Plasma Cortisol Level during Hemodialysis with Kolff's Artificial Kidney

Seigi Tsuchida and Hiroatsu Sugawara

*Department of Urology (Prof. S. Shishito),
Tohoku University School of Medicine, Sendai*

Soitsu Fukuchi

*Department of Internal Medicine (Prof. T. Torikai),
Tohoku University School of Medicine, Sendai*

Levels of plasma cortisol were determined by the competitive protein-binding radioassay technique in patients with chronic nephritis undergoing hemodialysis by Kolff's twin-coil kidney.

Marked rise in plasma cortisol occurred in most of the patients studied during artificial hemodialysis. The plasma cortisol level gradually diminished following completion of a six-hour dialysis and returned to predialysis levels 12 to 24 hours after the dialysis. This indicates that the patients adrenal function normally responds to dialytic stress with a secretion of cortisol fully making up for the dialytic loss of plasma cortisol. It, however, still remains probable that a decreased pituitary-adrenal responsiveness may cause an adrenal crisis as the hemodialysis proceeds.

Hemodialysis undoubtedly affects plasma cortisol level because of many stress factors inherent in the use of an artificial kidney involving extracorporeal circulation. As artificial kidneys are provided with cellophane membranes for external dialysis and consequently allow substances of molecular weight below 35,000 to diffuse away freely across the membrane, it is conceivable that cortisol dissipates from the blood plasma during hemodialysis. If the dialytic dissipation of plasma cortisol overbalances the adrenocortical production, an adrenal crisis may be resulted from.

A few studies have been published concerning changes in plasma cortisol levels associated with the external hemodialysis, and conclusions drawn from them are not yet consistent.

Colorimetric assay techniques, based on the principle of Porter-Silber's reaction using phenylhydrazine-sulfuric acid reagent, are used for a routine plasma assay for steroids. The colorimetric and fluorescent methods have disadvantages in that they lack sufficient specificity and hence are liable to give falsely higher values. In contrast to the above methods, the double isotope derivative method is a remarkably sensitive technique, but it is unfortunately cumbersome. Recently, an

important assay method with predictably high sensitivity and reproducibility has been introduced by Beverley and Murphy¹ on the basis of the ability of corticosteroids to combine with plasma protein. Fukuchi *et al.*² obtained highly reliable data concerning levels of hydrocortisone in the blood by using Murphy's technique.

The present paper describes the results of plasma cortisol levels estimated by the competitive protein-binding radioassay method in patients with chronic renal failure undergoing hemodialysis by Kolff's twin-coil kidney.

SUBJECTS AND METHODS

Studies were performed in a series of eight patients with chronic renal failure during a

TABLE 1. Serum electrolyte, BUN and plasma

Case No.	Sub-jects	Age (yrs)	Diagno-sis	He-mo-dia-lysis number	Potassium (mEq/L)		Sodium (mEq/L)		Chloride (mEq/L)		BUN (mg/100 ml)	
					Before dialysis	After dia-lysis	Before dialysis	After dia-lysis	Before dialysis	After dia-lysis	Before dialysis	After dia-lysis
1	N.O.	15	Chronic nephritis	1	6.4	5.0	139	143	103	107	146.4	49.4
				2	6.4	5.0	141	145	109	108	157.2	44.0
				3	7.3	4.9	141	130	112	102	127.4	58.8
				4	7.0	5.2	133	135	99	99	130.0	58.0
				5	7.5	5.9	141	138	102	107	160.2	81.0
2	S.S.	23	"	1	5.4	4.5	143	133	109	92	139.2	65.0
				2	6.3	4.7	134	138	102	102	95.0	45.0
				3	7.4	5.2	136	134	101	103	100.0	49.2
				4	7.2	5.9	136	143	103	109	130.0	66.6
3	R.A.	23	"	1	5.3	4.3	136	142	104	108	116.0	76.0
				2	5.1	4.6	136	135	102	109	93.0	56.0
4	O.S.	24	"	1	5.6	4.2	137	138	109	119	92.0	32.0
				2	5.6	4.2	137	135	109	119	95.0	42.0
5	N.W.	26	"	1	4.6	3.9	138	133	98	108	98.4	77.2
				2	5.0	4.2	143	135	112	117	99.0	70.0
6	C.S.	34	"	1	6.3	4.9	135	130	95	101	96.0	58.6
7	K.S.	23	"	1	4.5	4.4	139	139	103	104	92.0	55.0
				2	5.3	4.5	139	144	110	95	104.8	59.0
8	Y.T.	19	"	1	6.0	4.1	143	143	96	106	99.6	38.4

total of nineteen hemodialyses. Out of the eight patients, one was given cortisone at dosage level of 30 mg q.d. for a therapeutic purpose, and three received orally 2 mg of dexamethasone 12 hours prior to dialysis on five occasions in all for observation of dialytic effects under pituitary adrenal suppression.

