			
Norepinephrine	558±240	271±119‡	254±204†
Epinephrine	84±35	35±14‡	37±18†
Corticotropin (pg/ml)	28.6±16.1	28.1±31.5	33.6±28.7
Cortisol (mg/dl)			
8 a.m.	18.7±3.5	13.8±3.6	14.3±3.6†
4 p.m.	12.0±4.3	7.7±2.7	7.5±3.1†
Midnight	6.1±3.5	3.5±2.9	3.6±2.4†
Insulin (μU/ml)	12.7±7.5	10.7±5.6§	8.9±2.5‡

*Values are means ±SD. To convert values for aldosterone to picomoles per liter, multiply by 27.74; to convert values for norepinephrine to nanomoles per liter, multiply by 0.005911; to convert values for epinephrine to picomoles per liter, multiply by 5.458; to convert values for corticotropin to picomoles per liter, multiply by 0.2202; to convert values for cortisol to nanomoles per liter, multiply by 27.59; and to convert values for insulin to picomoles per liter, multiply by 7.175.

†P<0.001 for the comparison with the value obtained in the alcoholic patients on admission.

‡P<0.01 for the comparison with the value obtained in the alcoholic patients on admission.

§P<0.05 for the comparison with the value obtained in the alcoholic patients on admission.

potassium load.25 Decreased fractional excretion of potassium, incomplete renal tubular acidosis, and im- paired urine-concentrating ability are the main fea- tures of renal tubular dysfunction in infants with the fetal alcohol syndrome.26 Although the molecular basis of the tubular acidification defect remains to be established, some pathophysiologic mechanisms may be hypothesized. The decrease in urinary excretion of titratable acids may be a consequence of the inappropriately elevated urine pH. The diminished rate of phosphate excretion is presumably a further contrib- uting factor. The limitation of urinary excretion of ammonium may reflect depressed renal ammonia genesis, due lo the overproduction of keto acids,27 and the failure to produce protons distally to titrate the ammo- nia. Low-grade loss of bicarbonate is a common find- ing in distal renal tubular acidosis28 and is partly due to phosphate depletion. Impairment of urinary concentrating ability was a relatively uncommon finding in the alcoholic patients. This defect was due to de- creased renal

sensitivity to vasopressin, as previously reported.29 Since some of these patients consumed large quantities of beer, the prolonged ingestion of large volumes of hypotonic fluids may have caused a decrease in medullary interstitial osmolality, with a consequent reduction in the concentrating ability of the renal medulla.

This study indicates that ethanol is responsible for derangements of monovalent- and divalent cations metabolism and acid-base homeostasis independent- ly of malnutrition, liver disease, pancreatitis, and other intercurrent illnesses. There is little doubt that the pathogenesis of hypophosphate ia'. hypoalce ia, hypomagnesemia, and hypokalcm1a 1s multifactoral. During the acute phase of alcohol withdrawal, the increased plasma insulin concentration, the hyperven- tilation with respiratory alkalosis, and the elevated plasma epinephrine concentrations probably contributed to hypophosphatemia, hypokalemia, and hypo- magnesemia by promoting the movement of ions into cells.30-31 However, since the principal defense against the depiction of minerals and electrolytes is the ability to reduce their losses through the kidneys, the tubular dysfunction undoubtedly contributed to the changes in serum ionic composition. In fact, defects in tubular function were more common in the patients who had corresponding serum abnormalities of serum electrolytes.

Approximately one third of the alcoholic patients had metabolic acidosis on admission. Alcoholic keto- acidosis was the most common disturbance, but a wide variety of simple and mixed acid-base disorders were encountered. There is little doubt that the in- creased generation of kelo acids has a major role in the pathogenesis of alcohol-induced metabolic acido- sis.32,33 However, 55 percent of the patients with metabolic acidosis had impaired renal acidification ability, and 6 of IO patients in whom metabolic acidosis was not accompanied by respiratory or metabolic alkalosis had abnormally low net excretion of acid despite systemic acidemia. These results suggest that in pro- longed, severe ethanol abuse, metabolic acidosis may be induced or aggravated by defects in the renal mechanisms of acid excretion.

Impaired renal acidification and other renal tubular defects are common in patients with chronic liver disease - e.g., chronic active hepatitis, primary biliary cirrhosis, and alcoholic cirrhosis.1•3•34 This study, based on a large battery of tests of tubular damage or dysfunction, suggests that the nephrotoxicity of alco- hol may be independent of any associated liver dis- ease. The prognostic importance of such renal abnormalities cannot be easily assessed, since the tubular damage is generally mild and transient and does not appear to be associated with progressive renal disease.

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