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Oliguria in Patients with Normal Renal Function

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Oliguria is common in critically ill patients and may result from prerenal, renal, and postrenal causes. Oliguria also frequently develops in patients with normal concentrations of blood urea nitrogen and creatinine. Most of these patients do not develop renal failure. The authors prospectively studied 100 patients admitted to the ICU to determine the etiology of oliguria in these patients. Eighteen patients (18%) developed oliguria (<0.33 ml · kg^{-1} · h^{-1} × 2 h). Seven and eleven patients were felt on clinical assessment to be hypovolemic or normovolemic, respectively. Compared with the hypovolemic patients, the normovolemic oliguric patients had significantly lower serum osmolalities (278 ± 3 *vs.* 290 ± 5 mOsm/kg H_2O) and serum sodium concentrations (138 ± 3 *vs.* 132 ± 1 mEq/l). In addition, normovolemic patients had significantly higher urine sodium concentrations (83 ± 12 *vs.* 13 ± 2 mEq/l), fractional excretion of sodium (1.14 ± 0.2 *vs.* 0.15 ± 0.03), and renal failure indices (1.5 ± 0.3 *vs.* 0.21 ± 0.04). ADH concentrations in six hypovolemic and six normovolemic patients were increased in both groups but not significantly different. The hypovolemic patients increased their urine output from 17 ± 2 ml/h to greater than 0.5 ml · kg^{-1} · h^{-1} following a 500-ml bolus of normal saline. The normovolemic oliguric patients remained oliguric following the saline bolus (13 ± 2 to 19 ± 3 ml/h). The authors conclude that oliguria is common in critically ill patients and results from renal hypoperfusion and ADH excess. Urine sodium, fractional excretion of sodium, and renal failure index are not useful for predicting renal failure in these patients but are useful for separating the two prerenal etiologies for oliguria. (Key words: Hormones: antidiuretic hormone. Kidney: oliguria.)

OLIGURIA is a common problem in the intensive care unit (ICU) and may result from a variety of prerenal, renal, and postrenal causes.[1] We frequently see patients who develop oliguria in the ICU despite normal concentrations of blood urea nitrogen (BUN) and creatinine. These patients were excluded from previous studies of oliguria that assessed patients with elevated BUN and creatinine values. This study was designed to determine the etiology of oliguria in patients with normal BUN and creatinine concentrations. The results indicate that oliguria with normal renal function results from either hypovolemia or normovolemia with excess ADH secretion.

Methods

One hundred consecutive patients with normal renal function (BUN ≤ 30 mg/dl, creatinine ≤ 1.5 mg/dl) admitted to the ICU were prospectively studied. Patients were evaluated with regards to age, sex, diagnosis, clinical volume status, type and amount of iv fluids, nutrition, medications, fluid input and output, serum electrolytes (sodium, potassium, chloride, bicarbonate), serum creatinine, BUN, serum glucose, and urine specific gravity. Urine electrolytes, urine creatinine, and urine osmolality were measured on "spot" urine samples (from urinary catheters) in all patients for whom two consecutive hourly urine outputs were less than 0.33 ml · kg^{-1} · h^{-1} (defined as oliguria). Simultaneous measurements of serum electrolytes, osmolality, BUN, and creatinine were made. The fractional excretion of sodium (FENa) was calculated as the urine to plasma sodium concentration ratio divided by the urine to plasma creatinine concentration ratio, multiplied by 100. The renal failure index (RFI) was calculated as the serum sodium concentration divided by the urine to plasma creatinine concentration ratio. All oliguric patients also had a microscopic examination performed on their urine.

Flow-directed pulmonary artery catheters were not routinely inserted in patients with oliguria. Data from these catheters do not provide a direct assessment of intravascular volume or renal blood flow.[2,3] It is our standard policy to first administer a fluid bolus to patients with oliguria (unless they are hemodynamically unstable and it is felt that the fluid bolus would be harmful). Further therapy for oliguria is based upon response to fluid bolus, clinical assessment, and urine electrolytes. Therapy may include insertion of a flow-directed pulmonary artery catheter if it is felt that assessment of pulmonary capillary wedge pressure and cardiac output would be useful. In patients with pulmonary artery catheters in place cardiac output (CO) was measured by thermodilution.

