11281

Intravenous Administration of Bovine and Human Plasma to Man: Proof of Utilization.*

OWEN H. WANGENSTEEN, HARRY HALL, ARNOLD KREMEN AND BEATRICE STEVENS.

From the Department of Surgery, University of Minnesota Medical School, Minneapolis, Minn.

In this and other clinics, human plasma has been given intravenously in preparing patients with obstruction at the gastric outlet, exhibiting the effects of hypoproteinemia, for operation. Whipple[1, 2] and his associates have demonstrated that dog plasma administered intravenously to dogs is utilized. In this study it is proposed to indicate that: (1) Human plasma administered intravenously to patients is retained and utilized, (2) plasma presents distinct advantages over whole blood for the purpose of maintaining nitrogen equilibrium and to elevate depleted plasma proteins in starvation states, (3) bovine plasma may be given intravenously to man in fairly large quantities; it too is retained and utilized.

We wish to make it clear that the intravenous administration of bovine plasma to man has not been established as a safe routine hospital procedure. The data submitted herewith afford proof, however, that bovine plasma may be administered intravenously to some patients in fairly large quantities. When the possibilities and limitations of the method become understood well enough, it is not unlikely that the method may become a practical hospital procedure useful in civil as well as in war surgery for various purposes having to do with contracted blood volumes and protein stores.

Method. All the patients upon whom metabolic tests were made in this study and to whom human and later bovine plasma was given, were afflicted with cancer and presented some of the effects of protein starvation. All patients, however, were essentially afebrile. The human plasma was obtained from the surgical blood bank of citrated blood in the hospital, the cells being removed by centrifuga-

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1 Pommerenke, W. T., Slavin, H. B., Kariher, D. H., and Whipple, J. G., *J. Exp. Med.*, 1935, **61**, 283.

2 Daft, F. S., Robscheit-Robbins, F. S., and Whipple, J. G., *J. Biol. Chem.*, 1938, **123**, 87.

tion. The bovine plasma was prepared similarly, (10 cc of a 2.5% sodium citrate solution per 100 cc of blood) the blood, after collection from a living animal by venipuncture, being placed in centrifuge tubes with a capacity of 250 cc. Centrifugation was carried out for one hour at 2500 revolutions per minute. The supernatant plasma was pipetted off into sterile flasks for storage in the ice box (temperature 5°C) where it was allowed to remain for a week or more before being used. The sterility of the bovine plasma was determined by culture on veal infusion broth before administration. Several batches of plasma were passed through a Berkefeld filter as an added precaution, but extensive trial showed that this procedure was not necessary to insure sterility. Sulfanilamide, 0.2 gram to a liter of plasma, was used in some instances as a preservative (Novak).[3] Through the coöperation of the Department of Veterinary Medicine† of the University of Minnesota, it was possible to secure fairly large weekly stores of bovine blood from cows that were free from tuberculosis and Bang's disease.

During the period of the study, the patients were on a protein-free diet. Tea, orange juice, nectar and water were allowed by mouth to supplement intravenous administration of 5 or 10% glucose solution. Enough carbohydrate was given in this manner to afford a caloric intake of about 1200 calories daily and to avoid ketosis.

The total daily output of urine passed was preserved with toluene. Daily determinations of the total urinary nitrogen,[4] non-protein nitrogen, urea[5] nitrogen and sugar were made. At the beginning of the study and at the end, and at intervals of 2 to 3 days between, values for plasma proteins, non-protein nitrogen[5] and blood urea nitrogen[6] and chlorides[7] were determined. The specific gravity of the blood of the recipients was kindly determined for us by Dr. C. J. Bellis by the falling drop method.[8] The weight of the patient was determined at intervals through the period of study.

As indicated in Table I, the usual procedure was to allow the excretion of nitrogen in the urine to reach a basal level, the patient being supported by a carbohydrate intake only in the 3- to 5-day

[3] Novak, M., *J. A. M. A.*, 1939, **113**, 2227.

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[4] Koch, F. C., and McMeekin, T. L., *J. Amer. Chem. Soc.*, 1924, **46**, 2066.

[5] Folin, O., and Wu, H., *J. Biol. Chem.*, 1919, **38**, 81, 111.

[6] Karr, W. G., *J. Lab. and Clin. Med.*, 1924, **9**, 329.

[7] Cavett, J. W., and Holdridge, C. E., *J. Lab. and Clin. Med.*, 1933, **18**, 944.

[8] Barbour, H. F., and Hamilton, W. F., *J. A. M. A.*, 1927, **88**, 91.

TABLE I.

