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Research Article

RENAL FUNCTION DURING AND AFTER DIABETIC COMA [1]

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Though it has long been clinically recognized that diabetic coma may be associated with renal inefficiency, there is a paucity of quantitative studies of renal function during and after diabetic coma. There are no reports at all in which complete evaluation of renal function by the specific clearance methods of Homer Smith (1) and his coworkers (2) have been attempted. McCance and Widdowson (3) found the glomerular filtration rate lowered in five subjects with diabetic coma. From the low creatinine/inulin clearance ratios which they obtained, these authors believed that tubular injury occurred during coma. It was for the purpose of getting more information on the nature of the renal disturbance in diabetic coma that the present investigation was undertaken. This report deals with the results of serial studies of specific renal function tests in six subjects during diabetic coma and at short intervals thereafter.

METHODS

Clearances of mannitol, p-aminohippurate (PAH), and urea, and measurements of Tm_{PAH} were performed on six patients admitted to the wards of the hospital in diabetic coma. Several clinical features and laboratory findings at the time of hospitalization are presented in Table I. In five subjects the first studies were carried out within five hours of their arrival. Emergency supportive measures had already been started, including insulin and physiological salt solution, but the patients were still comatose (Cases 3, 5, 6) or semicomatose (Cases 2 and 4). Neither the clinical condition nor the emergency management were identical in these cases, but all had comparable hyperglycemia, acidosis, dehydration and electrolyte loss. Tachycardia and hypotension were present in all cases. In no instance was glucose used in the intravenous fluids before or during the clearance tests. In the sixth subject, the renal studies were not begun until the 11th hospital day. However, the routine blood

chemical analyses were available from the first day. In addition to the initial renal studies, from one to three tests were carried out later.

For the measurement of glomerular filtration rate (GFR), the mannitol clearance (C_M) was determined. At the time of initiation of these and similar studies, the fact that mannitol clearances were slightly lower than inulin clearances had not been firmly established. The deviations, however, from the true value for GFR are too slight to invalidate the use of mannitol clearances in these studies, for the abnormalities found were significantly large. Each clearance test was performed in four periods, the first two with low serum PAH levels and the last two with high levels for the Tm_{PAH} measurements. In all instances the load of PAH was much greater than was required for saturation of the tubular excretory system. Urea clearances were determined only in the first two periods.

PAH was analyzed by the method described by Goldring and Chasis (2); mannitol, by Corcoran and Page (4); urea, by Hoffman (5). In the mannitol analyses, samples with elevated glucose concentrations were calibrated against standard mannitol solutions to which an equivalent amount of glucose was added. The correction was usually not significant.

RESULTS

The results of the tests for mannitol clearance (C_M), p-aminohippurate clearance (C_{PAH}), urea clearance (C_{Urea}) and Tm_{PAH}, and their ratios, corrected to 1.73 sq. m. of surface area, are shown in Table II. The cases can be divided into two groups according to the pattern of recovery. The data in Group 1, which consisted of Cases 2, 3, 4, and 6, are presented graphically in terms of percentage of normal in Figure 1; those of Group 2, which consisted of Cases 1 and 5, are shown in Figure 2.

The findings in Group 1 were of the same general pattern in all cases. There was, at the time of coma, a reduction to below normal of all clearances. These were restored to normal or supernormal values in a few days after correction of dehydration, acidosis, and electrolyte deficits. Azotemia subsided quickly, the changes of serum nonprotein ni-

TABLE I

Initial clinical features and laboratory findings

Case	1	2	3	4	5	6
Age	38	27	29	60	22	53
Serum chemical analyses						
NPN, mg./100 cc.	100*	53*	40	104	76	53
Glucose, mg./100 cc.	550*	644	712	985	390	692
CO_2 comb. power, cc./100 cc.	30*	8	10	34	18	8
Na, mEq./liter	—	135	137	146	139	132
Cl, mEq./liter	—	95	101	104	114	100
Urinalyses						
Albumin	4+	0	0	2+	3+	1+
Glucose	4+	4+	4+	3+	4+	4+
Nitroprusside test	4+	4+	4+	1+	4+	4+
Ferric chloride test	4+	4+	4+	0	2+	4+
Specific gravity	1.022†	1.018	1.023	1.030	1.021†	1.025
Blood pressure	105/75	100/70	90/60	82/60	80/55	80/60
Pulse	120	120	132	104	132	120
Respiration	25	40	40	24	40	28
Temperature, rectal, °F.	102.4	102.0	98.6	102.8	99.0	99.0
Precipitating cause of coma	No insulin for 2 weeks	Submandibular abscess; vulvitis	Inadequate insulin therapy (one injection weekly)	Vaginal moniliasis; unknown diabetic	No insulin for 4 weeks. Alcoholic spree	Unknown untreated diabetic

* Serum analyses after 18 hours.
** Isosthenuric urine occurred within a few hours, and persisted for several days thereafter.

trogen levels within 48 hours being 53 to 34, 40 to 20, 100 to 53, and 53 to 45 mg./100 cc. respectively. In contrast with these patients, those of Group 2 showed an azotemia which became more intense in spite of correction of the several deficits. The uremia, however, was of limited duration.

