Over de invloed van plasmasubstituten op de suspensie-stabiliteit en de viscositeit van het bloed
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SUMMARY

Although blood or plasma transfusion is usually the method of choice for the replacement of lost blood and the prevention and treatment of shock, there remain occasions where the use of a plasma substitute is indicated. In the Korean war, for instance, dextran solutions were used on a large scale, both with and without subsequent infusion of blood. Also, however, under normal conditions it often occurs that blood group determination, cross matching and transportation of blood will take too much time while therapy should be started immediately. Moreover, recent research\textsuperscript{16} indicates that plasma substitutes may be developed with properties making their use in some cases preferable to the infusion of blood or plasma.

The first aim of an infusion is to restore the circulating blood volume. A lasting effect on the blood volume can only be obtained when the infusion fluid contains a macromolecular substance capable of keeping the colloid osmotic pressure at a near normal level. The requirements to be fulfilled by a satisfactory plasma substitute have been formulated by various authors\textsuperscript{10,33}. Most plasma substitutes have been investigated thoroughly as to how far they meet these requirements.

Most experimental data concerning the influence of plasma substitutes on the suspension stability of blood come from measurements of the erythrocyte sedimentation rate (ESR). It is doubtful, however, whether the sedimentation rate of the erythrocytes \textit{in vitro} is a reliable measure for the suspension stability of blood \textit{in vivo}. The investigations of Weis-Fogh\textsuperscript{39} showed that rouleaux formation of the erythrocytes is the most important factor in obstructing the smaller blood vessels whenever a decreased suspension stability of the blood occurs. The use of the ESR as a quantitative measure of rouleaux formation may easily lead to incorrect conclusions. It is a fact that the sedimentation of erythrocytes is related to rouleaux formation; rouleaux formation is even a necessary requisite for erythrocyte sedimentation. However, the relationship between the rate and extent of rouleaux formation and the sedimentation rate is
far from simple\textsuperscript{33}. Dilution of the blood with plasma, for instance, increases the sedimentation rate, whereas rouleaux formation is slowed down by it.

A method for the quantitative evaluation of rouleaux formation of erythrocytes\textsuperscript{6, 25, 43, 44, 47}, thus was adopted to study the effects of plasma substitutes on the suspension stability of blood. This method (described in chapter 4) depends on the relationship between rouleaux formation and light reflection of the erythrocytes. When the erythrocytes arrange themselves in rouleaux a considerable drop in the amount of reflected light can be observed. To use this phenomenon for the quantitative evaluation of rouleaux formation, a blood sample is brought into a small cuvette equipped with a magnetic stirrer (figs. 8 and 9). A small reflectometer (measuring eye of a reflection oximeter, fig. 10) is placed on the cuvette. Light reflection of the blood is recorded continuously. After a few seconds the cuvette is rapidly shifted out of the magnetic field. First there is an upstroke in the reflection curve (o-p in fig. 14), due to the termination of a directional effect of the stirring on the cells\textsuperscript{47}. Next light reflection falls rapidly (fig. 11 and 14). From the curve ('syllectogram') the half-time of the reflection decrease due to rouleaux formation is calculated (fig 19). The half-time, which is the best single quantity to indicate rouleaux formation, appeared to be dependent on the erythrocyte concentration (fig. 20). By plotting log half-time against log hemoglobin concentration, a straight line is obtained (fig. 21). By dividing a blood sample in three portions and transferring some plasma from the first portion to the third one, three blood samples are obtained differing only in hemoglobin concentration. When both half-time of rouleaux formation and hemoglobin concentration are determined for each sample, a double logarithmic plot may be used to find the half-time corresponding to a hemoglobin concentration of 15 g/100 ml. This quantity is called the corrected half-time.

It will be clear that the corrected half-time reflects the tendency of the erythrocytes to form rouleaux, whereas the half-time indicates the actual rate of rouleaux formation in a particular blood sample. In studying the effect of plasma substitutes on the suspension stability of blood, it proved to be useful to determine both half-time and corrected half-time.

In chapter 2 the composition and properties of various plasma substitutes are described, with special reference to the dextran containing solutions. The molecular weight distribution of four
plasma substitutes is presented in fig. 1. Fig. 2 shows how the dextran clearance depends on the molecular weight. The difference between plasma expanders and flow improvers is stressed. Unfortunately, an effective plasma expander often has a disturbing effect on the microcirculation. To keep water within the vascular bed, the infusion fluid must contain a substance with molecules large enough to withstand rapid renal excretion or loss into the extravascular space, thus exerting a considerable colloid osmotic effect. But these macromolecular substances often promote rouleaux formation and, consequently, tend to impair capillary flow. On the other hand, substances with a molecular size small enough to inhibit rouleaux formation usually leave the vascular system too rapidly to have a lasting effect on the blood volume. Only a few infusion fluids combine plasma expanding and flow improving effects to a reasonable degree.

In chapter 3 is reported upon a preliminary investigation on the influence of dextran and PVP containing infusion fluids on the suspension stability of blood. ESR was used to evaluate the effect of the infusions in this respect. A part of these data is shown in figs. 3-7. The results are summarized in table 3. Although Macrodex infusions appeared to raise the ESR in all patients, no conclusive evidence was obtained from these experiments. Consequently, the method for quantitative evaluation of rouleaux formation described in chapter 4 was used in further experiments performed to collect more relevant data.