Metabolic studies attending intravenous administration of human blood and plasma and bovine plasma

		Urine				Blood							
						Plasma Protein							
	Period 1939	Total N_2 g	N.P.N. g	Urea N_2 g	Sugar g	Total	Albumin	Globulin	N.P.N. mg%	Urea N_2 mg%	Spec. Grav.	Protein Intake cc	Weight lb
Case No. 1:	5/10- 5/13	20.64				6.8	3.7	2.8	40.6		1.057	0	
	Av. Daily	5.16											
	5/14- 5/18	19.34				6.8	4.2	2.7			1.063	2250 H.Pl. I-v.	118½
	Av. Daily	3.87											
	5/19- 5/24	29.904	29.314	17.863		8.8	5.1	3.8			1.063	3000 H.Bl. I-v.	115
	*Av. Daily	5.981	5.863	3.573									
Case No. 3:	7/ 1- 7/ 3	21.708	20.146	11.087	262.71	6.1	2.9	3.2	27.1	8.2	1.045	0	143
	Av. Daily	7.236	6.715	3.696	87.57								
	7/ 4- 7/ 6	22.833	22.123	13.268	69.388	5.8	2.6	3.0		10.7	1.052	1500 H.Bl. I-v.	138
	Av. Daily	7.611	7.374	4.423	23.128								
	7/ 7- 7/10	17.360	17.793	11.236	367.064	6.9	3.2	3.4	41.1	9.7	1.050	1000 B.Pl. I-v.	141
	Av. Daily	4.340	4.444	2.809	91.766								
Case No. 7:	10/ 4-10/ 8	38.332	33.826	22.982	96.38	7.48	4.14	3.34	26.4	17.5		0	126
	Av. Daily	7.666	6.766	4.596	19.27								
	10/ 9-10/12	21.410	25.629	12.173	83.475	7.18	5.00	1.52	41.4	9.61		2000 H.Bl. I-v.	130
	Av. Daily	5.353	6.407	3.044	20.869								
	10/13-10/17	29.168	30.084	19.283	103.546	7.14	4.3	2.84	48.0	20.4		1500 B.Pl. I-v.	133½
	Av. Daily	5.834	6.107	3.857	20.709								

* Part of one daily specimen lost. This day omitted from calculation of total and average daily N_2 Excretion.

Case 1. Mr. F. K., Age 56, U. H. No. 680697 (Carcinoma of esophagus; Gastrostomy 5/8/39).

Case 3. Mr. W. M., " 53, U. H. No. 680255 (" " stomach; Exploratory Laparotomy 6/27/39).

Case 7. Mr. H. W., " 64, U. H. No. 684341 (" " lower esophagus and stomach; Jejunostomy 9/19/39).

interval. The effect of the administration of human blood or plasma upon the excretion of nitrogen was noted first; then, similar studies were made during the administration of bovine plasma. The daily administered amounts of human blood or plasma and bovine plasma indicated in the table were given in 2 divided doses (morning and evening). An intracutaneous injection of 0.05 cc of bovine plasma was first made as a test. If no enlargement of the wheal was observed at 20 and 40 minutes, the test was interpreted as being negative and 2 cc of bovine plasma was injected intravenously, before larger amounts were given. None of the patients were diabetic and the urinary excretion of sugar represents spillage from too rapid administration of 10% glucose solution.

Results. Representative results are indicated in the table. For purposes of conserving space, the detailed information in Cases 2, 4, 5 and 6 are omitted in the table. Only Cases 1, 5 and 6 failed to receive bovine plasma intravenously. Case 2 received 750 cc of bovine plasma over a 4-day interval; Case 4 received 1000 cc of bovine plasma and the daily urinary excretion of nitrogen was definitely lower than in the 4 days preceding during which 2000 cc of whole human blood was given. Tests for protein in the urine were uniformly negative; in all instances, the total urinary nitrogen was accounted for by non-protein nitrogen. The urinary nitrogen studies in Case 1 (see table) suggest a definitely greater urinary excretion of nitrogen during intravenous administration of whole human blood than when human plasma was given. This observation appears to be borne out in other instances, *viz.,* that administration of whole blood pyramids the urinary excretion of nitrogen. In Case 5, after 4 days of protein starvation, the urinary excretion of nitrogen fell to 1.26 g per day; 500 cc of whole human blood was then given intravenously for 6 days. On the 5th day the urinary excretion of nitrogen was 9.12 g, on the 6th day 8.3 g. In Case 1, over the 5-day period that 2250 plasma was given (protein content 7 g per 100 cc), a total of 157.5 g of protein or 25.3 g of nitrogen was introduced. During this same time 19.34 g of nitrogen was excreted in the urine, indicating a nitrogen retention of 6 g.