Normovolemia was defined as normal blood pressure (compared with outpatient values), lack of tachycardia (heart rate < 110 beats per min), absence of orthostatic changes (lying to sitting), normal skin turgor, normal CVP (5–10 cmH_2O) and normal PCWP (8–15 mmHg, when available). Hypovolemia was defined as the occurrence of a low blood pressure (mean arterial pressure less than 90% of outpatient values), presence of tachycardia (>110 beats per min), occurrence of orthostatic changes (mean arterial pressure decrease > 10% or heart rate increase > 10% upon changing position from supine to sitting), CVP < 5 cmH_2O, and a PCWP ≤ 6 mmHg, when available. Plasma ADH concentrations were measured by radioimmunoassay (Nichols Institute, San Juan Capistrano, CA) in six normovolemic and six hypovolemic oliguric patients (normal values in hydrated patients < 1 pg/ml).

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Normal serum sodium in our lab ranges from 135–154 mEq/l. The syndrome of inappropriate antidiuresis (SIAD) was said to be present when hyponatremia and serum hypo-osmolality developed in normovolemic patients with normal renal function in association with inappropriately concentrated urine and a urine sodium greater than 30 mEq/l.

Data are presented as mean ± SEM and were analyzed by 2-tailed Student's *t* test and chi-square analysis where appropriate.

Results

None of the patients who developed oliguria were receiving diuretics nor had they been given fluid boluses prior to evaluation. In addition, none of the oliguric patients received radiocontrast dyes or nephrotoxic drugs at the time of initial evaluation.

Eighteen patients (18%) developed oliguria (table 1). Daily fluid intake was similar in oliguric and nonoliguric patients (3064 ± 252 *vs.* 3076 ± 230 ml/day). There were no differences in type of iv fluids or colloids used in either group. None of the oliguric patients had diarrhea or evidence of excessive fluid loss through the skin (*i.e.*, high temperature, severe sweating, burns). Eleven oliguric patients (61%) were classified on the basis of clinical data as normovolemic. Five of the normovolemic patients had pulmonary artery catheters in place that revealed normal PCWP (8–15 mmHg) and cardiac indices (2.5–3.1 $l \cdot min^{-1} \cdot m^{-2}$). Seven oliguric patients were classified as hypovolemic (table 1). Both groups were composed of medical and surgical patients and there was no significant relationship between oliguria and a specific diagnosis (table 2). When compared to the hypovolemic group (table 1), the normovolemic patients had a significantly ($P < 0.05$) lower serum osmolality and serum sodium concentration. The normovolemic oliguric group had a significantly higher urine sodium concentration, FENa, and RFI. There were no significant differences between oliguric patients with regards to age, urine osmolality, urine sediment, BUN, serum creatinine, BUN/creatinine ratio, lowest urine output, drug usage, or diagnoses.

TABLE 1. Characteristics of Oliguric Patients

Characteristic	Normovolemic	Hypovolemic
n	11	7
Age (yr)	63 ± 4	53 ± 9
Male:female	6:5	2:5
Urine output (ml/h)	15 ± 2	18 ± 2
Serum osmolality (mOsm/kg H_2O)	278 ± 3*	290 ± 5
Serum sodium (mEq/l)	132 ± 1*	138 ± 3
Urine osmolality (mOsm/kg H_2O)	522 ± 36	525 ± 34
Urine sodium (mEq/l)	83 ± 12*	13 ± 2
BUN (mg/dl)	14 ± 3	15 ± 3
Creatinine (mg/dl)	0.9 ± .08	1.0 ± .13
BUN/creatinine	15 ± 3	15 ± 3
Urine/plasma creatinine	61 ± 7	54 ± 8
FENa	1.14 ± 0.2*	0.15 ± 0.03
RFI	1.5 ± 0.3*	0.21 ± 0.04
Urine sediment	Normal	Normal
PCWP (mmHg)	8–15 (n = 5)	5, 6 (n = 2)
CVP (cm H_2O)	5–10 (n = 5)	2, 4 (n = 2)
Cardiac index ($l \cdot min^{-1} \cdot m^{-2}$)	2.5–3.1 (n = 5)	2, 2.6 (n = 2)

* $P < 0.05$ compared with hypovolemic group.