TABLE II

Specific renal function tests*

Case	Surface area	Hospital day	C_M	C_{PAH}	Tm_{PAH}	C_{Urea}	C_M/C_{PAH}	C_{PAH}/Tm_{PAH}	C_M/Tm_{PAH}
			cc./min.	*cc./min.*	*mg./min.*	*cc./min.*			
1. G.H.	1.55	11	21.6	77.4	5.2	16.9	0.28	15.0	4.2
		21	62.9	519.0	56.5	50.7	0.12	9.2	1.1
		36	70.0	454.0	68.2	48.0	0.15	6.6	1.0
2. A.L.	1.4	1	98.0	381.0	37.4	48.8	0.26	10.2	2.62
		9	128.0	725.0	104.0	76.9	0.18	7.0	1.23
3. A.H.	1.68	1	95.0	398.0	49.7	36.2	0.24	8.0	1.9
		13	170.0	902.0	111.0	101.0	0.19	8.2	1.53
		21	172.0	816.0	142.0	77.0	0.21	5.8	1.21
4. L.R.	1.42	1	13.2	148.0	71.5	10.3	0.09	2.1	0.19
		8	99.0	488.0	79.5	68.2	0.20	6.2	1.25
5. J.C.	1.66	1	0.0	0.0	0.0	0.0	—	—	—
		6	11.5	25.3	2.53	5.95	0.46	10.0	4.5
		15	66.0	303.0	61.7	44.2	0.22	4.9	1.1
		21	85.2	577.0	93.5	56.2	0.15	6.2	0.91
6. M.R.	1.8	1	24.2	162.0	28.2	14.0	0.15	5.8	0.86
		12	75.2	580.0	89.7	49.5	0.13	6.5	0.85
		36	94.0	595.0	114.0	40.2	0.16	5.2	0.83
Normal Values			117±15.6	594±102	77.5±12.9	75±15	0.20	7.6	1.51

* Corrected to 1.73 sq. m. of surface area.

The serum nonprotein nitrogen levels, which reached peaks of 158 and 122 mg./100 cc. respectively, returned to normal within two weeks (see Figure 2). The serum creatinine concentrations in these two cases reached levels of 8 mg./100 cc., which is much higher than is seen in simple dehydration. C_M, C_{PAH}, and Tm_{PAH} were markedly reduced in the initial tests, and the ratios were decidedly abnormal. Only slowly was there evidence of a return to normal function. As will be discussed later, it is probable that in these two patients a reversible organic lesion had occurred.

In all cases, the return to essentially normal values of renal function excluded the possibility that the initial renal disturbances were due to intrinsic renal disease not related to the diabetic acidosis.

DISCUSSION

Much of the interpretation of the clearance values and their ratios found in these studies depends upon the significance of C_{PAH} and Tm_{PAH}. If it can be assumed that, in the cases of Group 1, the extraction of PAH was not appreciably reduced by the disease, C_{PAH} can be regarded as a measure of effective renal plasma flow, and Tm_{PAH} as a meas-
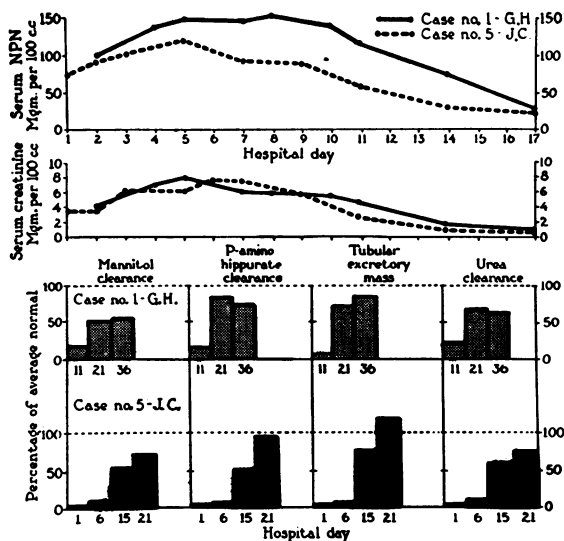

FIG. 2. SERIAL SERUM NPN AND CREATININE VALUES, AND THE SPECIFIC RENAL FUNCTION TESTS OF GROUP 2

Renal function tests are presented as per cent of average normal after correction for surface area.

