DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 14(11), 1617-1622 (1988)

The Interaction of Dobutamine Hydrochloride and Heparin Sodium in Parenteral Fluids.

J.H. Perrin, Ron Pereira-Rosario and [1]Toshiko Utamura

University of Florida,
College of Pharmacy,
Box J-494 JHMHC,
Gainesville, Florida 32610

SUMMARY

Dobutamine hydrochloride and heparin sodium have been reported to interact in large volume parenteral solutions. The potential for such interactions has been investigated in water, D5W and NS by microcalorimetry. A strong reaction is observed in water and D5W. No reaction is observed in NS and no incompatibility can be expected when the drugs are mixed in NS.

INTRODUCTION

In a previous publication the interaction of heparin sodium and dopamine hydrochloride have been investigated by microcalorimetry. An apparently ion-ion interaction was found. In this report, the potential interaction of the less water soluble catecholamine, dobutamine hydrochloride, with heparin sodium is investigated by flow microcalorimetry in the manner previously reported (1).

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[1]Mukogawa Women's University, 4-16 Edagawa, Nishinomiya, 663, Japan

EXPERIMENTAL

MATERIALS

Dobutamine hydrochloride powder and injection (Dobutrex 12.5 mg ml^{-1}) were obtained from Eli Lilly and Co. Indianapolis IN. Sodium heparin from bovine lung was obtained from Sigma Chemical Co. (St. Louis MO). Injections of heparin sodium were obtained from LyphoMed Melrose Park IL. 0.9 per cent sodium chloride injection U.S.P. and five percent dextrose injection were obtained from Travenol Laboratories Inc. Deerfield IL. All other reagents were of analytical grade. All solutions were used within four hours of preparation. Dobutamine hydrochloride solutions were protected from light by covering the glass vessels containing the solutions with aluminum foil. All drug solutions prepared from powder sources were filtered using a Gelman 0.45 m filter (Gelman Sciences Inc. Ann Arbor, MI.)

METHOD

The heats of reaction were measured in a LKB flow microcalorimeter 2107-121 (L.K.B. Bromma Sweden). The measurements were made at 25°C in the same manner as described from the dopamine hydrochloride - heparin sodium interaction (1).

RESULTS AND DISCUSSION

Unlike the investigations of the dopamine hydrochloride and heparin sodium interaction where preliminary investigations in test tubes never gave a precipitate at reasonable concentrations of the drugs, it was relatively easy to obtain a precipitate with the dobutamine hydrochloride - heparin sodium mixtures in dextrose solutions. For example in D5W precipitation was obvious for a mixture of 50 units ml^{-1} of heparin sodium and 1.5 mg ml^{-1} of dobutamine hydrochloride. Early reports in the literature (2,3) state that the admixture of heparin sodium and dobutamine hydrochloride in both NS and D5W was physically stable for two hours, but more recently (4) precipitation was noticed for a mixture in D5W containing 50 units ml^{-1} of heparin sodium and 1.0 mg ml^{-1} of dobutamine hydrochloride. This precipitation can be expected because of the greater hydrophobicity of the dobutamine cation than of the dopamine cation. All experiments reported here are designed so that

