PLASMA SUBSTITUTES WITH SPECIAL REFERENCE TO PLASMOSAN

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The aim of the treatment of shock is to restore as quickly as possible the venous return, the cardiac output and consequently the blood pressure. For patients who have lost blood its early replacement by a transfusion with whole blood is the treatment of choice. There are occasions when this cannot be done easily and recourse must be made to plasma or a plasma substitute, the prompt use of which may be life-saving.

REQUIREMENTS

A plasma substitute should satisfy certain basic requirements which have been summarized by Bull et al. (1949) as follows:

Positive Qualities:

1. Its colloid solutes should be retained in the circulation until their place can be taken by the natural proteins.
2. The solution used for infusion should have an osmotic pressure and viscosity similar to those of plasma.
3. The composition from batch to batch should be constant, within narrow and definable limits.
4. The material should be stable during storage and preferably not require special conditions of temperature.
Negative Qualities:

(5) It must not be toxic, either locally or generally.
(6) It must not induce fever.
(7) It must not induce sensitization.
(8) It must not be stored for long periods in the tissues.
(9) It must not act as a diuretic.

Possible Plasma Substitutes

The 1914–18 war gave the first impetus to transfusion practice on a large scale, whole blood and various alternative solutions being used for treating casualties. Of the blood substitutes or, more correctly, plasma substitutes the gum saline solution (6 per cent arabic in physiological saline) developed by Bayliss (1919) proved to be the best and for a period enjoyed considerable popularity. Unfortunately, inconsistencies in gums, the natural raw material, and side effects due to long retention in the body, particularly in the liver, hindered general clinical use of this fluid. Various alternatives have since been examined, particularly solutions of gelatine which have been recently used in the United States, but these have not proved to be entirely satisfactory. Attempts have also been made to improve the oxygen-carrying power of possible plasma substitutes principally by adding various haemoglobin preparations to saline solutions, but these proved to be unreliable and even dangerous because of renal complications due to free haemoglobin in the blood stream (Holmes and Thrower, 1924). In an endeavour to compensate for or prevent the catabolic destruction of protein tissue following major surgical operations, Billing et al. (1951) have studied the effect of protein hydrolysates given intravenously. They found that these infusions could safely be given but had little or no beneficial effect.

During the past eight years interest has been aroused by the introduction of dextran and various reports on it have appeared, first in Scandinavian, and more recently in British literature (Bohmanson et al., 1946; Thorsén 1949, etc.). It is a purified natural product prepared by the fermentation of sugar and presented for clinical use as a 6 per cent solution in physiological saline solution. Being a mixture of polysaccharides of high molecular weights these retard the renal excretion of the saline solution in which they are dissolved. It has been given by one of us to 10 patients and its effect compared under similar conditions with another plasma substitute, Plasmosan, now to be described. The general effect of dextran in controlling the blood pressure is similar to that of Plasmosan, but in five cases blood was required in addition, whereas two major orthopaedic operations were carried out with a satisfactory blood pressure throughout the operation with 1,000 ml. Plasmosan alone, although the blood loss in these 2 cases was significant (cup arthroplasty and femoral shortening). No reactions following the use of dextran have been seen but these are known to have occurred after using certain preparations of it. The explanation for them is not clear but Voorhees et al. (1951) have
shown that albino rats give a demonstrable reaction of redness, swelling of loose tissue, pruritus and stupor when injected with doses of dextran comparable to those suggested for human use. Complete clinical evaluation of dextran will not be possible until greater uniformity in molecular size has been obtained and more is known about its metabolism.

**Plasmosan**

Hecht and Weese (1943), after examining several colloid substances suggested as agents to retard the excretion of saline solutions by the kidneys, showed that polyvinyl pyrrolidone (P.V.P.) seemed promising. A saline solution containing a P.V.P. compound and known as Periston was prepared and used in Germany with some success as a plasma substitute during the 1939-45 war and after. Side-effects such as pyrogenic reaction, albuminuria and haematuria which sometimes followed its use prevented adoption elsewhere. There is no evidence that any late harmful effects occur. Improved methods of preparing P.V.P., which is a white solid very soluble in water, have permitted the development of a solution known as Plasmosan. Work on the product started in Great Britain in 1947 but only recently have details of its properties appeared (Thrower and Campbell, 1951; Arden et al., 1951). The solution used by us appears to be free from the objections attributed to the original German product and has proved safe and effective in clinical use. The solution keeps well and needs no special conditions for storage. The composition of Plasmosan is as present as follows:

<table>
<thead>
<tr>
<th>Substance</th>
<th>Content</th>
<th>Per 100 ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polyvinylpyrrolidone</td>
<td>3.5 grammes</td>
<td></td>
</tr>
<tr>
<td>Sodium (Na+)</td>
<td>361 mg.</td>
<td></td>
</tr>
<tr>
<td>Potassium (K+)</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>Calcium (Ca++)</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Magnesium (Mg++)</td>
<td>0.06</td>
<td></td>
</tr>
<tr>
<td>Chloride (Cl-)</td>
<td>582</td>
<td></td>
</tr>
<tr>
<td>Bicarbonate (HCO₃⁻)</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>Dissolved carbon dioxide (CO₂)</td>
<td>75</td>
<td></td>
</tr>
</tbody>
</table>

It will be observed that the proportion of the various ions is similar to that in human plasma.

**Effects of Plasmosan in the Body**

**Immediate Toxicity.**—From the pharmacological point of view P.V.P., the important ingredient of Plasmosan, is not toxic even when given in high dosage, the lethal dose for laboratory animals being 8 gramme per kg. of body-weight, death being due to cardiovascular insufficiency attributable to hyperviscosity of the blood (Combined Intelligence Objectives Subcommittee 1945). Therapeutic doses are well tolerated. No ill-effects follow the subcutaneous and intramuscular injections of 25 per cent aqueous solutions of P.V.P., in which form it is extremely used in France as a retarding agent for penicillin, insulin, and certain sex hormones.

Remote Toxicity.—The most likely late toxic effect of injecting foreign colloid substances into the circulation is the risk of deposition in fixed tissue cells of the body, although this is unlikely with the present preparation, which is so highly soluble and shows so little interaction with other materials. It has been shown (Thrower and Campbell, 1951) that in rabbits subjected to deliberate overdosage with Plasmosan no significant changes could be observed in the tissues examined. In 4 patients to whom 500–1,500 ml. of Plasmosan had been given and who later died from their injury or disease, no macroscopic or microscopic changes could be observed post mortem which could in any way be ascribed to Plasmosan.

Nelson and Lusky (1951) have compared the effects in rabbits of repeated intravenous injections over a two-month period of 10 c.c. per kg. of 6 per cent dextran in distilled water and a 3·5 per cent aqueous solution of a polyvinylpyrrolidone called Periston manufactured in the U.S.A. The one outstanding lesion of the entire experiment was a foam cell storage phenomenon in the animals receiving polyvinylpyrrolidone. The changes were best seen in the spleen and other structures containing reticulo-endothelial tissue. Changes in other organs were noted which also followed dextran infusions. These animal experiments indicate what might be expected from prolonged overdosage on a scale unlikely to arise in clinical practice.

Estimation

When considerable quantities of a substance such as a plasma substitute is introduced into the human body it is important to know what happens to it. The original biochemical tests for P.V.P. were unreliable but by an improved technique it is possible under ordinary circumstances to recover from the urine 75 per cent of the P.V.P. content of Plasmosan, and in one instance as much as 90 per cent. With suitable adjustments this technique can also be used to determine blood concentration levels of P.V.P. (Thrower and Campbell, 1951).

Another method for estimating P.V.P. in body fluids has been recently described by Reinhold and Drabbe (1951) but we have had no experience of its reliability.

Effects of Plasmosan on Whole Blood

In vitro different quantities of Plasmosan and whole or citrated blood mix readily, and the same applies under clinical conditions. The clotting-time and bleeding time of patients recently given infusions of Plasmosan are unaffected; blood-grouping reactions are not disturbed; and no haemolysis is produced. As might be expected the E.S.R. rises after Plasmosan infusions. Magendie et al. (1947) using 10 per cent citrated blood in vitro, drew attention to the possibility of clotting of transfusion blood given through the same apparatus as Plasmosan due to the interaction of the Ca ion in Plasmosan on citrated blood. We have had no trouble in this respect with blood to which 3 per cent trisodium citrate and 15 per cent glucose have been added.
CLINICAL USE

Plasmosan has been used by us in more than 60 cases, principally to control shock during major operations. Most of these operations have been cup arthroplasties, spinal fusions or equally severe procedures. A smaller number were abdominal operations such as gastrectomies and colectomies.

Whenever possible Plasmosan infusions were commenced before the onset of shock. In a few patients with burns and multiple injuries the opportunity has occurred to give Plasmosan after the onset of shock when its effect has been such as might be expected after using fresh or reconstituted plasma.