ure of maximal tubular excretory capacity. Several features of the data point to the validity of such an assumption. In the first place, Tm_{PAH} was nearly normal in Case 4 during the coma period, even when C_M, C_{Urea}, and C_{PAH} were greatly reduced. Thus a normal PAH extraction is at least possible in the presence of severe diabetic acidosis. Secondly the ratios C_M/C_{PAH}, C_{PAH}/Tm_{PAH}, and C_M/Tm_{PAH} were not unreasonably deviated from normal in any of the four cases of Group 1. If the tubular extraction of PAH were poor, the ratios C_M/C_{PAH} and C_M/Tm_{PAH} should have been unusually high, unless an independent reduction in C_M equal to the reduction in extraction of PAH had occurred. On the other hand it is theoretically plausible that the combination of dehydration, renal ischemia, cellular deficiency of potassium, phosphorus, and other constituents, as well as disturbances in endocrine secretions, would markedly alter the ability of the tubular cells to excrete PAH from the renal interstitial fluid. The recent findings (6), that the amount of available acetate and possibly other metabolic intermediates influences the tubular excretory capacity, serve to emphasize the dependence of tubular function upon normal cellular metabolism.

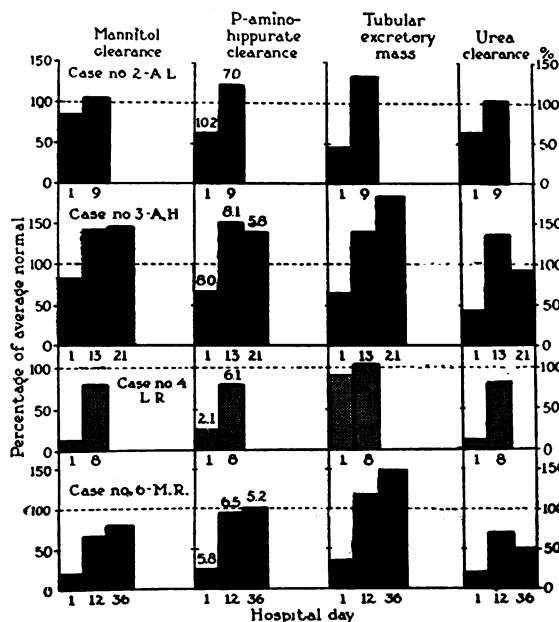If the extraction of PAH was subnormal in the initial studies on the patients of Group 1, the data

FIG. 1. SPECIFIC RENAL FUNCTION TESTS OF GROUP 1

Values are presented as per cent of average normal after correction for surface area. The numbers above the p-aminohippurate bars are the ratios of C_{PAH} to Tm_{PAH}.

defy interpretation, other than the generalization that both glomerular and tubular functions were depressed during diabetic coma and that they were quickly restored to normal or better than normal. If, however, the assumption, based on the above mentioned considerations, is made that the impairment of extraction of PAH was not great enough to alter the validity of the usual interpretations of clearance data, then a reasonable analysis of the events is possible. In Cases 2 and 3, the effective renal plasma flows were considerably reduced while the glomerular filtration rates were nearly normal. The filtration fractions were elevated. At the same time, Tm_{PAH} was markedly lowered. These findings implied a virtual exclusion from functioning, at least momentarily, of a large number of nephrons, but a normal or supernormal blood supply to those which were functioning. On the other hand, in Case 4 a normal Tm_{PAH} was associated with greatly depressed values for C_M and C_{PAH} and C_{Urea}. The ratio C_{PAH}/Tm_{PAH} was 2.1 instead of the normal 7.6, which finding implied severe ischemia of all nephrons. This diminished renal blood flow was undoubtedly related to a decreased cardiac output. The fact that the filtration fraction was also very low—0.09 instead of the normal 0.20—indicated that any renal arteriolar constriction involved in the renal ischemia failed to produce a rise in effective intraglomerular pressure. The presence of fever in this patient may account for the low filtration fraction by the production of a relative efferent arteriolar dilatation. The low filtration rate in the presence of normal Tm permits a reasonable explanation for the unusual (but not rare) findings of moderate glycosuria in spite of intense hyperglycemia, and of an almost complete absence of acetoacetic acid in the urine (see Table I). That the renal ischemia was prolonged and severe but still reversible is seen in the serum nonprotein nitrogen concentration of 100 mg./100 cc., and its fall to nearly normal in 48 hours. In Case 6, too, the data point to ischemia of the working nephrons, with many nephrons showing virtually no function, since Tm_{PAH} was reduced to a third of normal.

