STUDIES ON ANTI-DIURETIC ACTION OF PROTEIN HYDROLYSATE

By

A. N. BOSE AND A. ROY

Bengal Immunity Research Institute, Calcutta

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Intravenous transfusion is resorted to in various conditions of malnutrition, hypoproteinaemia and in surgery requiring intravenous alimentation (Elman, 1952; Levy and Siller, 1942; Krishnan, 1944). Being a preparation derived from proteins, several tests for its preparation, freedom from toxicity, and antigenic reactions are laid down in the pharmacopoeia (cf. Basu, Bose and Sen, 1946; U. S. P. XV).

In course of an investigation on the pharmacology of protein hydrolysate, it was noticed in this laboratory (Bose, 1955), that hydrolysis of both meat protein and casein tends to liberate certain plain-muscle stimulating factors, which exert a depressor response in chloralosed cats. Detailed work on various biological systems, particularly on rat uterus, however, showed that the factors were not much related to histamine, but were likely to be similar to 5-hydroxytryptamine (5-HT), which is reported to have a powerful anti-diuretic action. Tests on hydrated rats with protein hydrolysate, casein hydrolysate and pituitary (post lobe) extract carried in this laboratory demonstrated that hydrolysates of meat as well as casein exert a considerable anti-diuretic effect, which was more powerful than 5-HT (Bose, 1956, 1958). Histamine was without any effect on rat diuresis.

In continuation of this work, it was considered to be of interest to see whether any anti-diuretic effect, as noted in rats, could be observed on hospital patients undergoing treatment with protein hydrolysate.

METHODS AND MATERIALS

A number of cases suffering from various disorders with or without manifestation of oedema were observed. Records of daily water intake and output of each case were kept. After necessary clinical and pathological examinations, protein hydrolysate was transfused in doses varying from 25 ml. to 400 ml. at a rate of 3 ml. per minute. Some cases were also tested for urea clearance before and after the transfusion.

A few cases without manifest oedema were recorded to study the effect of hydration prior to intravenous transfusion of protein hydrolysate. For this, 0.5 to 1 litre of water was allowed to be drunk and saline infused intravenously, half an hour before the start of the transfusion.

RESULTS

The results of the enquiry are embodied in the following tables :

Table 1.

Showing the effect of transfusion of protein hydrolysate on intake and output of fluid.

Case No.	Provisional diagnosis.	Oedema.**	Dose transfused in ml.	Average fluid balance in ounces.					
				Before transfusion.		Following transfusion, up to 24 hrs.		3 days after transfusion.	
				intake. oz.	output. oz.	intake. oz.	output. oz.	intake. oz.	output. oz.
1	Post-dysenteric hypoproteinemia	+ + +	25–200	30-0	25-35	30-40	5-10	30	25
2	Splenic anaemia	+	400	30-40	30	30-40	30	35	40
3	Pyloric stenosis	+ + +	„	50	40	35	8	30	20
4	Peptic ulcer	— — —	„	60-70	50-60	50-60	50	60	50
5	Pyloric stenosis	+ +	„	30-40	25	30-40	20	30-40	25
6	Post-dysenteric hypoproteinemia	+ +	„	30	25	35	20	30	30
7	Hepatitis	— —	„	35	25	35	25	35	25
8	Post-dysenteric hypoproteinemia	+ + +	„	40	25	40	75	40	30
9	Peptic ulcer	— --	„	50	35	50	35	50	40
10	Diabetic neuritis	— —	„	80	60	80	60	80	60

** + indicates the degree of mainfest oedema.

TABLE 2

Showing the percentage inhibition of diuresis before and after a single transfusion of protein hydrolysate.

Group of cases.	Total number of cases.	Dose transfused in ml.	Average percentage of urinary output in relation.		
			Before transfusion.	After transfusion (up to 24 hours.)	7 days after transfusion.
1. Cases with oedema.	5	400	85%	50%	86%
2. Cases without oedema.	,,	,,	75%	74%	75%
3. Cases without oedema but after hydration.	,,	,,	84%	70%	85%
4. Control cases without transfusion.	,,	0	88%	×	89%

TABLE 3. Showing the results of urea clearance and other biochemical findings after intravenous transfusion of protein hydrolysate in cases of malnutrition (U. C. T=urea clearance test expressed as ml. of blood cleared of its urea per minute).

