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Dextrose intravenously: principles, reactions and technic

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DEXTROSE INTRAVENOUSLY;

PRINCIPLES, REACTIONS

AND TECHNIC

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INTRODUCTION

Glucose, used intravenously as a therapeutic measure, is a common practice today. The purpose of this paper is to review in brief the development of this form of therapy, discuss its physiologic principles, review causes and prevention of reactions and the technic and solutions used. Because of the large mass of literature that has been written on the clinical uses of intravenous glucose, it could not be adequately reviewed in this short paper; therefore the above phases of the subject have been chosen for discussion.

Originally, the work glucose was synonymous in a chemical sense with dextrose. Practically, however, there was a great difference, because then, as now, glucose was prepared on a large scale for commercial purposes. Dextrose is the chemically pure product, but most physicians use the two terms interchangeably. Dextrose or d-Glucose is the substance used in intravenous medication.

A knowledge of certain fundamental facts regarding dextrose metabolism and dextrose therapy is essential in order to obtain uniform results from its use. Glucose is the product assimilated and it is the oxidation of glucose that provides the body with 60 to 90 per cent of the energy essential to existence. Bollman (1925) says that recent work has shown that muscular activity is almost, if not completely, dependent on glucose or glycogen for the necessary chemical changes. The minimal daily requirement of the body at rest is the equivalent of six to eight grams of glucose for each kilogram

of body weight. Glandular activity likewise requires energy which is furnished in large part by the oxidation of glucose. The body temperature is, for the most part, maintained by the glucose of the body. The numerous chemical changes in conserving material for food and body repair and in preparing waste material for elimination are aided by energy derived from glucose. Toxic substances may be rendered harmless by oxidation by glucose, or glucose may actually combine with toxic substances so that nontoxic compounds, glycuronates, are formed and excreted. Since glucose is essential for so many and so important normal body functions, it is not surprising that it is such an efficient therapeutic agent in a variety of pathologic conditions. Since there are few specific medicines, resistance of the body to infection and disease is important to life. Glucose is one of the agents which will aid in resistance because of its importance in normal functions.

The intravenous route of administration was chosen because it leaves out the many variables of absorption encountered in oral, subcutaneous, rectal and intraperitoneal administration. Dunn (1917) says that certain forms of medication, as well as the giving of fluid for the purpose of stimulation or of supplying loss to the blood, are best given directly into the blood itself rather than by mouth or by the subcutaneous route. Since glucose is the only food substance that exists outside the body in the same form that it circulates in the blood and tissues, he concludes that its

injection must be beneficial and should be harmless.

Talbot (1925) states that the administration of sugar by mouth is limited to those cases in which it is possible to retain it, and recommends intravenous administration in children in certain conditions. Horsley (1930) quotes Sanford and Hertmeyer in saying that the intraperitoneal giving of dextrose in children's diseases when the intravenous method is impossible due to the size of the veins, is satisfactory, but it could not be oft repeated without ill effects. Jerome Glasser, according to Horsley's article, has given 10 per cent dextrose intramuscularly. However, indurated areas persisted for several days in three cases and may have been hematomas secondary to blood vessel injury.

To further justify the discussion of the intravenous route, it might be well to mention the work that has been done on the absorption of dextrose from the colon. McNealy and Willems (1930, 1931) carefully conducted experiments in which a loop of colon and a loop of ileum were isolated by ligatures and filled with the fluid to be tested. The loops were approximately equal in absorbing surfaces. It was found that the amount of dextrose in grams absorbed by the loop of ileum in a given time varied from 23.2% to 59%, and by the loop of colon, from 0.4% to 2.6%. The dextrose was in 5% solution. They conclude that a 5% solution of dextrose is not absorbed from the colon to any appreciable extent. Smith (1930) agrees with these authors.

It is well recognized that absorption of glucose

when given by mouth is a very variable factor. Woodyatt, Sansum and Wilder (1915), give the maximum rate of absorption as 1.8 grams of glucose per hour per kilogram of body weight. It is often desirable to give glucose in much larger quantities than this and at faster rates, in which case the intravenous route must be resorted to. In emergencies, the latter may be the only route available for much needed fluid, food and stimulation. Thus, a knowledge of principles and dosage may be required on short notice.

The following brief history of the beginnings of intravenous glucose medication in this country is compiled from the researches of Woodyatt, Sansum and Wilder (1915); Rathmann (1932); Palmer, Turner and Gibb (1929); Kleiner (1916); and the Supplement to the Journal of Intravenous Therapy (July, 1928):

Fleig, in 1907, made roughly timed intravenous sugar injections and was struck by the remarkable diuresis produced. He was impressed by the clinical possibilities but made no recommendations. Kausch in 1911, saw the possibility of therapeutic application in pernicious vomiting of pregnancy, surgical conditions and acute gastro-intestinal diseases. He attempted this form of treatment in some cases, and obtained some good results. M. H. Fischer (1915) recommended its use in conditions of edema, nephritis and intoxication, and especially in oligurias and anurias of various sorts on the basis of his observations concerning the power of sugars to

dehydrate colloid gels and the diuresis produced. Henriques in 1914, reported the use of 250 to 300 cc. of 30% glucose solution in fifty cases of heart disease, intoxication and severe infections, finding special indications in oligurias of nephritis and heart disease. Turrettini in 1915, gave details of three cases of acute nephritis and three of mercuric chloride poisoning, in all of which the urinary output was favorably affected. The work of Woodyatt, Sansum and Wilder (1915) was the first accurate work on intravenous dextrose, and will be discussed in detail in the section on physiologic principles. In 1917 Erlanger and Woodyatt used intravenous glucose in shock. Litchfield (1918) reported extensive use of glucose in the treatment of pneumonia without serious complications. Also, in 1914, he had published a paper in which he recommended glucose intravenously in acidosis and shock.