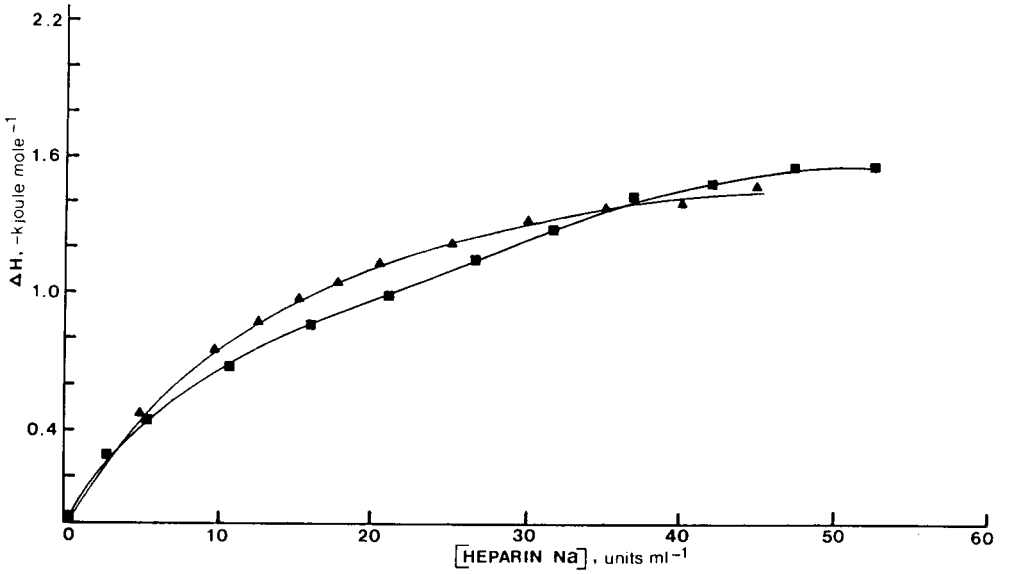

Figure 1 Heat of reaction per mole of dobutamine hydrochloride at 25°C and pH 4.9, as a function of heparin sodium concentration with the dobutamine concentration fixed. Solvent: D5W. Drug sources: (▲) injections, (■) powders.

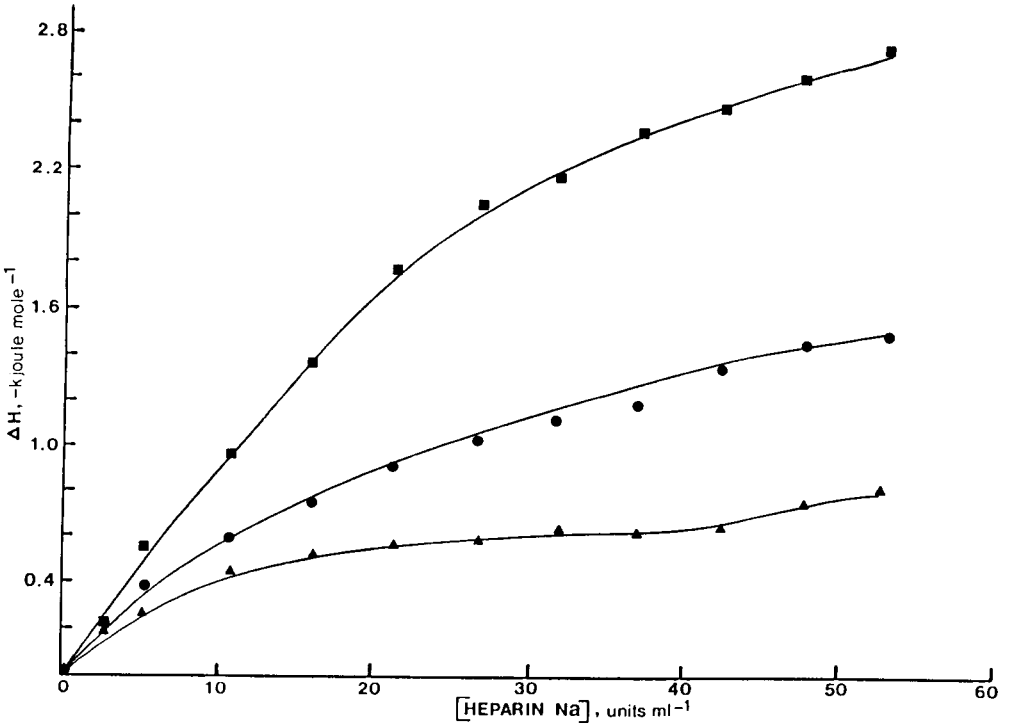

Figure 2 Heat of reaction per mole of dobutamine hydrochloride at 25°C as a function of heparin sodium concentration with the dobutamine concentration fixed. pH: (■) 5.9, (●) 4.9, (▲) 3.9.