TABLE 2. Admitting Diagnoses of Oliguric Patients

Diagnoses	Normovolemic (n = 11)	Hypovolemic (n = 7)
Surgical		
Colectomy	2	
Whipple (pancreatic CA)	1	1
Vascular	2	1
Multiple trauma	2	
Medical		
Cardiac arrest		1
GI bleeding	2	1
Sepsis	1	2
Malignancy	1	1

The hypovolemic patients were given a fluid bolus (500 ml of normal saline over 5–10 min) and all increased their urine output to greater than 0.5 $ml \cdot kg^{-1} \cdot h^{-1}$ (17 ± 2–42 ± 6 ml). Six of the normovolemic oliguric patients were given the same fluid bolus and in none of these patients did urine output increase to normal (13 ± 2–19 ± 3 ml/h). In two of these patients 3 and 4 fluid boluses were given and pulmonary edema developed.

Plasma ADH concentrations were similar in the normovolemic (mean 4.2 ± 0.7 pg/ml, range 1.6–6.3 pg/ml) and hypovolemic oliguric patients (mean 3.7 ± 0.6 pg/ml, range 2.4–6.0 pg/ml). The normovolemic oliguric patients met the criteria for SIADH and were subsequently treated with furosemide at doses sufficient to maintain a urine output greater than 0.5–1 $ml \cdot kg^{-1} \cdot h^{-1}$. All oliguric patients left the ICU and none developed renal failure (*i.e.*, an increase in BUN or creatinine). All patients maintained urine outputs greater than 0.5 $ml \cdot kg^{-1} \cdot h^{-1}$ following treatment with fluid or furosemide.

Discussion

Oliguria is felt to be present when urine volume is less than 500 ml/day[4] or 0.3–0.5 $ml \cdot kg^{-1} \cdot h^{-1}$. In critically ill patients with indwelling urinary catheters, oliguria is usually defined using hourly urine outputs. Eighteen percent of the patients in this study developed oliguria using this criterion. Oliguria developed in the setting of a normal BUN and creatinine. However, because BUN and creatinine may remain normal for hours following renal insult, normal values can not be relied upon to rule out prerenal or renal causes for oliguria.[5] Early recognition

of the cause of oliguria is important because hypovolemic prerenal oliguria, if left untreated, may progress to renal failure.

We report that oliguria developed in 18% of our critically ill patients as a result of either hypovolemia or during a combination of normovolemia and excess ADH secretion. Using the definitions of normovolemia and hypovolemia as defined in the Methods, we were able to separate out two groups of oliguric patients. Oliguria from hypovolemia probably resulted from a combination of decreased renal blood flow, decreased atrial natriuretic hormone (ANH) release, and increased ADH secretion. We believe that oliguria in our normovolemic patients probably resulted from excess ADH secretion. It is also possible that decreased ultrafiltration pressure (*i.e.*, efferent arteriolar dilation, afferent arteriolar constriction), increased glomerular capillary osmotic forces, and some degree of decreased renal blood flow contributed to the oliguria. We postulate that ADH played a significant role because these patients had inappropriately concentrated urine that was high in sodium in the face of relative normovolemia (with a normal BUN and creatinine) and serum hypo-osmolality. These patients lacked both an osmolar and a volume stimulus for ADH secretion and would be designated as having the syndrome of inappropriate secretion of antidiuretic hormone (SIADH). Plasma ADH concentrations were found to be equally elevated in both hypovolemic and normovolemic patients. ADH concentrations were appropriately increased in hypovolemic patients due to low intravascular volume. However, the normovolemic oliguric patients had low plasma sodium values and should have had suppressed ADH concentrations. Manoogian *et al.*[6] reported similar concentrations for ADH in their patients with SIADH (*i.e.*, 2–4 pg/ml). However, in both reports the ADH concentrations were inappropriately elevated for the prevailing serum osmolality.

