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Brief review of pharmacology and physiology of dextrans

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A Brief Review of Pharmacology and Physiology of Dextrans

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Introduction

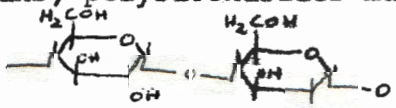
Dextrans have been available since World War II and are becoming more commonly used all the time; yet they are poorly understood, in many instances even by the people using them. This paper will attempt to review some of the pharmacological and physiological effects of dextran. A short review of other plasma expanders is included in order to help place dextrans in their proper perspective.

A source of confusion is the terminology used in referring to the various dextran preparations available. Below is a summary of the more common names and abbreviations used to refer to these dextran preparations:

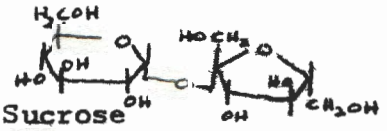
1. High molecular weight dextran--British dextran
2. Clinical dextran--Macrodex; Dextran 75; Swedish/American dextran
3. Low molecular weight dextran--LMD; low viscosity dextran; LVD; Rheomacrodex; Dextran 40

Physical Properties

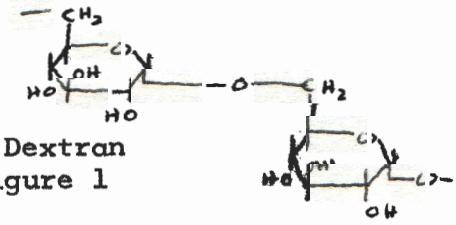
Dextrans, polysaccharides much like glycogen and starch, are



Starch



Sucrose



Dextran

Figure 1

polymers of glucose consisting primarily of alpha 1:6 glucosidic linkages (see Figure 1).[14] However, 1:4, 1:3, and 1:2 linkages occur at branch points; the number of branches and the distance between them depends on the strain

of bacteria, Leuconostoc Mesenteroides employed in the production of dextran.[14,40,42] Most dextrans currently in use have a low degree of branching; 90% of the linkages are alpha 1:6 glucosidic linkages.[14,42] The bacteria, grown in a solution of sucrose, produce an enzyme, dextransucrase, which converts sucrose into dextran according to the formula below:

$$n \text{ sucrose} \xrightarrow{\text{dextransucrase}} \text{dextran} + n \text{ fructose}$$

The resulting dextran is a polymolecular polysaccharide in which the strands are made up of varying numbers of glucose molecules.

Raw dextran consists of molecules of varying chain lengths and molecular weights; these weights may be extremely high.[42] Dextran preparations of lower molecular weight and fairly narrow molecular weight distribution may be obtained by partial acid hydrolysis and fractionations.[14,42]

Three different dextran preparations are available; these are British dextran ($\overline{Mw}$ 150,000), clinical dextran ($\overline{Mw}$ 75,000), and low molecular weight dextran ($\overline{Mw}$ 40,000). In the United States clinical dextran and low molecular weight dextran are the most frequently used preparations clinically.

The three dextran preparations differ in a number of ways. Figure 2 shows the molecular distributions of these preparations. As shown in this figure, LMD has 90 per cent of its molecular weight distribution between 10,000 and 80,000; for clinical dextran, 90 per cent falls between molecular weights of 25,000 and 200,000.[42]

Table 1 gives a comparison between LMD and clinical dextran.