Aided by delicate methods of dextrose determination in the blood and urine already developed, the practical application of the principles set forth by Woodyatt and others, were demonstrated by the appearance of a voluminous literature on the intravenous administration of dextrose. Numerous clinical reports were published covering the treatment of the toxemia of pregnancy; vomiting of pregnancy and eclampsia, pneumonia, thyrotoxicosis, diabetes, acidosis, surgical shock, septicemia, various acute infections, glaucoma, edema and skin diseases, encephalitis and various other conditions.

PHYSIOLOGIC PRINCIPLES

In 1915, Woodyatt, Sansum and Wilder carried on memorable experimental work on sugar tolerance and the perfection of accurate clinical methods for estimating the sugar-using powers of different individuals. They anticipated, using intravenous glucose injections, that the data which would be obtained could not fail to have other applications, and that the method employed might be in itself of general interest as a means of studying problems of absorption, metabolism and elimination and have therapeutic application. Expectations concerning all of these things have been fulfilled. Their experiments were carried out on normal rabbits, dogs and men.

They conclusively proved that man can utilize between 0.8 and 0.9 grams of dextrose per kilogram of body weight per hour of time without glycosuria. They used concentrations of from 10% to 50% and the injections were made over a period of from 6 to 12 hours. They contend that the nearest possible approach to a scientifically accurate method of sugar tolerance measurement must consist in direct intravascular administrations, since only by this method is the variable factor of absorption rates reduced to a minimum. "When sugar is introduced directly into the circulating blood, each tissue receives its share in proportion to its vascularity, and absorption plays no part except as it may be concerned in the transfer of sugar from the local capillary to the perivascular lymph, and the taking up by each

individual cell of the sugar with which it is bathed."

Thus they showed that, with a knowledge of the concentration of glucose to be used, and the rate appropriate for this particular concentration, that it is possible to abstract any quantity of water from the body which is deemed safe or desirable, or a great flushing stream may be passed through the body to wash out poisons. Their work is the first important work done in the United States, although similar but less accurate work had been done in Europe before that. These authors had proven before that, that other methods of administration could not introduce glucose into the blood faster than 1.8 grams per kilogram per hour. They concluded then that intravenous injections may exceed this rate, and so cause, in addition to the ordinary chemical effects of glucose, new physico-chemical effects due to the presence of unburned sugar molecules in the tissues and expressed outwardly as diuresis. However, they warn that there are two important things to avoid: (1) Too great dehydration; (2) Heart failure from imposing too much mechanical work on the circulatory system.

Kleiner (1916) found that after the intravenous injection of large amounts of dextrose in dogs, the blood sugar returns to its normal quantity within an hour and a half. Of the excess dextrose introduced, the major part is eliminated through the kidneys and about 40% escapes from the blood vessels by the process of dialysis into the surrounding tissues and the smaller amount was destroyed by increased

oxidation.

Woodyatt and his co-workers (1917) again published the result of experimental work on dogs in shock and brought to light many of the beneficial effects of glucose of a physico-chemical nature. They give the reasons for these experiments on this statement: "In accordance with a prevailing opinion, the low blood pressure in shock is associated with a diminished effective volume of blood in the vessels, and the two factors constitute in themselves essential parts of the shock mechanism. On this assumption, benefits should result from procedures having the effect of holding water within the vessels."

They discovered that with rates higher than 0.9 grams per kilogram per hour, the glucose utilization failed to keep pace with that of the injection, and there was a tendency for the accumulation of some unchanged glucose in the tissues. When the kidneys are functioning properly, they found that this glucose is excreted on the urinary side of the renal membrane and thus tended to draw water with it, probably for the same reason that glucose in the blood produces hydremia. Thus diuresis is established. They further state that if the diuresis exceeds the rate of water administration, water will be continually drawn from the tissues to the blood and then to the urine, and thus a state of hydremia is kept up, as long as the water supply is adequate. Of course, if the kidneys are not active, the glucose accumulates in the tissues and draws water with it wherever it

goes. Thus the principle of diuresis with hypertonic solutions of glucose was put on a scientific basis. This principle is used in the relief of local edema, as shown by the work of the same authors on glaucoma in 1917. The relief of cerebral edema by hypertonic intravenous glucose solution has also arisen from this principle.

They also found that overdoses of glucose solution tend to diminish the coagulability of the blood. They produced clean wounds in the experimental animals and waited for the bleeding to stop spontaneously. Then they injected large amounts of glucose solution, which caused the wounds to start oozing blood, sometimes quite considerable in amount. But they state that none of this secondary hemorrhage was serious but that it is a factor to be kept in mind when sugar solutions are employed in the treatment of shock in the wounded.

