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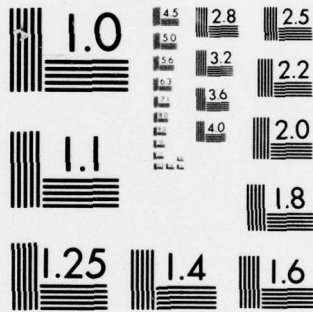
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SOLUBILITY OF INJECTABLE VALIUM IN INTRAVENOUS SOLUTIONS

Marvin F. Grower, D.D.S., Ph.D.

Emery A. Russell, Jr., D.D.S., M.S.D.

Lee Getter, D.D.S., M.S.D.

U. S. Army Institute of Dental Research

Walter Reed Army Medical Center

Washington, D.C. 20012

SUMMARY

A study of the solubility of Valium in commonly used intravenous solutions showed Valium to be equally insoluble in 5% dextrose in normal saline, 5% dextrose in water, normal saline, and Ringer's lactate. However, the precipitate which was formed became completely resuspended when mixed with as little as 39-42% plasma in vitro. This would indicate that the chalky precipitate seen in the I.V. tubing when Valium is injected into a running I.V. near the venipuncture site becomes resuspended when mixed with plasma in vivo. If one elects to inject Valium into the tubing of a running I.V., it is recommended that the drug be administered slowly to assure adequate mixing with blood plasma in order to prevent the circulation of particulate matter.

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Valium is currently one of the most popular drugs used in the psychosedative management of the apprehensive dental patient. Various techniques are advocated for its administration from direct injection into a vein to injection of the drug into a running I.V.<sup>1,2</sup> However, the manufacturer states that the drug should not be added to I.V. fluids or other solutions or drugs.<sup>3</sup> Presumably this is because of the formation of a cloudy precipitate immediately upon addition to aqueous solutions. Grower *et al.*<sup>4</sup> have shown that saturated aqueous solutions of Valium in normal saline redissolve when added to plasma; however, they presented no data on the behavior of solutions of Valium added to other commonly used intravenous fluids. The present study was, therefore, undertaken to study the behavior of Valium when added to lactated Ringer's solution, 5% dextrose solutions, and normal saline; and to see how human blood plasma affects the solubility of Valium in these solutions.

#### MATERIALS AND METHODS

The injectable Valium used (Roche Laboratories) was a straw-colored liquid packaged in 2 ml disposable syringes containing 10 mg of diazepam compounded with 40% propylene glycol, 10% ethyl alcohol; 5% Na benzoate and, benzoic acid as buffers, and 1.5% benzyl alcohol as a preservative. Diazepam itself is a colorless crystalline compound, insoluble in water, with a molecular weight of 284.74. The injectable Valium commercially available shows an intense UV absorption in the region of 220 - 320 nm (nanometers) but does not show any significant absorbance at higher wave lengths in the visible light spectrum.

The intravenous solutions tested in this study were Ringer's injection, lactated, U.S.P. (Travenol Laboratories); sodium chloride injection, U.S.P. (sodium chloride 0.9% in water, Travenol Laboratories); 5% dextrose and 0.9% sodium chloride injection, U.S.P. (Cutter Laboratories); and 5% dextrose in water (Abbott Laboratories).

When the stock solution of injectable Valium was added directly to the intravenous solutions tested, the solutions became cloudy. Since Valium in solution itself does not absorb light in the visible light range, the cloudiness of the solutions was due to the Valium precipitating out of solutions. This behavior allowed the turbidity of the solution to be measured using the technique of nephelometry.<sup>5</sup> The absorbance of the resulting turbid solutions was read in a spectrophotometer at a light wave length of 560 nm. Utilizing this method, the solubilities of Valium in the intravenous solutions tested, plasma,\* and the resuspension of Valium intravenous solution mixtures into plasma were studied.

The solubility of Valium added directly to plasma or intravenous solutions was determined by adding measured volumes of injectable Valium to lactated Ringer's solution, normal saline, 5% dextrose solutions, and plasma; and measuring the turbidity (absorbance) of the solution with a Gilford Model 220 Spectrophotometer equipped with a digital read-out. Since propylene glycol is the major vehicle used in the commercial preparations of injectable Valium, the blank used to standardize the spectrophotometer at each concentration of Valium tested was an equivalent volume of propylene glycol added to the corresponding intravenous

\*Human blood plasma obtained from a blood bank.

solution or plasma. (Propylene glycol when added to the I.V. fluids or plasma tested, does not produce a cloudy solution.)

The solubilizing effect of human blood plasma on saturated solutions of Valium in lactated Ringer's, saline, and 5% dextrose solutions was determined by the addition of measured volumes of plasma to 0.8 ml samples of the saturated Valium-I.V. solutions. The saturated solutions had a Valium concentration of 1 mg of Valium per ml of solution. The blank for this experiment was an equivalent volume of propylene glycol-I.V. solution to which the same plasma volumes were added.