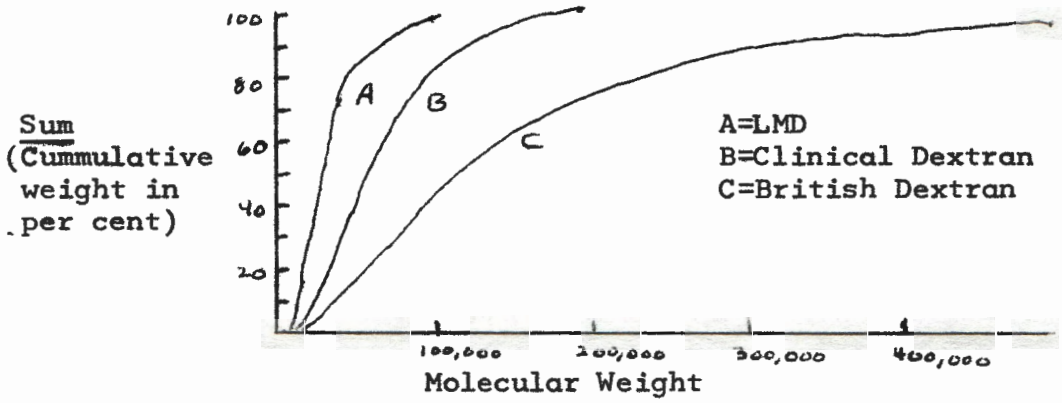


Figure 2[42]

Dextrans produce expandion of plasma water because of their colloid osmotic effect; because of the greater number of particles per gram, low molecular weight dextran may be transiently more effective than other clinical preparations. Low molecular weight dextran causes plasma expansion not only by retaining infused water, but also by attracting water from the tissues into capillaries more effectively than clinical or British dextran.[44] When the dextran preparations are infused over a short period of time, low molecular weight dextran causes a 16 ml. maximum expansion of plasma water per gram of dextran, while clinical dextran causes a 19.3 ml. maximum expansion per gram; the effect of low molecular weight dextran lasts one and one half hours while that of clinical dextran lasts four hours.[15]

Table 1[3]
Comparison
Between LMD
Clinical Dextran

	LMD	Clinical Dextran
Mean molecular weight (Mw)	40,000	70,000
Range (90% of molecules)	10,000-80,000	25,000-200,000
Volume expansion quality	fairly good, transient	good; lasts several hours
Excretion	rapid	fairly slow
Relative increase in viscosity of red blood cell (RBC) suspension	slightly more than albumin or plasma	more
Effect on aggregation	prevention deaggregation	slight, variable
Effect on microcirculation	appreciable	slight, variable
Antithrombogenic effect	Appreciable	appreciable
Dosage	10-15 ml/kg/ 24 hrs	10-15 ml/kg/ 24 hrs
Speed of infusion	over 12-24 hrs (1) to improve microcirculation (2) for antithrombogenic effect	(1) 1-2 hr. for volume replacement (2) 6-8 hrs. for antithrombogenic effect
Untoward effects		
Anaphylactoid reaction	not observed	occasionally seen
Pulmonary edema	may occur if given rapidly	more apt to occur if given rapidly
Increased bleeding	rarely seen at recommended dose	occasionally seen
Interference with blood typing	not significant	has been reported
Contraindication	pulmonary edema thrombocytogenia	congestive heart failure, coagulation defects

Blood Viscosity and Erythrocyte Aggregation

Dextrans may contribute to or prevent erythrocyte aggregation depending on their molecular weight; clinical dextran induces intravascular erythrocyte aggregation while low viscosity dextran causes disaggregation.[16,18,19] A critical molecular weight for dextran apparently exists. According to Thorsen and Hint, this weight is 59,000; higher weights tend to cause red cell aggregation while lower weights do not.[38] The aggregation tendency thus increases with increasing molecular weights of dextran.

Table 2

Some Factors Increasing Blood Viscosity[3]
1. Increased concentration of blood cells and platelets.
2. Increased aggregation of the RBC's.
3. Decreased internal fluidity of the RBC.
4. Decrease of macromolecules, increased level of fibrinogen, abnormal proteins, and reversal of albumin globulin ration
5. Small and narrowed vessels.
6. Vasoconstriction.
7. Low shear rate (decreased velocity gradient and slow flow rate).
8. Low pressure gradient.
9. Axial concentration of the blood cells (plasma skimming effect).
10. Decreased elasticity of the vessel wall.
11. Rough endothelial surface of the vessels.
12. Hypothermia
13. Low oxygen tension (as in sickle cell disease).
14. Acidosis.

Higher molecular weight dextrans cause increased erythrocyte sedimentation rates and increased whole blood viscosity; these effects can

be reversed with low molecular weight dextran.[17,36] Aggregation of the red blood cells causes the increased sedimentation rates and whole blood viscosity. Some factors increasing blood viscosity are listed in Table 2.