In experiments in normal individuals, they found marked increase in the mean arterial pressure after the injection (sustained) of amounts of glucose above the tolerance rate of 0.9 grams per kilogram per hour. But after several injections were made, a decline in the blood pressure appeared, subsequent to the injection, to a level well below that obtained previous to the injection. This was despite a pulse amplitude which was higher under the low pressure after the injection than it was under the higher pressure present preceding the injection. The increased pulse amplitude is undoubtedly a measure of the increase in blood volume. This condition probably is made possible through a diminution in

the vasomotor tone they believe, and a decrease in the viscosity of the blood, which together defeat the tendency of the plethora to increase the arterial pressure. They contend that the normal center is keyed to hold the pressure at a certain level, and that the damaged center is keyed to hold the pressure at a lower level. "The reactions of the center, therefore, to increased blood volume, no matter what the new pressure normal may be, will always be such as to return the disturbed pressure to that normal. Thus an increased volume and lowered pressure are accounted for."

On the animals in experimental shock they also used glucose at subtolerant rates, and get practically the same effect. Their conclusions are: (1) The mean arterial pressure is uniformly increased. (2) There is an increased pulse amplitude, indicating plethora. (3) The increased pulse amplitude is more striking than the increase in arterial pressure. (4) A subtolerant dose has raised the arterial pressure and increased the pulse amplitude as effectively as many of the injections made at more rapid rates. (5) Hemorrhagic tendency may develop. (6) No other deleterious effects were observed.

Barbour (1918) did some research work on the giving of glucose by mouth to normal individuals and concluded that there was some reduction in temperature in each individual. The same results probably attend intravenous administration. He states he believes this antipyretic action is due to the

increased elimination through the kidneys which the glucose produces.

Litchfield (1918) states that the first effect of glucose injected into the blood stream is the absorption of water from the tissues, as shown by a fall of the hemoglobin percentage, indicating greater dilution than the water injected will account for. The secretion of the kidneys is temporarily diminished, owing to the need of water in the blood stream to properly dilute the injected crystalloid substance. He assumes that this taking of water from the tissues removes waste products with it in solution. The glucose is burned or eliminated. The oxidation of the glucose causes a temporary increased heat production which does not follow the intravenous introduction of water or of water with sodium chloride or urea, as shown by Lusk (Litchfield). Lusk believed that there is a definite stimulation of the cell mechanism by the food in the blood stream. After the water is eliminated or absorbed, the blood pressure falls; but the pulse amplitude remains good because the heart muscle has been nourished and stimulated by the glucose.

Rigler and Ulrich (1923) report the results of 20% intravenous glucose given to diabetic and non-diabetic patients with the blood sugar reaction which followed, and the red blood corpuscle counts to determine whether or not hydremia occurred. From their red blood corpuscle counts it is readily seen that in most cases a hydremia occurs which has a

tendency to decrease in direct ratio to the decrease in blood sugar. The characteristic finding in regard to the blood sugar is the marked rise occurring just after the injection, followed by a definite fall to normal usually within one hour, and almost invariably a fall to subnormal at the end of two hours. These authors state that Opitz, and Nonnenbruch and Szyszka have also made sugar tolerance tests in this way. All their cases showed the same result in blood sugar reaction, as well as definite evidences of a hydremia following the injection, as evidenced by the red blood corpuscle counts and hemoglobin percentages.

Albritton (1924) obtains similar results in continuous intravenous glucose injections. He states that hemoglobin percentages indicate that dilution of the blood occurs.

Boyd, Hines and Leese (1925) administered glucose continuously for considerable periods of time to normal animals, by means of an electric pump which had been described by Woodyatt, and made observations on blood sugar, hemoglobin, volume and sugar content of urine, plasma pH and carbon dioxide content, body temperature, respiratory quotient and heat production before, during and following the glucose administration. The physiological conditions of the animals were controlled by administration of a constant diet during periods preceding observation, and by comparing the response of the same animal to repeated injections. They used an administration rate of 4 grams per kilogram per hour to test the

sugar-handling mechanism of supra-tolerant doses. The injection period was two to four hours.

They found that the response of a given animal to repeated injections is quite uniform. They find the same blood sugar variations as reported heretofore, and find about 20% of the injected sugar appeared in the urine. Heat production is increased about 50% during the injection and this rapidly subsides to preliminary value after injection is terminated. The respiratory quotient becomes higher, indicating predominant glucose combustion. There is a slight decline in plasma pH and carbon dioxide content which apparently bears no relation to the pH of the injected fluid. There is a slight rise in body temperature associated with the injection period. Barbour has reported that glucose by mouth reduces the temperature. Undoubtedly there is some reduction after the injection is stopped due to the loss of heat through the extra water excreted by the kidneys.

Bollman (1925) states that besides the stimulation of excretion of urine, other vital processes may be stimulated by this exchange of water and alteration of the concentration of the many chemical substances within the cell. As evidence of this stimulation he cites the apparent increase in the production or liberation of insulin following the administration of glucose, since the sugar content of the blood decreases below its former level soon after the excess glucose is disposed of; and since a second injection of glucose

at this time disappears more rapidly from the blood than did the first. The alteration of the character of metabolism following glucose administration is further proof of the changed reactions of the body cell.

This author also adequately reviews the value of glucose as a food. Glucose alters the nature of metabolism, the respiratory quotient being increased toward unity, which indicates a greater utilization of carbohydrate in the body and a lessened destruction of protein and fat. Perhaps this change in the cell metabolism may bear some relationship to the reaction to disease. The protein sparing action of glucose is well known. This allows less tissue destruction and more tissue repair, and there are less nitrogenous waste products formed so that the kidney is spared the effort necessary for their excretion. The oxidation of fatty acids in the body depends on the simultaneous oxidation of glucose, and insufficient oxidation of glucose results in the accumulation of fatty acid residues and acetone bodies with resultant acidosis. These facts are well known to students of diabetes.