It is worthy of note that following recovery from the diabetic coma, the patients in Group 1 showed not merely a rapid return of Tm_{PAH} to normal

levels, but actually an elevation to supernormal values (Cases 2, 3, and 6). That this occurrence of supernormal values is not an isolated finding peculiar to diabetes is seen from reports of similarly high Tm_{PAH} values under other disease or experimental conditions (7–10). Sirota (9), for example, reported a Tm_{PAH} of 168 per cent of normal (130 mg./min.) following recovery from "lower nephron nephrosis" due to carbon tetrachloride poisoning. What the significance of these supernormal findings in these different situations can be is a matter of conjecture.

In the two patients in Group 2 there need be less conjecture about the completeness of extraction of PAH by the tubules. The extremely low Tm_{PAH} (6.7 per cent of normal on the 11th day in Case 1 and 3.3 per cent of normal on the sixth day in Case 5) and the distorted, unreasonable ratios point to poor extraction of PAH. This phenomenon might be due to injury to proximal tubules caused by a poor renal blood flow. But if this were the nature of the injury, the glomerular filtration rate and serum nonprotein nitrogen concentration should have returned to normal by the time of these tests, for dehydration, ketosis, and electrolyte deficits had already been corrected. It was more likely that the poor extraction, the exaggerated ratios, the relatively prolonged azotemia, the isosthenuria, and the slow return of the renal function tests to normal values were associated with damage to the tubules and with interstitial edema. In other words these patients presented, in a relatively mild form, the picture seen in the type of acute renal failure commonly called "lower nephron nephrosis" (9, 11, 12).

Only in the absence of recognizable oliguria and in the mildness of the uremia did the syndrome shown by these two patients differ from that of usual "lower nephron nephrosis." However, though severe oliguria bordering on anuria is the presenting symptom in almost all cases of "lower nephron nephrosis," it is not necessarily essential to the disease. In such cases, oliguria appears to be due to a large nonspecific reabsorption of tubular fluid across the damaged tubular membrane in relation to the amount of modified glomerular filtrate presented to it. If the glomerular filtration is relatively large, the quantity of fluid un-

reabsorbed and ultimately excreted as an isosthenuric urine may be considerable. Indeed this phenomenon is what probably occurs during the first days of diuresis in all cases of "lower nephron nephrosis." In spite of the absence of oliguria, the nitrogenous excretion may be low enough to produce prolonged azotemia. One of Sirota's cases of carbon tetrachloride poisoning (9) had no demonstrable period of oliguria, and yet had a C_I of 3.78 cc./min., C_{PAH} of 14.4 cc./min., and Tm_{PAH} of 1.85 on the tenth day at a time when the urine output was 2290 cc./day. Burnett, Burrows and Commons (13) intimate such a phenomenon in their cases of alkalosis. We have seen comparable cases of alkalosis of pyloric obstruction with protracted uremia but with eventual return of normal function. The transient uremia without oliguria following diabetic coma reported by McCance and Lawrence (14) may be of the same type.

The alterations in renal function in the cases of both Groups 1 and 2 may be consequences of dehydration of varying degrees of severity. Depletion of body water and electrolytes results in decreased blood volume and diminished cardiac output causing a reduction of renal blood flow as part of a reduction of flow to all areas of the periphery. Renal hemodynamic changes secondary to hypotension accentuate the diminution in renal blood flow. The changes may involve all nephrons; or many nephrons may be temporarily deprived of function, the remaining nephrons having low, normal, or supernormal blood supply. If the ischemia and metabolic insult is not severe, the alterations in renal function are rapidly reversed by correction of the deficits of water, electrolytes, and insulin, as in the cases of Group 1. When the process is more severe, acute organic damage to the distal tubules may develop leading to "lower nephron nephrosis," as in Group 2.

SUMMARY

The specific clearance methods of Homer Smith were utilized for the study of renal function during and after diabetic coma. The six cases could be divided into two groups.

In the four patients of Group 1, there was, at the time of coma, a reduction of C_M, C_{PAH}, and Tm_{PAH}.

These were quickly restored to normal or supernormal values after repair of dehydration and electrolyte deficits. These rapidly reversed alterations of renal function were believed to be caused by dehydration with its accompanying decrease in blood volume, cardiac output, and renal blood flow, and by the exaggeration of the last defect by the renal hemodynamic response to such dehydration.

In contrast, the two patients in Group 2 showed azotemia which progressed in spite of correction of water and electrolyte loss, and which lasted two weeks. Several days after recovery from coma, C_M, C_{PAH}, and Tm_{PAH} were still markedly reduced, and the ratios were distorted. Only slowly did these values return to normal. In these patients the renal ischemia had apparently produced a reversible organic lesion similar to that found in "lower nephron nephrosis," except that it was milder and that it was unaccompanied by initial oliguria.

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