Erythrocyte aggregation is, in part, dependent on the balance of macromolecules in the plasma.[9,18,26] Dextrans are macromolecules. One of the major factors preventing RBC aggregation is the electronegativity of these cells.[4] Low molecular weight dextrans have been found to maintain or increase the electronegativity of red blood cells.[4,7,26,30,35] They also coat surfaces of erythrocytes.[4,30] This coating may crowd out proteins which have "sticky" properties that would lead to aggregation or sludging of the blood.[30]

Table 3[4]

Some Forces Tending to Cause Red Blood Cell Aggregation
Chemical bonding
Ion pair and triplet formation
Surface or interfacial tension
Some Forces Causing Cellular Repulsion
Electrical charge
Steric forces hindering chemical or ionic bonding

Four general factors have been elicited by which low molecular weight dextran preparations decrease blood viscosity; these are listed in Table 4.

Table 4[4,7,26,30,35]

Some Ways LMD Decreases Blood Viscosity
1. Plasma expanded by increasing plasma water, decreasing solute concentration and thus reducing plasma viscosity.
2. Erythrocyte concentration decreased by increasing plasma water, this decreased hematocrit and lowers blood viscosity because of RBC dilution.
3. Electronegativity of erythrocytes maintained, causing mutual repellency.
4. Erythrocytes coated, crowding out "sticky" protein substances which may cause aggregation or sludging of blood.

Coagulation and Hemostasis

Dextrans are macromolecules; macromolecules have been known to interfere with clotting since 1918;[5,22,23] however, this effect has not been found to be marked.[13,25,45] In one extensive investigation, dextran was found to cause twenty different changes in the hemostatic mechanism.[25] Many of these changes were dependent on changes in other related portions of the coagulation scheme, but most were of a minor nature. Some changes speeded rather than slowed coagulation.[25]

A principal inhibitory action of dextran was a decrease in the prothrombin consumption after *in vitro* admixture of dextran to blood.[25] This was related to the molecular weights of the dextran fractions used; heavier fractions caused a greater decrease of prothrombin consumption (see Table 5). The effect of the decreased prothrombin

consumption was variable, but the author of this particular study felt that the effect might cause defective hemostasis in certain cases. If hemostasis was already compromised by other factors, the administration of dextran could lead to even further deterioration of the

Table 5

Mw	% prothrombin consumption
17,000	76%
27,000	72%
41,000	60%
83,000	43%
250,000	35%
physiologic saline	62%

hemostatic mechanism.[25] In one study dextrans were noted to produce platelet aggregation; the relationship between this and hemostasis was unknown.[10] The formed elements of blood, including platelets, tend to be coated by dextrans.[5] Perhaps this coating interferes with the release of platelet factor 3 of in some other manner interferes with platelet function.

Dextran sulfate has a heparin-like action. As early as 1936, sulfuric esters of polysaccharides were found to have such heparin-like anticoagulant activity. This heparin-like activity of dextran sulfate has been attributed to the strong electronegative charge upon its acidic groups since its action is opposed by strongly basic substances such as protamine.[39]

Dextrans exert an activating effect on hemostasis in a number of places. The most important of these is the fibrinoplastic effect;

this refers to dextran shortening the time between the addition of thrombin and formation of fibrin in a fibrinogen solution. A number of investigations have confirmed this effect.[25]

Low molecular weight dextrans deserves special mention; it has little effect on hemostasis.[28,30,45] This is expected because of the low molecular weights involved;[25,45] nonetheless, LMD causes a pathologic thrombin generation.[13] Since LVD improves microcirculation, prolonged bleeding times occur.[30,41]

Type and Cross-Matching

Because of its effect on blood coagulation and cell suspensions, clinical dextran alters blood grouping and cross-matching procedures. However, LVD is reputed to be relatively free of such effects in therapeutic dosages.[3,41,43,45] Higher molecular weight dextrans, such as clinical dextran, cause pseudoagglutination, aggregation, or rouleaux formation.[43] LVD does not interfere with true agglutination, so typing and cross-matching procedures are not affected in a significant way.[41,43] Nevertheless, one wonders whether prolonged or massive amounts of LVD might not interfere with such procedures because of either the higher molecular weight fractions of LVD or because of the accumulation of the higher molecular weight fractions due to preferentially excreted low-weight fractions. Renal failure might also lead to increased levels of higher weight dextran fractions.