Weil (1925) observed the capillaries after intravenous injections of small amounts of glucose. He found in hypertension patients a widening of the previously narrow lumen and better circulation, which was parallel with the lowered blood pressure.

Wichels (1925) made similar observations as did Weil. He also found a decrease of about 3,000 white blood cells per cubic mm. The absolute lymph count did not change

except with previous lymphocytosis. He also made the observation that if strips of surviving intestine from guinea pigs, cats and dogs were made tonic by the addition of serum to the fluid in which they were suspended, and then 0.1% of glucose was added, the tonus rapidly decreased. Thus an action of relaxation on smooth muscle seems established. This may explain the widening of the arterioles and the reduced blood pressure in hypertension patients. As stated before, Woodyatt found there was a lowering of blood pressure in shock, but that the pulse amplitude was increased. Perhaps this action of relaxing the tonus of smooth muscle as described above would account for this reaction. It is just a possibility which might be considered.

Jacono (1924) experimented with agglutination in vitro of bacteria suspended in glucose menstrua. He found that the sera of normal individuals would agglutinate bacteria if in a glucose medium, but would not do so in physiological serum, or in hypertonic saline solution in distilled water. He also found that rabbits inoculated with emulsion of bacteria in serum containing glucose produced agglutinins in similar manner to rabbits inoculated with bacteria emulsified in physiological serum; and the former solution revealed marked indications of a minor degree of toxicity. From this and a larger mass of evidence he concludes finally that solutions containing glucose, when employed as a vehicle for vaccines, not only diminish toxicity of bacteria but promote and increase production of defensive antibodies like agglu-

tinins. Thus, perhaps there is an action of glucose that increases the protective power of the blood against infection.

In the Blumer edition of Forchheimer's Therapeutics (1929) is mentioned the action of intravenous glucose on the human electrocardiogram, but the experimental basis from which their conclusions are reached, is not given. They state that there is a prolongation of the A-V conduction time, slight changes in the R wave, the appearance of Q and S waves if they were previously absent, and a shift in the position of the T wave. The significance of these changes was not discussed.

The foregoing is an attempt to tabulate most of the physiological effects of glucose injected into the vein, and which, briefly, are as follows:

1. The blood sugar increases and if the injection is continued, it returns to normal or slightly below in about 90 minutes.
2. The tolerance limit (maximum rate of injection without glycosuria) is between 0.8 to 0.9 grams per kilogram per hour.
3. The glucose replenishes the glycogen stores of the liver and acts as a source of energy to the organism.
4. There is definite heat production associated with the injection, which disappears when the injection is stopped.
5. The respiratory quotient approaches unity, indicating increased carbohydrate metabolism, with consequent

lessened fat and protein metabolism.

6. Glucose injected at rates faster than the tolerance limit causes hydremia and diuresis with the relief of local or generalized edema.
7. Injections of glucose increase blood pressure for a variable time, but which drops to a level lower than at the beginning of the injection; the pulse amplitude increases.
8. There is slight decrease in pH and carbon dioxide content of the blood following injection.
9. There is evidence of some dilatation of the arterioles and capillaries in hypertension patients.
10. There is evidence of some changes in the human electrocardiogram after injection.
11. There is evidence of an increase in antibodies in the blood following injection.
12. There is evidence of glucose having the effect of decreasing tonus in smooth muscle.

SYSTEMIC REACTIONS FOLLOWING INTRAVENOUS GLUCOSE INJECTIONS

Since the beginning of intravenous glucose medication, physicians have noted with a varying degree of frequency the occurrence of systemic "reactions" coming on shortly after the injections. There has been considerable speculation as to the cause of these reactions and various methods of procedure have been adopted in an effort to avoid them. The following is a review of the literature pertinent to the subject, giving the opinions of various authors as to the cause, and means of preventing the reactions. Glucose, in itself, is non-toxic as is obvious since it exists in the blood in the same form in which it is injected. Consequently, the cause of any toxic effects or reactions would seem to lie in the purity of the glucose, the method of administration or the apparatus used.

It is interesting to note that some of the earliest experimental workers in this country gave several hundred injections of glucose of different concentrations and at different rates to animals and men without reactions. It is to the work of Woodyatt, Wilder, Sansum and Erlanger from 1915 to 1917 that I refer. Because their work was experimental, they controlled the factors that produce reactions much more carefully than would the average clinician. That is, they controlled the purity of the solution, the rate of injection and other factors with mathematical exactness, so that their results could be taken as fact, which is one of the aims of all experimental work.

Litchfield (1918) stated that he believed the reactions following glucose injections into the blood stream were artefacts to be avoided. In his work on pneumonia patients he had a few reactions, but without any serious results. He alludes to the similarity of the reaction to that produced by the use of foreign protein in arthritis. He cites a case with extraordinarily high temperature following glucose intravenously:

"A boy, aged 12, who had been desperately ill for several days with lobar pneumonia with a temperature of 105.3 F., after receiving 300 cc. of glucose solution had a severe chill of ten minutes' duration and a rise to 108.4 F., followed by a drop to 98F. in ten hours. Two days later his temperature had risen to 104.5 F., when he received 300 cc. of glucose, which was followed by a chill with a rise to 107.5 F., dropping to normal in about six hours, followed by a moderate rise for twenty-four hours and an uneventful convalescence." The author states that it was his general condition, and not his temperature, that indicated the use of glucose. He makes no suggestions as to the cause or reaction in this case.