Shock may develop quite suddenly during certain orthopaedic operations on patients in good conditions when the hip is dislocated or bony surfaces are being reamed for a cup arthroplasty. The sudden fall in blood pressure can usually be controlled by increasing the rate of an existing Plasmosan drip, but blood was sometimes necessary as well.

Plasmosan is supplied in the standard blood transfusion bottles with a closure adapted for use with the two-needle giving set and easily removed for use with the standard giving set. The appearance of Plasmosan varies from batch to batch, some being tinged with varying degrees of yellowness, others being crystal clear. In a few bottles from an early batch small floccules of a solid material could be seen floating about, but must either have redissolved or been trapped by the filter because no reaction was noticed. It has not been necessary to discard any of the bottles supplied, although some have been stored for a period up to twelve months at ordinary room temperature. The quantity of Plasmosan given varied from 500 ml. to 2,000 ml. The majority of patients to whom the transfusions were given were elderly adults, the oldest being 84, but in a few cases it was given to children with burns. One of the two deaths in this particular series occurred in a child with burns; the other was an adult also severely burnt.

The rate of transfusion varied according to the patients' blood pressure, this being regarded as the main guide to the presence or degree of shock. Serial blood-pressure recordings were noted during each operation and plotted on a shock chart together with the pulse-rate.

During the operation the oral temperature was recorded in a small series but no rise was found. Some patients developed a moderate post-operative rise of temperature, but no more than is usual after a major operation.

Plasmosan was given together with blood in about half the cases, as alone it failed to maintain the blood pressure, if the blood loss was excessive (more than 1,000 ml.) or if the operation was prolonged (over ninety minutes).

Plasmosan and stored blood mixed freely and both flowed satisfactorily through the same giving set. Plasmosan flowed much more freely than blood. On some occasions Plasmosan leaked into the extravascular tissues but no harm resulted. Procaine was also given in the Plasmosan drip (2 grammes/500ml./hour) in a number of cases during and at the end of the operation.

In the average case 500-1,000 ml. of Plasmosan were required at a rate of
500 ml./45 mins. to maintain a satisfactory blood pressure, but on some occasions the rate had to be increased to 500 ml./20 mins.

No post-operative reactions were seen and the wounds in all clean surgical cases healed normally except for an occasional haematoma. No cases of late jaundice were seen.

**Case Reports**

**Case 1.**—A man aged 40 had a Wilson spinal fusion carried out for an old recurrent disc lesion; duration two hours; 1,000 ml. Plasmosan and 500 ml. blood given. B.P. well maintained. Estimated blood loss 1,000 ml.

**Case 2.**—A woman aged 74 had a Judet arthroplasty performed for osteoarthritis of the hip. Given 500 ml. Plasmosan and 500 ml. blood. B.P. well maintained. Estimated blood loss 500 ml. Duration 90 mins.
Case 3.—A man aged 45 with bilateral compound fracture of the tibia and fibula was operated on within five hours of injury. Given 1,000 ml. of Plasmosan. Wound toilet carried out, fractures manipulated and plasters applied. Duration 90 mins. B.P. satisfactory throughout.

Clinical Pathological Tests

Post-operative blood counts twenty-four hours later were done on a small number of patients in our recent series, and these revealed a low haemoglobin and red cell count with anisocytosis probably due to haemodilution. There is no evidence that Plasmosan causes any haemolysis or jaundice. Blood-grouping tests were repeated the day after Plasmosan infusions; these tests confirmed the pre-operative groups and no difficulty was experienced in the grouping technique in contradistinction to experiences with dextran. Pre- and post-operative bleeding and clotting times were compared in several patients but no alteration was observed. Urine analysis post-operatively was in all cases normal, no haematuria or albuminuria being detected.

Various workers during their clinical use of Plasmosan have noticed that the results of some clinical pathological tests may be modified at times by the presence in body-fluids of the large P.V.P. molecule, which has reducing properties. In the blood this may be manifest in a measurable deviation from the true blood-sugar level of the patient. Again, reducing substances may be identified in the urine without sugar being actually present because of the properties of P.V.P. A false positive test for albumin with the trichloracetic-acid reagent or Esbach's quantitative method may be met. Tests involving the use of cold nitric acid and heat tests are unaffected.

Summary

The chemical and physical properties of a plasma substitute called Plasmosan are described together with practical and clinical details of its use for the maintenance and restoration of the circulatory blood volume.

References

Combined Intelligence Objectives Subcommittee (1945) item 24, file XXV-54.