Excretion and Metabolism

The kidney plays a central role in the physiology of dextrans, for dextran is removed by means of glomerular filtration. Once dextran has been removed by means of glomerular filtration, it is not reabsorbed. The higher the molecular weight of the dextran, the less its likelihood of being filtered by the kidney; this is the primary factor determing the length of action of the various dextrans. An inverse relationship exists, the higher the molecular weight the more slowly the dextran is excreted by the kidney (see Figures 3, 4, and 5).[1,6]

Figure 3[6]

Amount of dextran (G) in the volume of plasma equivalent in volume to the glomerular filtrate plotted against urinary excretion of dextran per minute (U)

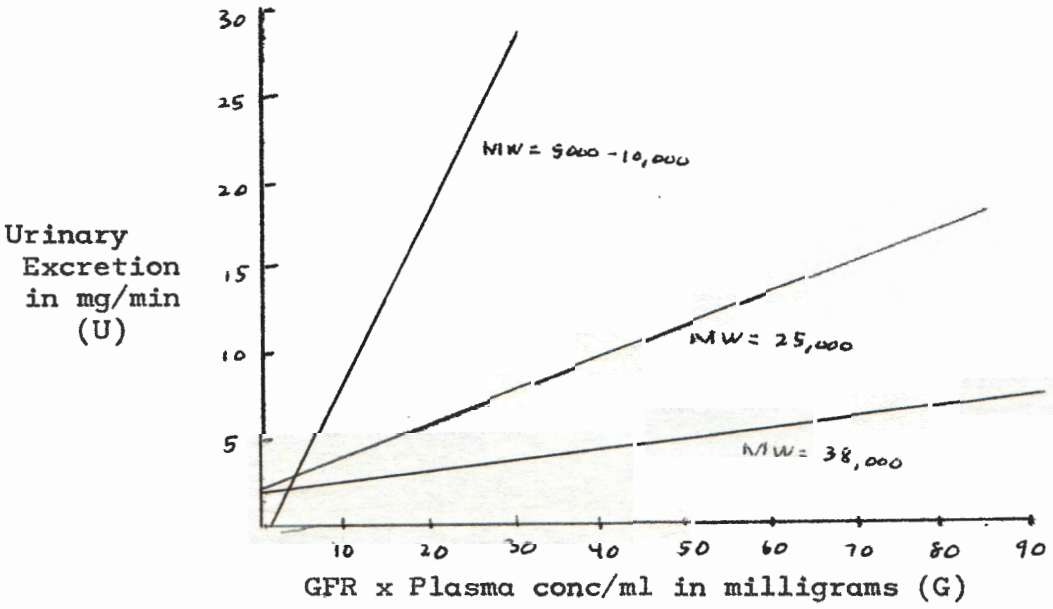


Figure 4[6]

Range of glomerular permeability
(Slope of lines in figure 3 plotted against
molecular weights of dextrans)