Williams and Swett (1922) believed that many of the reactions following glucose injections were due to the acidity of the solution. Acid solutions in small amounts may be injected into the blood with impunity, because of the quick action of the buffers in the blood and the small amount injected. But they say that when a solution with an abnormal

hydrogen ion concentration is injected intravenously in greater amount than the blood can buffer, or at a rate in excess of the capacity of the blood to neutralize it, then reactions or death may occur. They tested the pH of stock glucose solutions and found most of them to be strongly acid. They believe that solutions with a pH below 6.5 are likely to produce reactions, and those below 5.5 must be regarded as quite toxic when given at a rate or in an amount in excess of the capacity of the blood to buffer. They then used phosphate salts as buffers, and found that the acidity of the solutions was corrected immediately.

They also found that the acidity of the solutions was markedly increased after boiling, autoclaving or standing for a few hours. They used buffered and non-buffered solutions, and state that they have had no reactions using the buffered solution.

Stoddard (1924) does not agree with the above workers in believing that the acidity of the solutions could cause reactions. He draws attention to the extremely small amount of acidity of a glucose solution with a pH of 4.4 as was mentioned by Williams and Swett and that it required an infinitesimal amount of alkali to bring it to a pH of 7 or neutrality. He believes that the buffer substances of the blood are more than able to take care of this small amount of acidity. His argument is as follows: "Assuming the reliability of the evidence that the acid solution is toxic and the solution buffered by phosphate is non-toxic, we can only surmise a

detoxicating effect of the phosphate in an obscure manner on an unknown decomposition product of the glucose, neither the toxicity nor its absence probably caused by the variation in the hydrogen ion concentration or in the total amount of acid, but only varying with the acidity changes; or else a hitherto unknown effect of acidity on blood to produce a toxic effect." However, he admits the value of the findings of Williams and Swett, as he reports that since the addition of buffer salts to glucose solutions in the Massachusetts General Hospital, all reactions from its injection immediately stopped. He believes it to be an empirical discovery of practical importance but the explanation of which is unknown. He also warns that the buffer should be added to the solution just before injection, because glucose breaks down more quickly in alkaline or neutral solutions than it does in an acid solution.

Matas (1925) in describing a technic of intravenous glucose administration by the drip method, more lightly considers the reactions. He says that they do not seriously engraven the prognosis. He does not know the causes of the reactions, and makes no suggestions. However, he does not believe them to be due to the temperature of the solution, the presence of foreign materials in the apparatus, or the hydrogen ion concentration.

Probably the most exhaustive study made on the subject was done by Titus and Dodds (1927). Titus was one of the first men to develop the use of intravenous glucose therapy in the toxemias of pregnancy and his large experience with

the injections will lend some weight to his arguments. He says that the treatment is used a great deal, but would probably be utilized more if it were not for the reactions which occasionally follow such injections. From his wide experience he makes the following statement: "Without hesitation, the bold statement may be made that reactions are almost invariably due to faulty technic either of the preparation of the glucose solution or its method of administration. Consequently, reactions should be largely preventable."

The causes these workers give for the reactions are as follows: (1) The use of impure glucose. (2) Its being dissolved in something other than freshly distilled, uncontaminated water. (3) Improper preparation and sterilization of the solution and the apparatus for its administration. (4) The administration of the glucose either too rapidly, too cool or in too weak a solution. The rules to follow in dosage and technic of administration of the glucose as advocated by these men, will be reproduced in the following section of this paper.

Bollman (1925) also believes that any toxic effects of the intravenous injection of glucose may be entirely due to faulty technic in the preparation of the solution which in itself is entirely free from any toxic effects. He states that a few years before his article was written, a number of commercial brands of "pure" glucose produced death in dogs a few minutes after the intravenous injections of such small amounts as 200 mgm. of glucose for each kilogram of body

weight. In experimental work, he always tests the glucose biologically before use, by injection of 5 grams of the glucose to be tested for each kilogram of body weight of the test animal. If no reaction is observed in this animal, the glucose is considered safe.

He describes the symptoms in animals of the use of these impure brands of glucose. The usual course begins with vomiting a few minutes after injection. The vomitus is usually clear but may become bloody later. Accompanying this is a slow pulse and a subnormal temperature. The respiration tends to be slow and is frequently irregular. Thus most of the symptoms are those of shock. Later muscular twitchings may be present and increase in extent and severity until generalized convulsions occur. Usually a severe diarrhea occurs which may become markedly hemorrhagic. The animal gradually becomes comatose and death ensues. At necropsy all organs are found to be markedly congested and frequently show numerous petechial hemorrhages. Bollman does not attempt to explain what is in these impure brands of glucose to produce such a train of symptoms and death. This reaction is different than the ordinary febrile reaction. Further, he ascribes the febrile reactions to the same causes which Titus and Dodds (1927) conclude in their work.

Talbot (1925) also mentions reactions following glucose and recommends the buffer solutions used by Stoddard (1924).