#### RESULTS

Figure 1 shows that the solubility of Valium in I.V. solutions (dotted line in the figure) was the same regardless of which solution was tested. Valium was soluble in the I.V. solutions when added at a concentration of 0.35 mg/ml or less. At 0.45 mg of Valium/ml of fluid, some turbidity of the solution was noted. The addition of 0.04 mg of Valium to this solution, to produce a solution containing 0.49 mg Valium/ml, caused a four-fold increase in absorption; and at a Valium concentration of 0.55 mg/ml a very turbid solution was noted which reached maximum absorbance at 1 mg of Valium/ml of I.V. solution.

Figure 1 also shows that the solubility of Valium added to blood plasma (dashed line) was three times as great as when added to I.V. solutions. Turbidity of the Valium plasma mixture was not noticeable until a concentration of 1.48 mg Valium/ml of plasma was reached (0.42 ml of stock Valium solution added to 1 ml of plasma). In addition,

Figure 1 shows that three times as much Valium in plasma was required to cause an equivalent maximal solution turbidity as that measured when Valium was added directly to aqueous I.V. solutions.

Figure 2 shows the results of an experiment to determine the minimal amount of plasma necessary to cause the undissolved Valium present in saturated I.V. solutions to redissolve.

When as little as 20% plasma (0.2 ml of plasma added to 0.8 ml of saturated Valium I.V. solution) was mixed with a saturated Valium I.V. solution showing maximal absorption as seen in Figure 1 (1 mg Valium/ml of solution), more than 80% of the precipitated Valium went into solution. Complete solubility appeared to be achieved at a plasma concentration of 39-43%. Figure 2 also shows that Valium in lactated Ringer's, saline, and 5% dextrose solutions all showed similar solubility behavior when added to blood plasma.

#### DISCUSSION

It is apparent from this study that although the solubility of injectable Valium in all of the intravenous solutions tested is very low, the solubility of injectable Valium in plasma, or suspension of Valium in I.V. solutions mixed with plasma, is much greater. The limited solubility of injectable Valium when added to I.V. solutions indicates that only small amounts of Valium should be added to an I.V. solution at one time in order to insure that the Valium redissolves when it enters the vein. In addition, the slow injection of the Valium I.V. suspension into the veins will insure that a sufficiently high volume of blood is present (i.e., greater than 40-50%) to insure complete resuspension of the Valium and thus preclude the circulation of

particulate matter.

The similarity in behavior of all of the I.V. solutions tested when mixed with Valium suggests that any of the four solutions could be used as a vehicle to deliver the Valium to the vein. The use of 5% dextrose solutions in small veins has, however, been associated with the production of thrombophlebitis<sup>6</sup> as has I.V. administration of Valium, which would tend to contraindicate their combined use since 5% dextrose does not provide any advantage over normal saline.

In conducting this in vitro study, it was necessary to use plasma rather than whole blood because the absorbance of whole blood is so great that any turbidity due to undissolved Valium could not be detected. The blanks consisted of (1) plasma or I.V. solutions to which was added a volume of propylene glycol equal to the volume of Valium solution used, or (2) propylene glycol I.V. solutions added to plasma when the absorbance of Valium I.V. solutions added to plasma was studied. This procedure was necessary, especially in the case of the addition of Valium to plasma and the addition of Valium I.V. solutions to plasma, because of the dilution of the plasma by the vehicles in which the Valium itself was dissolved. The dilution caused a negative change in absorbance; therefore, it was necessary to use the above blanks for each sample.

The data obtained from the present study indicate that the Valium precipitate formed in I.V. solutions (similar to those produced by the slow injection of Valium into a running I.V. drip) immediately resuspends in plasma in vitro, and hence should exhibit the same behavior in vivo.

However, caution must be observed in the use of this method. Valium

should be added only to the tubing of the I.V. drip close to the venipuncture site at the time of administration and should not be prediluted with the I.V. solutions in the mixing bottle. Valium diluted in the bottle will form a green precipitate on standing if not immediately stabilized by mixing with blood or plasma.

\* \* \* \*

Commercial materials and equipment are identified in this report to specify the investigative procedure. Such identification does not imply recommendation or endorsement, or that the materials and equipment are necessarily the best available for the purpose. Furthermore, the opinions expressed herein are those of the authors and are not to be construed as those of the Army Medical Department.

Requests for Reprints to:

LTC Marvin F. Grower, DC  
Division of Oral Biology  
U. S. Army Institute of Dental Research  
Walter Reed Army Medical Center  
Washington, DC 20012

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Figure 1. Solubility of injectable Valium added to intravenous solutions or plasma.