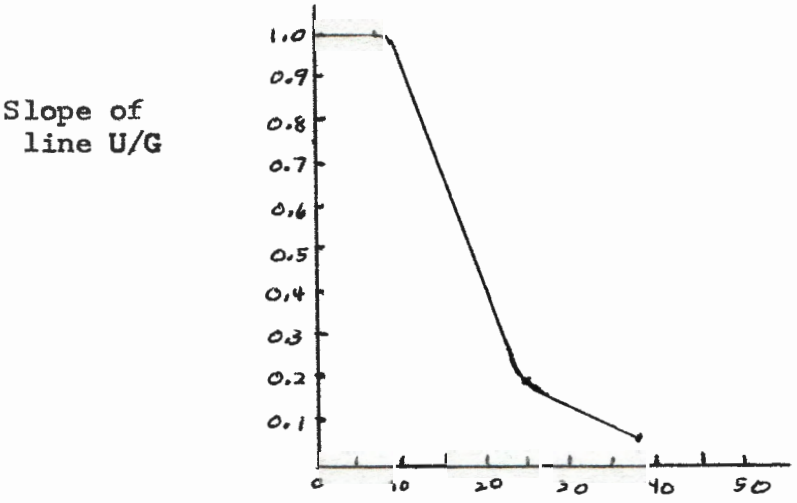
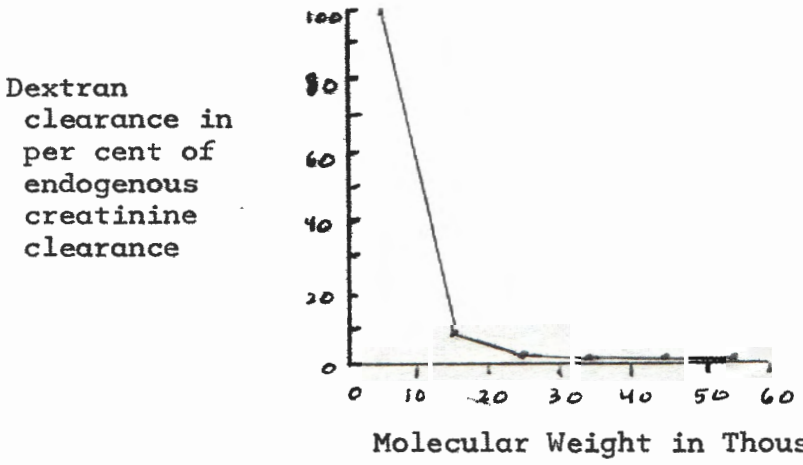


Figure 5[1]

Clearance of dextrans of different molecular
weights as percentage of endogenous
creatinine clearance



Two critical weights seem to exist; below a molecular weight of 15,000, dextran has the same renal clearance as creatinine; this indicates that dextran below this weight has essentially no noticable restriction in passing the glomerular filter.[2] The other critical weight is about 67,000; with weights below this, the dextran is rapidly removed by diuresis despite the glomerular filter.[1,2,20,24] 67,000 is the approximate molecular weight of albumin. In one study, dextrans with a molecular weight of 50,000 - 60,000 had very low clearance values, even approaching zero.[2] Despite this, the same study gives the values for the elimination of dextrans found in Table 6

Table 6[2]
Elimination of Dextrans

Mw 14,000 - 18,000	½ life 15 minutes
44,000 - 55,000	½ life 7.5 hours
Low molecular wt. dextran Mw 40,000	70% excreted in 24 hours
Clinical dextran Mw 75,000	45% excreted in 24 hours

The dextran solutions available do not contain dextrans of just one molecular weight; that is, the clinical dextran of Mw 75,000 has a wide range of molecular weights and this applies to LVD (Mw 40,000) as well (Figure 1). This means that the dextran in the blood stream will be constantly shifting its spectrum of molecular weights toward the higher weights as the low weights are eliminated.[20]

There are two main routes for dextrans to leave the circulation; one is excretion by the kidneys and the other is transport into the extravascular phase of the body water.[1] A dextran-splitting enzyme

has been found in the liver, spleen, and other human and animal tissues. It is an acid alpha exopolyglucosidase and splits the alpha 1:6 bonds, resulting in free glucose and "limit dextran," or dextran which has been split to branch points. However, experiments *in vivo* on rabbits resulted in complete degradation of dextrans in their livers, while *in vitro*, the dextran is only hydrolyzed up to the branching points by the dextranglucosidase preparations; this suggests that other enzymes may be present, one of which may act on alpha 1:3 bonds.[33]

In addition to excretion and to metabolization, a small amount of dextran accumulates in the reticuloendothelial system; the long-term effects of this are unknown.[37]

LVD has been noted to affect the kidneys in animals when high levels were used. This effect consisted of hydropic changes in the proximal renal tubules similar to the nephropathy caused by other substances such as sucrose, mannitol, glucose, and insulin.[27] Other effects which have been noted are subcutaneous and pulmonary edema, capillary bleeding, hepatic congestion, and decreased hemoglobin values.[26,27] The pulmonary edema and decreased hemoglobin values are due, at least in part, to the plasma-expanding effects of LVD.[27]

Renal failure has resulted from the use of LVD; certain of these cases have been fatal.[31] Renal biopsy demonstrated swollen tubual cells containing dextran; although no dextran casts were found intraluminally.[31] Infusion of dextrans in dehydrated individuals is

probably dangerous because the dextran would attract water into the vascular network. If the extravascular space is already dehydrated, this water would come from the cells.