Palmer, Turner and Gibbs (1929)discuss the prepara-

tion and technic of glucose administration. They give a set of rules to follow which is much like that of Titus and Dodds. They believe that glucose solutions several days or several weeks old have been used and this is, in their opinion, the most important factor in the causation of reactions. They state that the pH of these solutions is very low and probably other changes have taken place.

Robertson, Oliensis and Stein (1927) carried on studies as to causes and methods of prevention of such reactions. They gave glucose in cases of uremia and toxemia which were advanced and of grave prognosis. They used concentrations varying from 10% to 60% and found that the mortality was highest in those patients receiving the 10% solutions and lowest in those receiving the more highly concentrated solutions. From their work they conclude that reactions or untoward results following the injection of intravenous glucose are due to the rapid rate of injection, the large volume of fluid, distilled water and improper temperature of solution. They then perfected a technic for the preparation and administration of the glucose, much like that of Titus and Dodds (1927), and after using this on fourteen patients before their paper was written, there were no more reactions.

Clark (1927) reports two deaths following injections of 500 cc. and 475 cc. of 10% dextrose, one in a cardiac patient and one in a patient suffering from post-operative shock. These are rather large amounts and the author realizes this and says that the use of dextrose solutions, even in the pres-

ence of a failing myocardium, is quite routine today. He states that the bad and possibly fatal effect of the extra load thrown rapidly on the heart is lost sight of in the attempt to give the patient the required fluid or antiketogenic substance.

From the reports of Robertson et al, and Clark, it would seem that hypertonic solutions of less volume were advisable unless there is marked dehydration. The former state: "We felt that the concentrated glucose injections of small volume were to be preferred because of their greater safety in the presence of an impaired cardiovascular system, and because of the lessened likelihood of reactions."

Ylanan (1930) reports an interesting case of reaction following glucose injection. He mentions the work of Seibert, who claimed that reactions after the intravenous use of glucose solution are principally due to the presence of a certain substance known as pyrogen, which is found to contaminate distilled water after it has been allowed to stand for some time. She advocates freshly distilled water. Ylanan also mentions the work of Secard and Leblanc who report reactions following the faulty distillation of the water. These workers proved that water distilled in certain copper, nickel and zinc condensers has the property of dissolving these metals. The use of water so distilled would therefore give rise to unpleasant reactions. Ylanan's case follows:

"E. G., male, Filipino, 50 years old, married, was admitted to the Southern Islands Hospital on 11-7-27, with the diagnosis of cirrhosis of the liver with ascites. Paracentesis was performed on the day of admission, and 2.5 liters of yellowish fluid were withdrawn, after which the patient felt much relieved of the abdominal distention. On the evening of Nov. 11, four days after admission, the patient had severe hematemesis, as a result of which he developed symptoms of shock. The treatment recommended by Fisher for shock was followed here. 500 cc. of a 10% solution of glucose prepared in the hospital pharmacy were injected intravenously by the open method. One-half cc. of insulin U-20 was injected hypodermically fifteen minutes after the beginning of the glucose injection and another one-half cc. at the end. The glucose solution was injected warm and slowly, so that one hour and twenty minutes were consumed in its administration. Fifteen minutes after the termination of the injection, the patient developed a severe reaction manifested by sharp chill, difficulty of breathing, high fever, and later by profuse sweating and collapse. The patient was immediately wrapped in thick blankets, surrounded by hot water bags and given stimulants like hot black coffee by mouth, and camphorated oil, strychnine sulphate and caffein-sodio-benzoate by hypo. The patient failed to respond to these treatments and died two hours after he developed the glucose reaction. Investigation showed that pure glucose was used, but it was dissolved in old, standing distilled water which most likely was contaminated. The solu-

tion was sterilized by boiling for about a half hour by the head nurse on duty in the hospital. The solution was golden yellow in color, not clear and was caramelized."

The ordinary reaction is not nearly so severe as this one, a chill, slight fever and some sweating later usually occurring. This is an example of the use of contaminated distilled water, and boiling the solution too long, which causes increased acidity as has been mentioned by many writers.

McNealy and Willems (1932) state that too rapid a rate may cause a reaction, as Titus and Dodds and many others have already stated. In using the drip method they state that the rate should never be faster than two drops per second.

Titus also believed that perhaps the cresol used as a preservative in the ampoules of glucose manufactured by one company could cause reactions. The report of the Council on Pharmacy and Chemistry states that this may be true and they recommend that more work be done before definite conclusions be made. As a rule the ampoules made by any reliable drug firm are quite safe if dissolved in uncontaminated, distilled water and administered properly.

THE SOLUTION AND TECHNIC OF ADMINISTRATION

A review of the development of the intravenous administration of dextrose to its present stage, shows a parallel to the development of intravenous therapy generally. Thus, we witness step by step, first oral and rectal, then hypodermoclysis, then finally the intravenous administration. In this step, also, we witness first the injection of large volumes of dilute solutions with frequent reactions, then the discarding of the large volume of dilute solutions with the adoption of the smaller volume of controlled concentrated solutions to avoid reactions, except where large volume is imperative.