In Case 3 (see table), the average daily urinary output of nitrogen was 7.61 g after 3 days of daily administration of 500 cc of whole human blood intravenously, preceded in turn by 3 days of no exogenous intake of protein. Accompanying 4 days of administration of bovine plasma, during which time 800 cc had been given, the daily urinary nitrogen excretion was 4.34 g, suggesting that the intravenously administered protein was being stored somewhere in the

body. Determination of the protein content of bovine plasma was made on 4 batches. Values between 7 and 8 g per 100 cc were uniformly found. Case 7 (see table) received a total of 1500 cc of bovine plasma over a 5-day period, without increasing the daily urinary excretion of nitrogen appreciably over what it had been after daily administrations of 500 cc of whole human blood over a 4-day period.

In no instance did we succeed in keeping the patient in nitrogen balance attending intravenous injection of bovine plasma. In Case 3, there was an excretion of 7.1 g more of nitrogen in the urine over the intake, during the 4-day period of the study. Similarly in Case 7, there was a negative nitrogen balance of 9.968 g for the 5-day period. However, in Case 3, the average daily excretion of nitrogen was definitely less than the basal level for the control period when there was no exogenous intake of nitrogen. While in Case 7, the daily average excretion of nitrogen in the urine, during the period when bovine plasma was given, was less than the basal level of the preliminary 4-day period of protein starvation. Further, few significant increases in the non-protein nitrogen of the blood occurred during the administration of bovine plasma. The relationship between the total non-protein nitrogen and the urea of both blood and urine showed no significant alteration suggestive of abnormal catabolism of protein.

Inasmuch as Case 3 was given only an average of 2.5 g of nitrogen per day and Case 7, 3.84 g, it is reasonable to infer that not enough protein (bovine plasma) was given to maintain a positive nitrogen balance. In Case 1, a positive nitrogen balance was maintained with human plasma, an average of 5.06 g of nitrogen being given each day of the 5-day period of study. Inasmuch as enough bovine plasma was not given to maintain nitrogen equilibrium, one could not reasonably expect that the plasma proteins of these patients would be increased.

To a patient with a bleeding gastric ulcer upon whom no metabolic studies were made, 25 and 100 cc of bovine plasma were injected intravenously on 2 successive days without reaction. Two days later when bleeding to a shock level occurred (blood pressure 80/40), 300 cc of bovine plasma was given over an hour's time; during the next 2.5 hours an additional 400 cc was given—all without reaction, the blood pressure having risen after the initial injection of 300 cc to 130/90, at which level it was maintained. This was the largest amount of bovine plasma injected over a relatively short period of time.

Reactions. Bovine plasma has been given intravenously in small amounts (2 to 10 cc) to a larger number of patients who will be reported upon in a later study. It may be said here, that of 66 patients so injected, reactions were noted in 10 cases (15%). Nine of these reactions were classified as mild to moderate in severity. In a patient with an inoperable carcinoma of the rectum, having a history of asthma dating back 20 years, a severe anaphylactoid type of reaction with severe dyspnoea attended the intravenous injection of 2 cc of bovine plasma. The patient responded satisfactorily to intravenous injections of epinephrin and aminophylin. The patient had no late effects.

A thermal reaction was noted in Case 3. In 3 of the patients given large quantities of bovine plasma upon whom metabolic studies were made, a generalized urticaria developed 5 to 6 days after the administration of bovine plasma was begun. The urticaria lasted usually 3 to 4 days and was fairly satisfactorily relieved by epinephrine. There was no joint manifestations.

Three patients in the series were given a single intravenous injection of bovine plasma in the amounts of 100, 50 and 25 cc after 8, 7 and 48 days respectively had elapsed since the last injection. No reactions attended these injections.

Discussion. It would appear that the use of bovine plasma for the treatment of clinical states, in which contracted blood volumes or decreased protein stores are present, may have real promise. Before intravenous use of bovine plasma can be recommended for clinical usage, however, it is important to determine with some precision what the limitations of the method are with reference to safety of administration. It may prove that partition of the proteins in the plasma, *viz.,* administration of the albumen or the globulin fraction alone may prove more useful than the whole plasma.

Conclusions. 1. Human plasma administered intravenously is retained and utilized. A patient to whom a daily average of 450 cc of plasma was given over a 5-day period was maintained in positive nitrogen balance. 2. Human plasma appears to be a better agent than blood to employ to maintain nitrogen equilibrium in starvation states. 3. Bovine plasma can be given intravenously to man in fairly large quantities; it is retained and apparently utilized.