Antigenicity

Dextran has antigenic properties.[12,24] These properties may be related to the degree of branching, to the ratio of alpha 1:6 linkages, to the non 1:6 linkages, and to the molecular weight; the antigenitic potential seems to decrease with decreasing branching and decreasing molecular weights.[8,24,25,41,43] Individuals with no previously known exposure to dextran have shown allergic responses; however, there are several ways by which they have been exposed. Dextran is known to be a common contaminant of commercial sugar; in addition, some workers have isolated dextran-producing organisms from the human gastrointestinal tract.[24]

The allergic responses to dextrans are not unusual; most consist of mild urtricarial reactions, but in some sensitive individuals more severe reactions may occur.[41]

A Brief Synopsis of Some Other Plasma Expanders

A blood substitute should fulfill three requirements; 1) carry oxygen; 2) maintain plasma volume; and 3) fulfill the functions of plasma.[32] So far, no substitute for blood has been found; however, many different plasma substitutes or expanders have been used with varying degrees of success; some substances which are currently used

or have been used in the past are listed in Table 6. Table 7 lists the characteristics of a good plasma substitute.

Table 6

Plasma Expanders
1. Plasma
2. Blood
3. Human Serum Albumin
4. Gum Acacia--Saline
5. Polyvinyl Pyrrolidone (PVP)
6. Gelatin
7. Dextran
8. Hydroxyethyl Starch (HES)

Table 7

Characteristics of a Good Plasma Substitute
1. Remains in circulation until replaced by normal plasma proteins
2. Viscosity and colloid osmotic effect the same as blood
3. Non-toxic, non-pyretic, non-antigenic
4. No interference with blood clotting, typing, or cross-matching
5. Easily sterilized, maintained, and stored
6. Not stored in body for prolonged periods

Plasma[32]

Plasma is essentially whole blood without cells. A number disadvantages are connected with its use. Old blood, besides containing excess sodium, may have potassium levels as high as 20 meq., which is irritating to peripheral veins. In addition, plasma from small pools may carry infectious hepatitus. Anti-A and anti-B antibodies have been found in plasma, even from small pools. Storage presents

problems; if stored at room temperature, bacterial toxins may accumulate in contaminated plasma. However, storage over six months does inactivate the virus responsible for infectious hepatitus.

Human Serum Albumin[28,32]

This is a good plasma expander; it does not transmit infectious hepatitus and is easily sterilized. Its short supply and high cost prevent it from being more widely and frequently used.

Gum Acacia--Saline[32]

This plasma expander was used in World War II. It is not well metabolized and is stored in tissues. Currently it is thought to be too dangerous for further use.

Polyvinyl Pyrrolidone (PVP)

PVP, a synthetic water-soluble pplymer, was developed during World War II. Metabolization is poor; large doses cause reticulum cell sarcoma in rats. It is not used because of these two factors.

Gelatin[32,38]

Gelatin is formed by partial hydrolysis of collagen obtained from bovine bone. As a plasma substitute, gelatin was used as early as 1915. Gelatin interferes with blood grouping and cross-matching procedures and tends to gel at low temperatures. Gelatin molecules large enough to avoid passing the glomerular filter cause significant aggregation of erythrocytes.

Oxpolygelatin (Haemacel) was introduced in 1940 and is well

tolerated, non-antigentic, but not as effective as dextran or PVP.

Hydroxyethyl Starch[32]

Starch is unsatisfactory as a plasma expander; it is rapidly broken down by amylase and ungelatinized starch in water causes emboli. Hydroxyethyl starch, a modification in an attempt to avoid these difficulties, is a substance much like dextran in both its molecular weight and its retention of fluid. Unlike dextran, it is non-antigenic and does not lend to erythrocyte agglutination. Inexpensive to produce and easily stored, it may prove to be one of the best plasma expanders available.