It was early shown by Woodyatt (1915) that the upper limit of glucose utilization is reached when 0.8 to 0.9 grams per kilogram of body weight per hour are injected. He considered that the normal limit ranges possibly from 0.3 to 0.6 grams of glucose per kilogram per hour. Where it is desired to supply food and energy, or combat acidosis and toxemia, this rate of injection probably should not be exceeded. However, it is often not desired to overload the circulation with large amount of fluid, so that hypertonic solutions have gradually come into favorable use. Where large amounts of fluids are needed as after hemorrhage or vomiting, the weaker solutions are desirable. The dosage for each patient is an individual problem, but there are certain general principles which must be adhered to. Of course, large amounts of hypertonic solutions are necessary where great diuresis or the relief of local edema is desired.

Litchfield (1918), was one of the early users of intravenous glucose therapy, and his work in pneumonia is notable. He states that his first experience with this treatment began in 1909. For several years he used only an isotonic solution (5%), using it in all cases in which he had previously resorted to salt solutions. Since 1914, he has used more concentrated solutions with greater and greater frequency and with greater and greater satisfaction. Such a clinical experience, even in the absence of experimental work, must be heavily considered in the decision as to what solution is to be used. At the time his paper was written he was using 250 cc. of a 25% solution, the caloric value of which is easily computed as 1 Calorie per cc. He took about one hour to give this to the patient. He stated that the electric pump was not necessary outside the physiologic laboratory, which is a very practical consideration.

He stated at that time that any method for arsphenamine administration is satisfactory for glucose solutions. He also mentioned that distilled, sterile water is not necessarily non-toxic. He stressed the use of a pure glucose, sterilization by boiling or the autoclave, and the maintenance of the temperature of the solution at 100 F. The latter was done by having the tube which was attached to the needle run through a basin of hot water placed at the bedside. He advised a hypodermic of morphine to control a delirious or hypersensitive patient. Since this paper by Litchfield was written much experimental work has been done on the dosage

of glucose and the method of administration, but little has been added to Litchfield's statements, even though we do know more about the causes of reactions after intravenous injections.

Titus and Dodds (1927) in their work on the causes of reactions which has been referred to heretofore, gave a list of rules to follow in the preparation and administration of glucose which I believe it would be well to reproduce here. Because of their large experience, their advice can be advantageously followed, and other contributors have added little:

1. Dosage: The average dose for an adult is 1 gm. per kilogram of body weight. Less than this is a common mistake and accounts for some disappointments with the treatment.
2. Glucose: This should be chemically pure. "Dextrose, U.S.P.X." will insure this.
3. Solvent: This should be freshly, double distilled, uncontaminated water, and not in salt solution or sodium bicarbonate solution as has been variously recommended. Filter five or six times. Many febrile reactions are caused by the bacterial contamination of the distilled water acting as a "pyrogen".
4. Concentration of solution: 25% solution is the generally desirable strength. Some extremely unpleasant consequences have followed in some instances, notably in pneumonia, when the vascular system has been rapidly overloaded by a large volume of weak glucose

solution. It is, we believe, a distinct advantage to use a strongly hypertonic solution because its hypertonicity actually favors a more rapid interchange between the tissues and the blood stream, so that toxins are diluted, edema lessened, and the sugar seized and stored more rapidly by the tissues. A 10% solution is probably the lower limit of safety.

5. Sterilization: The flasks should be stoppered with gauze or cotton plugs and the top sealed with lead-foil. Sterilize for one-half hour at 100 C., on three successive days, or in an autoclave under 15 lbs. pressure for 20 minutes.
6. Age of Solution: It is the opinion that the solution can be used for several days or weeks afterwards without untoward results if prepared in this way.
7. Ampoules: These, prepared by many different drug companies, are useful for small services or emergency work, but are more expensive when used for large hospital services.
8. Technic of administration: This should occupy several minutes, at the rate of 4 cc. per minute, keeping the solution at or slightly above body temperature by means of a hot water bottle about the tube or other simple device.

The same authors published another article the following year with many of the same conclusions. They again stress the harm that may come from too rapid injection of the

solution at too low degrees of temperature. In the majority of hospitals, they say, it is seldom that more than 20 or 30 minutes is consumed in giving any injections, and these are followed invariably by the appearance of quantities of sugar in the urine. It has been reasonably suggested that this may be a serious strain on the "sugar threshold" of the patient's kidneys. The argument of interns and clinicians utilizing such injections in their work to the effect that so time-consuming a procedure becomes unpractical may be a valid one but does not alter the fact that these injections must be given no faster than this definite rate in order to have an accurate dosage without loss through the kidneys. They describe a simple apparates for measuring the rate of flow.

It is very common to hear some physician order the intern to give the patient "some" intravenous dextrose, with no definite instructions. If a drug is to be used, it should be used rationally and scientifically. Titus and Lightbody (1929) reported some of their investigations in an attempt to determine the therapeutic dose of dextrose administered intravenously. They realize that individualization of cases must be done, but as an average they believe that 25% dextrose solutions seem to be best to use. In previous reports they established that 25 gms. of dextrose should be given in a time not less than thirty minutes.

From their work they concluded that the therapeutic intravenous dose of dextrose is 75 grams for an average sized adult. "Less than this will not give the maximum therapeutic

effect, and more than this is likely to produce a reaction from overstimulation of the insulin-producing activity of the patient's pancreas. Graphs of blood-sugar curves during dextrose injections show a beginning fall at about this amount, thus indicating that the maximum safe limit has been reached."