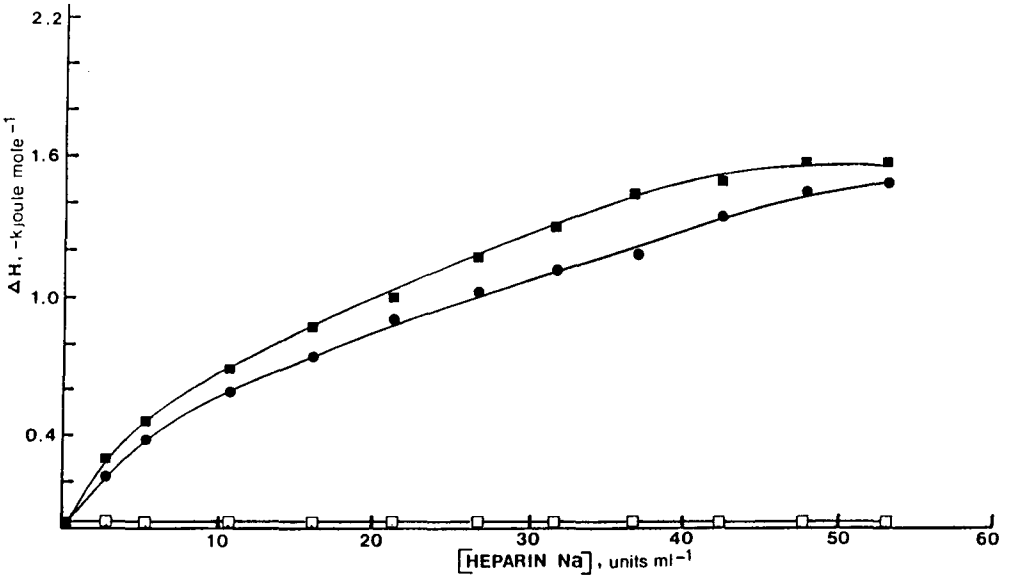

Figure 3 Heat of reaction per mole of dobutamine hydrochloride at 25°C and pH 4.9, as function of heparin sodium concentration with the dobutamine concentration fixed. Solvents: (■) D5W, (●) H_2O, (□) NS.

interaction but no precipitation occurs. Preliminary mixing of commercial injections gave pHs of 4.9, so this pH was chosen for the investigations.

Figure 1 show the heats of interaction per mole of dobutamine hydrochloride as a function of heparin sodium in D5W at pH 4.9, using heparin and dobutamine from commercial injections as well as the powdered heparin and dobutamine, the heparin concentration is expressed in units ml^{-1} since no conversion factor, to mg, was given by the manufacturer. The data clearly shows that the excipients present in both injectables did not have any significant effect on the interaction. The heparin source appears to have little effect on the reaction in D5W at pH 4.9. The plateaus of the curves indicate that all the dobutamine is bound to heparin. The stoichiometry and affinity constants of the reaction cannot be estimated because of the many and varied acidic groups present in the mixture of molecules called heparin. The effect of pHs 3.9, 4.9 and 5.9 on the heparin-dobutamine interaction in water is shown in Figure 2. Significant differences in the heat evolution were observed. The biggest heats being observed at the highest pH. This may

indicate that the carboxyl group of heparin, of pKa 5.7 (5), is involved in the reaction of dobutamine since the pKa of dobutamine is 9.4 (6) and its state of ionization is essentially the same at all the pHs investigated.

Interactions involving the carboxylic group could be ionic or the carboxylic group could be involved in hydrogen bonds with the phenolic groups which occur in both aromatic rings of the dobutamine molecule.

Figure 3 shows the heat evolution to be similar in D5W and water; however, no heat was evolved when the reaction was carried out in normal saline. The large number of sodium ions effectively stopped the dobutamine from binding to the heparin. Other studies were carried out in 0.03, 0.045, 0.06 and 0.075 M sodium chloride solutions, using heparin sodium 50 units ml^{-1}, and dobutamine hydrochloride 0.9 mg ml^{-1} again no heat was observed in the flow microcalorimeter.

CONCLUSION

In all cases where heat was evolved, more heat was evolved than observed for the dopamine hydrochloride-heparin sodium interaction. This is probably indicative of a stronger interaction between dobutamine hydrochloride and heparin sodium; a fact supported by the observations of precipitation reported in the literature. It is important to note that the interactions do not occur in NS because the high concentrations of sodium ions effectively stop the much lower concentration of dobutamine cations from binding to the negative sites on the heparin. NS is therefore the parenteral of choice, from a compatibility point of view, for administering these drugs in an admixture. These observations from solutions calorimetry enable the potential for precipitation under different conditions of concentration and media to be predicted.

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