The first part of chapter 5 describes experiments on rouleaux formation of washed erythrocytes resuspended in their own plasma and in various plasma substitutes. Table 5 shows that in a high molecular weight dextran (Dextran BP) rouleaux formation is very rapid, whereas in a dextran solution of intermediate molecular weight (Macrodex) rouleaux formation is of the same order as in plasma. In the other plasma substitutes rouleaux formation is slower than in plasma; in some of them, including low molecular weight dextran, the rate of rouleaux formation is too slow to be measured.

In a second series of experiments plasma substitutes were added to samples of human blood, one volume of plasma substitute to four volumes of blood. Syllectograms obtained in some of these experiments are presented in figs. 22-30. The results are summarized in table 6. The theory of Thorsén and Hint on the mechanism underlying rouleaux formation of erythrocytes, has been used as a starting
point in the interpretation of these results. Thorsén and Hint state that the erythrocytes stick together through the accumulation on their surface of macromolecular substances which tend to gel formation. Applying this assumption to our experimental data yields the following theory.

When a plasma substitute is added to the blood, the colloids accumulate on the surface of the erythrocytes and displace part of the plasma protein layer on the cell. Now some kind of interaction occurs between the substances adsorbed to the erythrocyte surface, making the tendency to gel formation different from that of each of these substances separately. Whether the erythrocytes are now kept together more tightly than before the addition of the plasma substitute depends on the following factors:

1. composition and concentration of the plasma proteins;
2. structure, concentration and molecular weight of the substance added;
3. interaction between plasma proteins and added colloids. Whether the rate of rouleaux formation is actually changed also depends on
4. the decrease in erythrocyte concentration due to the infusion of fluid.

Thus, as can easily be seen in tables 5 and 6, a plasma substitute usually favours rouleaux formation more when added to whole blood than when the erythrocytes are suspended in the pure plasma substitute. When an intermediate molecular weight dextran (Macrodex®) is added, the tendency to rouleaux formation, reflected by the corrected half-time, usually increases. This increase, however, is either absent or very slight, when a high rate of rouleaux formation is already present in the blood. In these cases rouleaux formation may actually be inhibited by the decrease in erythrocyte concentration due to dilution of the blood.

Observations on rouleaux formation in the blood of patients before and after infusion of a plasma substitute are described in chapter 6. In 34 patients the hemoglobin concentration, half-time and corrected half-time of rouleaux formation and ESR were determined once immediately before and several times after administration of the plasma substitute. All data obtained in this investigation are presented on pages 56-67. Generally speaking, there is an excellent agreement between these data and the results of the experiments in vitro (chapter 5). Administration of Macrodex® usually causes a significant fall in the corrected half-time, showing that the tendency to rouleaux formation has increased. When the cor-
rected half-time is already quite small, no further decrease is observed. The half-time even shows a significant increase in these cases, demonstrating that the infusion actually diminished rouleaux formation through the fall in erythrocyte concentration.

In some patients the increase in the rate of rouleaux formation caused by the administration of Macrodex® continues during a few days following the infusion. This may be explained by the fact that the smaller molecules are rapidly excreted (fig. 2), so that the average molecular weight of the circulating dextran increases considerably.

Infusion of Rheomacrodex® proved to give a significant inhibition of rouleaux formation in all patients. Plasmodex® also decreased the rate of rouleaux formation in most patients. Since the average molecular weight of this dextran-glycerol-glucoside corresponds with that of Macrodex®, it will display about the same plasma expanding effect. Thus it seems that Plasmodex® combines plasma expanding and flow improving effects to a reasonable degree.

Fig. 31-34 demonstrate that there is only a slight correlation between ESR and half-time c.q. corrected half-time of rouleaux formation. It is concluded that the determination of ESR is not a suitable method for studying the influence of plasma substitutes on the suspension stability of blood.

In chapter 7 some data on the viscosity of several plasma substitutes are presented (fig. 36 and table 7). Table 8 shows the influence of the addition of plasma substitutes on the viscosity of blood of various animals. There are no significant differences between bovine blood (no rouleaux formation, see fig. 17) and horse blood (excessive rouleaux formation, see fig. 18). These data however, are relevant only in relation to blood flow in large arteries, where the shear rate is of the same order as in the Epprecht viscometer (fig. 35) used in this investigation.

Chapter 8 first gives a survey of the most significant factors determining the influence of a plasma substitute on rouleaux formation of the erythrocytes in vivo. Next some further evidence is given for the causative part played by rouleaux formation in the obstruction of capillary blood flow in various conditions. Finally, a number of conclusions concerning the plasma substitutes used in this investigation is presented. Dextran BP gives a considerable increase of rouleaux formation. Rheomacrodex® on the other hand, proved to be an effective flow improver, inhibiting rouleaux formation to a significant degree. Macrodex® in most cases enhances
rouleaux formation, but the effect is not intolerably strong. Very promising observations were made using Plasmodex®. In spite of its rather large average molecular weight ($M_w = 75,000$), this dextran-glycerol-glucoside diminished rouleaux formation in most patients. Plasmagel®, an infusion fluid containing modified gelatin, increases rouleaux formation still more than is the case with Dextran BP. Haemaccel®, another gelatin containing plasma substitute, has less influence on rouleaux formation. Our PVP solution (Periston®) appeared to have an inhibiting effect on rouleaux formation. The average molecular weight of this solution was, however, too small to exert a lasting effect on the blood volume. The experiments in vitro indicate that PVP solutions with a higher average molecular weight will certainly increase the rate of rouleaux formation.