They also believe that single doses of glucose given from one to three times daily are preferable to prolonged injections for the same reason of the possibility of excessive endogenous insulin production. They bring up the possibility of the reactions being due to hypoglycemia, caused by prolonged overdosage with overstimulation of the pancreas. Their conclusions are as follows: "By averaging in one's adult patients such variable factors as body weight, individual differences in pancreatic activity, variations in nourishment, and previous medication, it is possible to make a broad statement as to the average routine administration of dextrose. The most beneficial results seem to follow the intravenous administration to an adult of 75 grams of dextrose in a volume of 300 cc., during a period of 90 to 100 minutes. It is suggested that the amount of dextrose thus administered to a half-grown child should be one half, and to an infant, one quarter of the adult dose but that the same total length of time (90 to 100 minutes) should be consumed for these injections. Other concentrations of solution or lesser amounts may be used according to individual requirements but the above represents safe and adequate average standards of dextrose dosage."

In another article by Titus (1930) he repeats many of the above points. He again emphasizes the point mentioned by Bollman (1925) that alkalies cause a rapid disintegration of glucose when heated, so that they should never be added to the sugar solution before sterilization. He also states that for prolonged venoclysis the solution should not be stronger than 5%, but this injection may even be continued for days if the rate of injection is reduced to one-third the maximum of Woodyatt.

Matas (1924) describes an apparatus for venoclysis, using the drip method so that the number of drops per minute may be counted, much like the Murphy drip for rectal administration.

Truelsen (1924) gives a review of the amounts and strength of solution used up until the time his paper was published. He states that from 100 to 300 calories can be supplied with each dose without having to go through the ordinary digestive processes.

Sprague and Camp (1932) favor the use of 50% glucose in the treatment of cardiac patients. It is one of the arguments against glucose that the hypertonicity of the solution produces an hydremic plethora which by increasing the blood volume may disturb the circulatory balance. However, they used injections of usually 50 to 100 cc. at a time , and did not note pulmonary edema or similar phenomena following the injections of the purified solution in this amount. They report a case of a woman of 68 years, with

hypertension and arteriosclerosis and left bundle branch block who entered the Massachusetts General Hospital with severe attacks of dyspnea occurring every night and requiring morphine. She received nineteen doses of 50% glucose, all but four consisting of 100 cc. each. After the second injection the paroxysms of dyspnea stopped and while under observation she slept without morphine. It is certain in this case that the hypertonic glucose did not produce circulatory embarrassment.

Hunt, McCann, Rowntree, Voegtlin, Eggleston (1927), in a report on the status of intravenous therapy up to that time, largely review the precautions and technic which must be used in any type of injections into the vein. Each of the precautions they urge has been previously mentioned in this paper. These authors are a special committee appointed by the Therapeutic Research Committee of the Council on Pharmacy and Chemistry.

As has been stated in the section on reactions, Robertson, Oliensis and Stein (1927) prefer concentrated solutions, since they obtained lower mortality rates on patients with uremia and severe toxemia when using the stronger solutions.

Palmer, Turner and Gibb (1929) give a list of precautions much like those given by Titus and his co-workers, in the preparation and administration of the solution.

Willems and McNealy (1929) experimented with a drop of glucose of different concentrations together with a drop

of blood mixed on a slide to note the effect on the red blood cells. They found that a 5% aqueous solution of the glucose is the optimum concentration, and that strengths below 3½% or above 6% are harmful to the blood. However, any amount or strength of glucose injected into the blood is rapidly diluted or otherwise made isotonic. Still it must be granted that, however small the quantity of foreign substance entering the circulation as compared to the blood volume itself, there can result some damage to some of the blood cells. However, with the great mass of clinical evidence as to the efficacy of concentrated solutions, these experiments must be overlooked except possibly in cases of grave anemia or emaciation.

Schwentker (1930) describes a simple method of preparing a dextrose solutions. He seals 10 gms. of chemically pure dextrose in hermetically sealed test tubes. These are always ready for use and should be boiled for three successive days. When ready for use he empties the contents of one of these in 200 cc. of freshly distilled water. His experiments on the pH of such solutions indicates that they are all close to pH 7.0 and are safe for use. He has experienced no reactions following the use of such solutions.

For single small injections of 50 cc. or less a syringe may be used, preferably with a 20 gauge needle. For larger amounts a graduated flask with rubber tubing attaching it to the needle, using the gravity method, is the simplest. The rate of injection can be calculated from the graduations

on the flask. Dozens of types of apparatus have been described, and each hospital has the apparatus necessary. The individual user must use the one most convenient to himself.

A few brief conclusions on reactions and technic follow:

1. Febrile reactions following intravenous glucose administration are due to faulty technic in preparation and administration.
2. Concentrated solutions seem desirable, chiefly to save cardiac embarrassment; and are necessary where diuresis or the relief of general or local edema is desired.
3. Weaker solutions should be used when large amounts of fluid are indicated, as in cachexia or after severe hemorrhage.
4. For the preparation of innocuous solutions, refer to the list of rules on p. 30.

COMMENT

The chief objection that must be answered relative to intravenous injections of dextrose, is that the injection of any substance directly into the blood stream is never a harmless procedure. I have heard some of my older teachers say that there are many superfluous intravenous injections being made at the present time. I have seen glucose given into the vein when it could have been taken by mouth, with, in my opinion, as beneficial results. This form of therapy has a large place in modern medicine, but should not be indulged in at random. A thorough knowledge of its physiologic principles and proper administration should put intravenous glucose therapy on a scientific and rational basis.

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