Case No.	Type of Case.	Dose of transfusion in ml.	Biochemical findings.	
			Before transfusion.	After transfusion.
1	Malnutrition due to dysentery.	400	U.C.T. 90 N.P.N. 23 mg% Urea 29 mg%	U.C.T. 90 N.P.N. 24 mg% Urea 22 mg%
2	Pyloric stenosis with hypoproteinemia.	400	U.C.T. 100 N.P.N. 28 mg% Urea 24 mg%	U.C.T. 105 N.P.N. 26 mg% Urea 24 mg%
3	Famine oedema.	400	U.C.T. 95 N.P.N. 25 mg% Urea 20 mg%	U.C.T. 90 N.P.N. 24 mg% Urea 20 mg%
4	Post-dysenteric malnutrition	400	U.C.T. 100 N.P.N. 25 mg% Urea 18 mg%	U.C.T. 95 N.P.N. 25 mg% Urea 20 mg%
5	Post-dysenteric malnutrition.	400	U.C.T. 90 N.P.N. 18 mg% Urea 18 mg%	U.C.T. 90 N.P.N. 20 mg% Urea 18 mg%

TABLE 4

Showing the results of urea clearance and other biochemical findings after intravenous transfusion of protein hydrolysate in cases after hydration (U.C.T.=urea clearance test expressed as ml. of blood cleared of its urea per minute).

Case No.	Type of case.	Hydration prior to transfusion.		Dose of transfusion in ml.	Biochemical findings.			
		per os ml.	I.V. ml.		Before transfusion.		After transfusion (4 hours).	
1	Hepatitis	1000	540	200	U.C.T. N.P.N. Urea	100 25 mg% 24 mg%	U.C.T. N.P.N. Urea	90 25 mg% 22 mg%
2	Peptic ulcer	1000	540	300	U.C.T. N.P.N. Urea	98 30 mg% 22 mg%	U.C.T. N.P N. Urea	86 28 mg% 24 mg%
3	Peptic ulcer	1000	540	400	U.C.T. N.P.N. Urea	100 36 mg% 22 mg%	U.C.T. N.P.N. Urea	100 32 mg% 22 mg%
4	Peptic ulcer	1000	540	400	U.C.T. N.P.N. Urea	80 20 mg% 25 mg%	U.C.T. N.P.N. Urea	80 24 mg% 22 mg%
5	Colitis	1000	540	300	U.C.T. N.P.N. Urea	90 35 mg% 18 mg%	U.C.T. N.P.N. Urea	100 30 mg% 19 mg%

TABLE 5

Showing the effect of repeated infusions of protein hydrolysate on the regeneration of plasma proteins, haemoglobin and red and white blood cells in blood. Total dose varied from 2-4 litres in two weeks.

Case No.		Haemoglobin in gm./100 ml.	R. B. C. in mill./cmm.	W. B. C. per cmm.	Total Protein in gm./100 ml.	Polymorph %.	Lymphocytes %.	Monocytes %.	Eosinophils %.
1	Before	10	2·4	7000	3·0	78	16	2	4
	After	12	3·8	7400	4·0	70	28	1	2
2	Before	4	2·2	6·8	3·0	65	30	2	3
	After	8·8	3·2	5·6	8·8	70	28	1	1
3	Before	4·2	2·1	5·2	2·8	68	25	2	5
	After	9·8	3·5	6·6	5·4	70	25	2	3
4	Before	6	2·5	5·8	3·1	64	34	1	1
	After	12·4	3·9	7·2	5·9	60	35	2	3
5	Before	7	3·0	6·4	3·5	64	30	2	4
	After	12	3·9	6·2	6·0	64	32	1	3