Administration of repeated fluid boluses to two patients with normovolemic oliguria, in an attempt to obtain an adequate urine output, resulted in fluid overload (*i.e.*, peripheral and pulmonary edema) before an adequate urine output was achieved. These data suggest that excess ADH caused fluid retention and that administration of large amounts of fluid to patients with nonsuppressible ADH concentrations may be deleterious.

We did not perform clearance studies (*i.e.*, creatinine clearance or PAH clearance) to document significant decreases in GFR or renal blood flow as the cause of oliguria in the hypovolemic patients. These studies require time to perform or time for adequate urine collections and we did not believe it was appropriate to wait for the results of these studies. In addition, it is difficult to evaluate creatinine clearance without knowledge of baseline values in critically ill patients (*i.e.*, many patients have some underlying renal disease). However, we believe that our clinical assessment, low urine sodium concentrations, and response to fluid bolus suggest impaired distal tubular delivery of solute as the cause for the oliguria in these patients.

Burrows *et al.*[7] found that 16 of 24 pediatric patients developed oliguria following posterior spinal fusion for correction of scoliosis. All but one oliguric patient had evidence for ADH-mediated oliguria. Deutsch *et al.*[8] reported a decrease in urine volume from 12 to 0.8 ml/min per 1.73 m^2 and an increase in urine osmolality from 84 to 609 mOsm/kg H_2O following halothane anesthesia. In seven of 11 subjects these alterations were reversed by iv ethyl alcohol, suggesting that ADH was responsible for the antidiuresis. Beck *et al.*[9] reported a 60% decrease in urine flow following injection of 1 mU of vasopressin in rats. Urine flow decreased by over 90% following 5 mU of vasopressin. Jaju *et al.*[10] demonstrated that bladder distention in dogs produced a dose-dependent oliguria that corresponded to rises in circulating ADH levels. Others[11,12] have implicated increases in ADH secretion as a cause of a decrease in urine output in the postoperative period. We now report that ADH-associated antidiuresis is a common cause of oliguria in critically ill patients. We believe that stress, pain, and nausea were the most likely stimuli for release of and nonsuppressibility of ADH. It is uncertain whether the ADH release alone caused the oliguria in our normovolemic patients. It is likely that concomitant hormonal stimuli and decreased ultrafiltration pressure contributed to the oliguria. Nevertheless, we were able to separate two groups of patients with prerenal causes of oliguria.

Urinary diagnostic indices have been used to ascertain the causes of early acute renal failure.[13–15] These studies involved patients with oliguria and acute elevations in BUN and creatinine. Patients with normal BUN and creatinine concentration and oliguria were not studied. Miller *et al.*[13] was able to separate patients into prerenal (hypovolemia) and renal etiologies of renal failure based upon urine sodium, osmolality, and creatinine values. Prerenal renal failure was characterized by a urine osmolality above 500 mOsm/kg H_2O, urine sodium less than 20 mEq/l, urine/plasma creatinine ratio greater than 40, RFI less than 1, and FENa less than 1. Intrinsic renal failure was suggested by a urine osmolality less than 350 mOsm/kg H_2O, urine sodium greater than 40 mEq/l, urine/plasma creatinine ratio less than 30, RFI greater than 1, and FENa greater than 1. Since Miller's report, numerous investigators[15–22] have studied the usefulness of urine osmolality and electrolyte values for determining prerenal *versus* renal etiologies of renal failure. These tests often fail to discriminate among the various etiologies of renal failure[15–22] and many clinicians have abandoned their use.