Blood

So far no replacement has been found for blood; although the plasma substitutes or expanders are used in an attempt to fulfill some of the functions of blood. Blood is the only substance that can carry adequate oxygen, maintain plasma volume, and fulfill the special functions of plasma. Plasma expanders probably will find their major usefulness in mass casualties when blood may not be immediately available in large quantities.[32] However, blood has certain qualities which do not always make it the ideal replacement substance, and in some instances it may be undesirable or even contraindicated.[32,37] Red blood cells are undesirable in situations in which the erythrocytes are not decreased or only slightly decreased in volume within the circulatory system; that is, plasma substitutes

or expanders are preferable to blood in situations in which losses are primarily of fluid from the blood stream.[37] Some situations in which replacement with blood may not be desirable are peritonitis, diabetic acidosis, sepsis, and burns.[37] Replacement of blood on a unit for unit basis may not even be desirable in hemorrhagic shock.[32,37] Although no substitute is available for blood, under conditions such as those mentioned above, blood itself is not desirable.

Clinical Use of Dextrans

Dextrans are used for two general purposes; one is that of a plasma substitute and the other is of a flow improver. Clinical dextran is used as a plasma substitute while LMD is used as a flow improver.

The use of clinical dextran as a plasma substitute is fairly straightforward. Various factors should be born in mind before it is used; these include its rate of excretion, its tendency to cause sludging of erythrocytes, its ability to invalidate blood grouping and cross-matching procedures, its possible antigenicity and toxicity and its effect on hemostasis.

Low molecular weight dextran also has a relatively clear role as a blood flow improver.[32] LMD is being increasingly recommended in the treatment of shock.[11,18,37] This effect is at least partially mediated by preventing intravascular aggregation. It may also be used as a plasma expander, but due to its fairly rapid excretion,

this effect is not as long lasting as clinical dextran; although this may be beneficial. When used, some of its characteristics should be considered; one of these is the improvement of microcirculation, which may not be desirable in some conditions such as head injuries or following an operation. Other characteristics are its possible alteration of coagulation mechanisms, its lack of significant effect on blood grouping and cross-matching, and its low antigenicity.

Most of the situations in which dextrans could be used are self-explanatory. One which is not is their use in thrombosis. A molecular weight of 77,500 has been found to be the most effective weight for use in cases of thrombosis;[34] clinical dextran has been recommended for this purpose.[21] Although in one study no difference was found in the incidence of clot formation between LMD and clinical dextran,[34] the use of clinical dextran would seem to be justified in cases of thrombosis. However, the long term use of dextran is questionable, and the effect of clinical dextran on erythrocyte aggregation should be remembered. Although dextran does have a heparin-like activity, heparin, itself, is greatly superiorr to clinical dextran in prevention of thrombosis.[21]

Dosage

To a certain extent, the dosage of dextran depends on the situation. The following dosages and speed of infusion are reco-

mmended by one source (see Table 1 also).[3]

Excerpt from Table 1[3]

	LMD	Clinical dextran
Dosage	10-15 ml/kg/24 hrs.	10-15 ml/kg/24 hrs.
Speed of infusion	Over 12-24 hrs. 1) to improve microcirculation 2) for antithrombogenic effect	1) 1-2 hrs. for volume replacement 2) 6-8 hrs. for antithrombogenic effect

With clinical dextran, the following schedule has been used successfully to replace blood:

Table 8[32]

Loss of Blood	Replace
1500 ml	dextran
1500-4000 ml	1:1 dextran:blood
4,000-7,000 ml	1:2 dextran:blood

Summary

This paper has dealt with some of the pharmacological and physiological aspects of dextran. Although difficulties arise in attempting to state that some properties are more important than others, the sections dealing with erythrocyte aggregation, blood viscosity, and electronegativity of erythrocytes probably deserve emphasis. These factors are related and become highly important in patients who are

already critical.

Indications for the use of dextrans and their relative importance have been discussed.

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