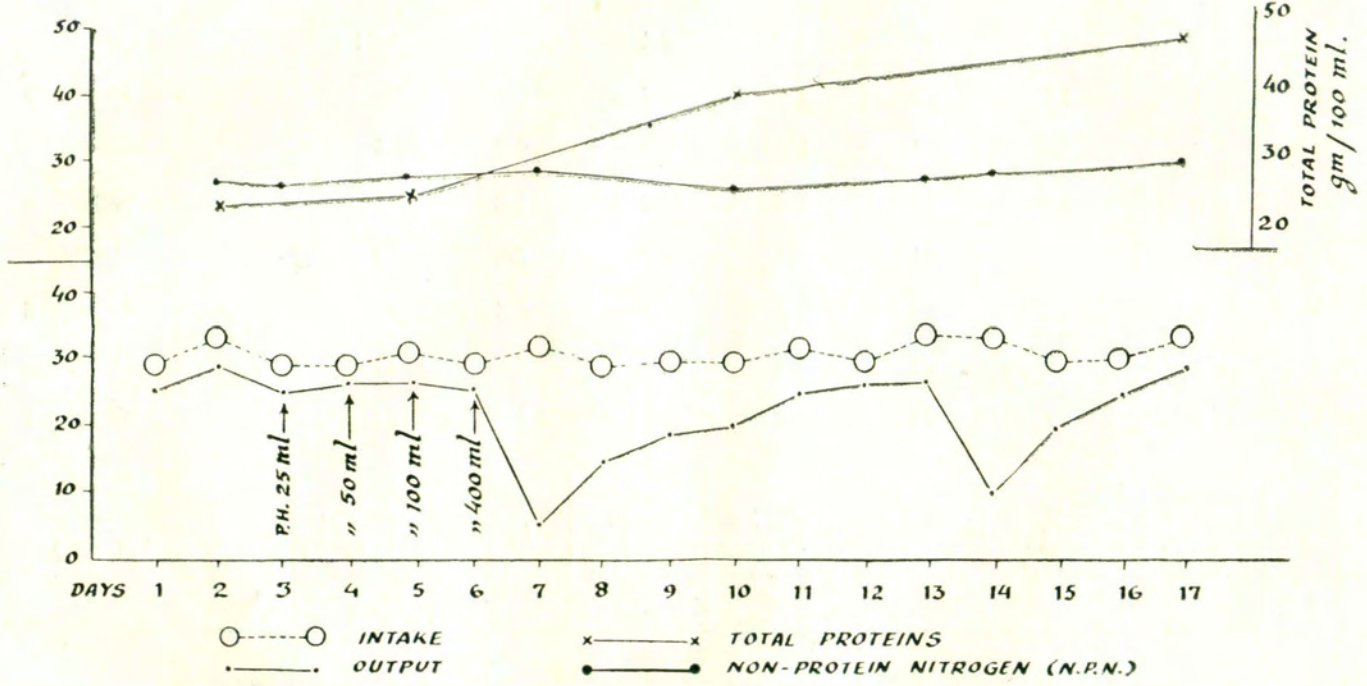
50
40
30
20
40
30
20
10
0
TOTAL PROTEIN gm/100 ml.
P.H. 25 ml
" 50 ml
" 100 ml
" 400 ml
DAYS 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17
INTAKE
OUTPUT
TOTAL PROTEINS
NON-PROTEIN NITROGEN (N.P.N.)

Fig. 1.

DISCUSSION

From the results of the studies carried so far, it appears that protein hydrolysate when infused in sufficient dosage, can under certain conditions, exert an antidiuretic effect as shown by the urinary output. In cases with generalised oedema, the effect appears to be more powerful and prolonged (Table 1, 2, Fig. I). Cases without oedema, do not cause any significant fall in diuresis, unless they are heavily hydrated (Table 2). This antidiurtic effect, however, does not produce any alteration in the urea clearance test. The blood urea and N.P.N. level also do not alter, inspite of repeated injections in some cases (Table 3 and 4, Fig. I). These findings naturally preclude the possibility of any permanent damage to the kidney being produced under the stress of the infusion of protein hydrolysate. That this antidiuretic action does not interfere with the proper regeneration of plasma proteins, haemoglobin and red blood corpuscles also is apparent from Table 5.

The behaviour pattern of the onset of anti-diuresis in patients without oedema but under heavy hydration, however, bears a considerable similarity with the findings of anti-diuretic action in rats after injection of protein hydrolysate (Bose, 1956, 1958). The fact that such action is more manifest in oedematous cases, brings into prominence the condition of existing tissue hydration as a factor for production of such type of anti-diuresis.

The cause of such anti-diuretic action of protein hydrolysate however is not apparent. It is possibly not due to histamine, since histamine has been shown to exert no anti-diuresis in rats (Bose, 1956). Whether this is due to the presence of 5-hydroxy-tryptamine in the hydrolysate, or due to the liberation of similar substances, from tissue conjugates under oedematous condition will be worth-investigating (*c. f.* Bose, 1958).

SUMMARY

1. An anti-diuretic effect, after transfusion of protein hydrolysate, has been noted in several cases of malnutrition and anaemia.

2. The anti-diuretic action is more manifest in cases complicated with local or generalised oedema.

3. Normal individuals, under a water load, also show much anti-diuretic action after intravenous protein hydrolysate.

4. The behaviour pattern of anti-diuretic action in human subjects with oedema or under a water load bears a striking similarity with the manifestation of anti-diuretic action in hydrated rats.

5. The anti-diuretic action is unaccompanied by any change in urea clearance, and does not alter the normal ranges of blood urea, non-protein-nitrogen, and creatinine. The regeneration of plasma proteins is also not affected.

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