Hemodialysis was accomplished by the Kolff's twin-coil kidney, with a rate of extracorporeal blood flow ranging from 150 to 200 ml/min. In view of possible diurnal variations of the plasma cortisol level, dialysis was begun at 10.00 to 11.00 a.m. for a duration of 6 hours in all instances.

Blood samples were obtained before and hourly after the institution of dialysis up to the 6th hour thereafter, and were assayed for BUN, potassium, sodium and chloride in serum. These blood samples as well as those obtained at 3, 6, 9, 12 and 24 hours after completion of the dialysis were assayed for plasma cortisol levels by the competitive protein binding radioassay technique.

cortisol levels in patients undergoing hemodialysis

Plasma cortisol (mcg/100 ml)														Remarks
Before dialysis	During dialysis						After dialysis							
	1	2	3	4	5	6	3	6	9	12	18	hrs 24		
12	9	8	7	5	3	3					16			Died after twelve occasions of dialysis in four months
17	13	17	16	17	20	25	26	25			17			
12	21	15	24	28	40	54	16	12	20		11			
20	17	12	16	19	38	38	12	18			24			
17	11	15	14	16	16	16	10	8	20		17			
16	21	22	28		22	28					14	15		Dexamethasone, 2 mg given Dismissed from the hospital after five occasions of dialysis
10	8	8	16	40	22	27	29	54	29	19				
7	7	8	8	13	13	19	19	10	5	13				
10	18	17	28	17	13	12								
16	18	14	20	31		48	46	36		42	23			Died at 48 days after renal transplantation
14	24	38	65	70	88	60	68	64		36	31			
8	9	8	7	13	14	18					7	7		Dexamethasone, 2 mg given Currently under dialysis
14	8	10	9	10		5					7	11		
					9									
6.6	7.6	9	9	10	12	12	12	10	11	12		11	Cortisone, 30mg given	Died after five occasions of dialysis
17	16	17	18	11				9		7		16	"	
1	0	0	0.6	0	5	7							Dexamethasone, 2 mg given	
17	19	46	2.2		5.4	8								Died after ten occasions of dialysis
2	2	4	4	12	9	20				16		16	Dexamethasone, 2 mg given	
7	8	9	9	10	12	12	12	10	11	12		11		Died after three occasions of dialysis

RESULTS

Table 1 summarizes the data obtained. As for changes of chemical ingredients in the blood during dialysis, blood urea nitrogen dropped by 50 per cent or even more through a 6-hour dialysis, whereas serum electrolytes including potassium, sodium and chloride, returned to practically normal levels.

The plasma cortisol level at dialysis (12 dialyses in all) in the seven cases, which had recieved no corticosteroid preoperatively, varied to a considerable extent with the individual, as can be seen from Table 1 and Fig. 1. Predialytic plasmacortisol levels in these ptients were generally slightly higher than the mean normal level of 12.2 mcg/100 ml reported by Fukuchi *et al.*,² and cortisol levels 1 to 2 hours after onset of dialysis remained practically unchanged from the predialysis level. However, there was a case with substantial elevation of plasma cortisol; Case 7 showed a rise to 46 mcg/100 ml 2 hours after the beginning of the first dialysis in which the extracorporeal blood flow rate was raised to over 200 ml/min, and blood pressure rose to over 200 mm Hg.

Similarly, in the majority of the remaining six cases, the plasma cortisol rose considerably as the dialysis proceeded to the 6th hour. The high plasma cortisol level was further sustained for the ensuing 3 to 6 hours, and dropped to the predialysis level 12 to 24 hours after completion of the dialysis.

Fig. 2 depicts plasma levels of cortisol and other data at dialysis in Case 1. The determination of plasma cortisol level was carried out at a series of five 6-hour dialyses. This 25-year-old patient with chronic nephritis was admitted to the hospital because the blood urea nitrogen had increased to 185 mg/100 ml and he

Fig. 1. Plasma cortisol levels during 12 dialyses in 8 patients, without corticosteroid treatment.

Fig. 2. Pertinent clinical data from case 1, during hemodialysis.