The solution turbidity measured at an absorbance of 560 nm represents the solubility of the injectable Valium added to the solutions tested. The absorbance versus the Valium concentration is plotted on a three cycle semilogarithmic scale so that the full range of absorbance changes can be conveniently seen. The solubility of Valium added to intravenous solutions are represented by the following symbols: open triangles = 0.9% sodium chloride in water; open diamonds = lactated Ringer's solution; open squares = 5% dextrose solutions. (Both 5% dextrose in 0.9% saline and 5% dextrose in water gave similar results. The open squares represent the average of the two solutions.)

The dotted line connecting the symbols represents the average solubility of the four solutions tested. The open circles connected by the dashed line show the solubility of Valium added to human blood plasma.

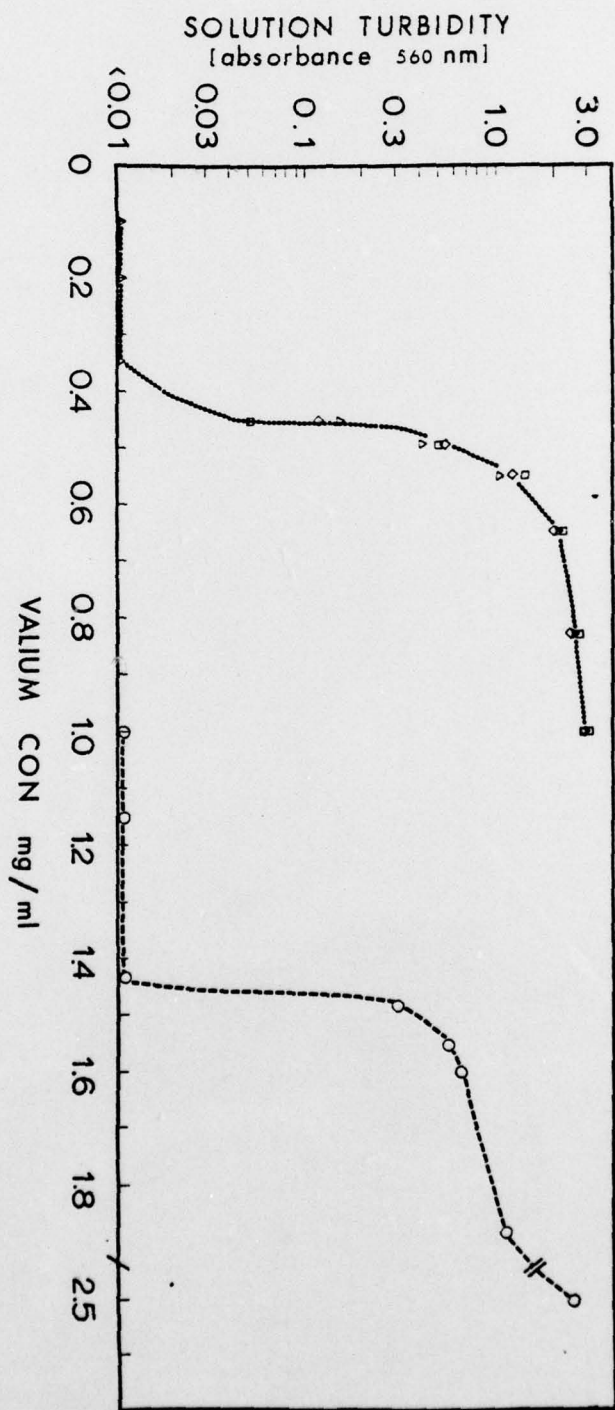


FIGURE 1

Figure 2. Effects of plasma on the solubility of Valium in intravenous solutions.

The saturated solutions of Valium in the intravenous solutions were made by adding 0.16 ml of stock Valium (5 mg/ml) to 0.64 ml of the solutions being tested. This produced saturated solutions with a Valium concentrations of 1 mg/ml. The reference control solutions were made up by adding 0.16 ml of propylene glycol to 0.64 ml of the corresponding I.V. solutions. These solutions were clear, and were used to zero-in the spectrophotometer for measurement of the absorbance (at 560 nm) of the solutions being tested. The absorbance of the control solutions and the I.V. solutions saturated with Valium were then measured after the addition of plasma (0.03 ml to 0.6 ml = 6% to 43% plasma).

The absorbance changes are expressed as the percent of control. (The absorbance of the control solution containing the I.V. solution, propylene glycol, and plasma was divided by the absorbance of the test solution containing the I.V. solution, Valium, and plasma.) The bars filled with black dots show the results for sodium chloride 0.9% (normal saline); the black bars filled with white dots show the results for 5% dextrose solutions, and the bars filled with diagonal lines show the results for lactated Ringer's solution.