Our data suggest that the FENa can be used to separate

TABLE 3. Urinary Indices in Oliguria

	Prerenal		Renal
	Hormonal Excess	Hypoperfusion	
Urine osmolality (mOsm/Kg H_2O)	>400	>400	<400
Urine sodium (mEq/l)	>40	<20	>40
U/P sodium	>0.25	<0.25	>0.25
U/P creatinine	>40	>40	<20
RFI	>1	<1	>1
FENa	>1	<1	>1
Urine sediment	Normal	Normal	Abnormal

U/P = urine/plasma. RFI = renal failure index. FENa = fractional excretion sodium.

acutely oliguric patients, with a normal BUN and creatinine, into two groups: hypoperfusion oliguria and ADH excess-associated oliguria. The data indicate that ADH excess-associated oliguria responds poorly to fluid administration. Use of diuretics in this group to mobilize fluid was safe. The utility of urine diagnostic indices for evaluating oliguria in patients with normal BUN and creatinine concentrations has not been evaluated previously. Our results indicate that high urine sodium (*i.e.*, >40 mEq/l), FENa (*i.e.*, >1), and RFI (*i.e.*, >1) are poor predictors of renal failure in these patients.

It is common practice to classify patients on clinical grounds as having an expanded, contracted, or normal intravascular volume. Chung *et al.*[23] evaluated a variety of clinical criteria (*i.e.*, orthostatic changes, CVP, skin turgor) for predicting volume status in hyponatremic patients and found them to lack sensitivity and specificity. However, they used the response of the plasma sodium to normal saline administration as the criterion for defining intravascular volume status. This criterion is not a proven indicator of intravascular volume status in critically ill patients. We used clinical criteria to estimate intravascular volume status in our patients, realizing that it is not always reliable. However, the response of urine output to saline administration and the urinary sodium value both suggested that our clinical assessment was accurate. Hypovolemic patients had an increase in urine output following fluid administration and had urine sodium values less than 20 mEq/l. Normovolemic patients had urinary sodiums greater than 30 mEq/l and failed to increase their urine output following fluid administration. Chung *et al.*[23] did report that urine sodium concentrations less than 30 mEq/l were sensitive (80%) and specific (100%) for hypovolemia. Thus, we believe that our assessment of intravascular volume was accurate based upon clinical exam, response to fluid bolus, and urine sodium concentration.

Atrial natriuretic hormone (ANH) is a potent natriuretic and diuretic hormone that possesses aldosterone inhibiting and vasopressin suppressing actions.[24,25] Secretion of ANH is stimulated by elevations in intravascular volume and increases in right atrial pressure. ANH levels are elevated in patients with SIADH and are felt to be involved in the escape from salt and water retention that occurs (*i.e.*, ANH antagonizes the water retention of vasopressin).[6] Elevations in ANH most likely contributed to the natriuresis seen in our SIADH patients. Aldosterone inhibition by both volume retention and ANH may also have played a role. ANH can also minimize water retention and prevent pulmonary edema. However, pulmonary edema was still possible when excess water (*i.e.*, fluid boluses) were given to two of our patients.

Based upon our data, we propose a new classification of oliguria in which prerenal causes are divided into hypoperfusion and hormonal excess etiologies (table 3). RFI, FENa, and urine sodium values are similar between patients with hormonal excess prerenal oliguria and renal oliguria. Thus, these indices are not specific for acute renal failure in oliguric patients with a normal BUN and creatinine. However, these patients can be separated based upon urine osmolality, urine/plasma creatinine ratio, and urine sediment analysis. Both groups of patients with prerenal oliguria have similar urine osmolalities, urine/plasma creatinine ratios, and urine sediments. They can be separated based upon urine sodium, urine/plasma sodium ratio, RFI, and FENa.

The results of this study provide new clinical findings. Oliguria is common (18% in this series) in critically ill patients and primarily results from prerenal etiologies as a result of renal hypoperfusion and hormonal excess. This is the first report implicating ADH excess as a common cause of oliguria. Normovolemic oliguria responded to furosemide therapy; none of these patients developed renal failure and all patients were discharged from the ICU. Hypovolemic oliguria responded to fluid administration and none of these patients developed renal failure. Urine sodium, RFI, and FENa were not useful predictors of renal failure but were useful for separating the two causes of prerenal oliguria.

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