Fig. 3. Plasma cortisol levels during 7 dialyses of 4 patients, without corticosteroid treatment.

underwent dialysis nine times at 7 to 10-day intervals. However, he died of cardiac arrest with severe pulmonary edema after 140 days of hospitalization.

At the first 6-hour hemodialysis, the predialytic level of plasma cortisol was 12 mcg/100 ml and it became gradually lower during the dialysis procedure, dropping to a lowest value of 3 mcg/100 ml at completion of the dialysis and regaining the normal level of 16 mcg/100 ml in the ensuing 12 hours. The patient remained in a favorable condition throughout the dialysis with the

constant extracorporeal flow rate of 130 to 150 ml/min and blood pressure of 160 to 170 mm Hg. Nevertheless, as in the majority of the other cases, the plasma cortisol showed a tendency to increase 3 to 5 hours after the beginning of dialysis on the 2nd, 3rd and 4th dialyses possibly because of relatively great alterations in the blood pressure. At the 5th 6-hour dialysis the patient was in a fairly good general condition throughout and hence was suspected to exhibit no significant alterations in plasma cortisol level.

In the 1st and 2nd dialyses in Case 5 where steroid was daily administered in the 2nd dialysis in Cases 4 and 7 and in the 1st dialysis in Cases 6 and 8, in all of which 2 mg of dexamethasone were administered 12 hours previously for the purpose of functional suppression of the pituitary, the patients showed normal to slightly subnormal cortisol levels before the beginning of dialysis, which tended to increase gradually during treatment (cf. Table 1 and Fig. 3).

The extent of this increase in plasma cortisol, however, was in most instances smaller than that observed in patients undergoing dialysis with no corticosteroid treatment.

DISCUSSION

In our cases of hemodialysis without corticosteroid therapy, pre-dialysis plasma cortisol levels were generally either within the normal range or slightly higher and remained unchanged for one hour after the onset of dialysis. There was in these cases a tendency to an increase in plasma cortisol value with a considerable individual variation 3 to 4 hrs. after the beginning of dialysis, and to reach a maximum level at 6 hrs. Plasma cortisol levels gradually dropped following termination of dialysis, returning to the predialysis level 24 hours after completion of dialysis.

The rise in plasma cortisol associated with dialysis may be caused by an increased release of ACTH from the pituitary in response to stresses including alterations in circulation balance, *etc.* It has been already described by Muto³ and Tsuchida⁴ that the use of artificial kidney eventuates in an increased cardiac output which influences the cardiopulmonary function. Such abnormalities of the circulation balance and marked glycemia arising from dialysis are undoubtedly considered to exert stresses. In Case 7, for example, an extracorporeal blood flow rate was increased to over 200 ml per minute with concomitant alterations in blood pressure and elevation of the plasma cortisol to a level as high as 46 mcg/100 ml during the first six-hour dialysis, whereas during the first six-hour dialysis in Case 1, no such abnormalities occurred during dialysis and the plasma cortisol level was rather lowered. These facts provide an evidence in support of the view that the circulation imbalance acts as stress to cause a rise in plasma cortisol.

Smith,⁵ through calculations with fluorescent technique, found that the mean plasma cortisol level rose to 23.0 mcg% after 240 min of dialysis. He also stated that the rise probably reflected an increasing adrenal secretion either due to continued stress or effects of removal from the plasma of a small amount of free

cortisol.

We observed a slight rise of the plasma cortisol level following dialysis in modest as compared with that observed in patients without corticosteroid treatment. This finding suggests that the rise in plasma cortisol during dialysis reflects an increased release of ACTH from the hypophysis.

Smith⁵ described that there was very slight increase in plasma cortisol during dialysis in a patient who had been treated with 20 mg of prednisone daily. He further stated that this response with a gradual rise in plasma cortisol might reflect a possible gradual increase in endogenous cortisol occurring in consequence of ACTH production following diminution of prednisone-induced pituitary suppression as dialysis proceeded. The results of our competitive protein-binding radioassays are quite consistent with this conclusion.

Functional impairment of the adrenal is usually not severe in patients with renal failure associated with chronic nephritis. It thus follows that these patients are capable of responding well to dialytic stresses with brisk secretion of cortisol to make up for dialytic dissipation of plasma cortisol. However, as has been described by Smith,⁵ there is a reduced reactivity of the pituitary adrenal system against stresses in patients under long-term therapy with steroids, which might possibly cause an adrenal crisis. Pretreatment with sufficient doses of a corticosteroid may therefore be advisable in such patients undergoing dialysis.

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