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Factors Influencing Drug Stability in Intravenous Infusions

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SUMMARY

In order to preserve the activity of drugs given by infusion, many factors must be considered. The infusion fluid must be chosen with care so that the presence of any electrolyte or sugar or the pH of the solution does not provide an unsuitable medium for the added drugs.

Where drugs are inherently unstable small infusion flasks may be used or the drug may be added to the last few hundred millilitres of the infusion. Additional drugs should be added only when no incompatibility occurs. With very unstable drugs, injection into the infusion tubing may be undertaken. Where a chemical incompatibility occurs between two drugs, they should be given in separate infusion bottles.

THE traditional role of the pharmacist in the hospital environment is undergoing rapid change. He has recently taken on clinical responsibility by leaving the pharmacy and in conjunction with physicians and nurses has attempted to bring safer and more effective procedures into practice in the everyday work of drug distribution and medication administration. A short time ago it was acceptable to think that the pharmacist's responsibility ended when a drug was dispensed from the pharmacy. This is no longer true and the pharmacist is often present in the ward to advise on drug administration. Advice is frequently sought on the preparation and administration of intravenous solutions. This is a complex field in which the careful consideration of drug properties and infusion stability is required to ensure that patients receive a drug mixture which will bring about the required therapeutic effect. If care is not taken in compounding infusions a patient may receive an infusion which may not be beneficial and may even be harmful.

There is an important area of investigational work to be covered in the determination of stability of intravenous solutions and the results and conclusions of the survey described here are the first stage in this work.

During a two-month survey, the use of intravenous drugs was observed in 17 departments of the Hadassah University Hospital. In the majority of the departments surveyed, drugs were added to the infusion fluid. A single drug was most frequently added, with occasional mixtures of two to four drugs concurrently administered in one infusion bottle. Five or even six drug combinations were not unknown. This reflects the physician's dilemma in attempting to administer a large number of drugs in an efficient manner when the oral route cannot be used. Some patients suffering from weight loss and emaciation cannot tolerate intramuscular injections and the unnecessary pain of multiple injections each day can be avoided when the intravenous route of administration is employed.

The survey showed that 56 drugs and 8 infusion fluids were commonly given. Among the drugs used there were 13 antibiotics, 11 sympathomimetic and cardiovascular agents, 2 antihistamines, 6 vitamins and 5 hormones.

Only in a few of the world's largest hospitals does the pharmacy department provide an intravenous additive service which prepares and dispenses individual infusion bottles containing the necessary drugs prescribed by the physician. One such unique and comprehensive intravenous solution service is provided by the Ohio State University Hospitals, and intravenous infusions containing added drugs are prepared under direct pharmaceutical supervision and are available on demand day and night.[1]

Whether the pharmacy provides such a service or not, pharmacists should have knowledge of the stability factors involved when a drug is added to an infusion fluid. They can then advise the nursing staff how the infusion can be prepared and safely given to the patient without decomposition and loss of activity, or the formation of toxic products.

The factors influencing drug stability in intravenous infusion include:

Time of preparation: The interval between the preparation and the administration of the infusion should be minimal. In the event of contamination this does not allow excessive multiplication of bacteria, reduces drug decomposition and, perhaps even more important, the possibility that the wrong patient may receive the infusion due to a change in nursing shift. This interval should never be longer than one hour. Infusions of drugs not used soon after preparation should be rejected. They must not be refrigerated and used at a later stage.

Duration of infusion: The survey showed that the duration of infusion was commonly from ½ hour to 12 hours, and occasionally 24 hours. Bacterial contamination would be more likely in infusions administered over long periods and many drugs decompose within a few hours. It is suggested that infusion time should not exceed 12 hours per flask and preferably 8 hours per flask.

pH of the solution: Many drugs decompose rapidly when added to a solution of unsuitable *p*H. (See table 1) Dextrose infusions are the common cause of stability problems since they are almost always acid in reaction. The lower pharmacopoeial limit is *p*H 3.5. In solutions of very low *p*H, methicillin sodium may be decomposed and free methicillin acid precipitated in the infusion flask. With other drugs, e.g. ampicillin, heparin, etc., no precipitate may be formed, but much of the drugs' activity is rapidly lost.

Electrolytes: The presence of electrolytes in the infusion, especially in high concentration, may cause drug decomposition or precipitation. (See table 2)

Sugars and polysaccharides: The presence of apparently innocuous sugars may cause instability. Sulphadiazine sodium injection has a *p*H of about 10.5. When this is added to dextrose solutions of *p*H 4.4, the *p*H of the solution is raised to 8.5 and a deep yellow colour develops over some hours.

Physical state of the infusion: Not all infusions are simple solutions. Blood is a coarse suspension, mannitol in the high concentration usually employed for forced diuresis is a supersaturated solution and emulsions of fats are also used, e.g. Intralipid.® In some cases room temperature can influence solubility. Infusion fluids may have to be warmed to 37°C to ensure that the solids are completely dissolved and that the solution is homogenous, e.g. 25% mannitol. Supersaturated solutions can be readily crystallised out and it is recommended that no additions be made to mannitol, inulin, etc., in these concentrations. Fat emulsions may be "cracked" and separation of the phases or enlargement of the globule size may occur if drugs are added

Table 1

DRUG STABILITY IN SOLUTION ACCORDING TO *p*H

Drug	*Stability characteristics*
Aminophylline	Unstable in neutral or acid solution.
Ampicillin sodium	Loses 10% activity in 4 hours in dextrose or dextrose-saline. Preferable to administer in saline or Ringers solution.
Amylobarbitone sodium	Should not be added to solutions with a *p*H below 8.0. May be given in saline.
Benzylpenicillin sodium	Unstable in highly acid solutions.
Carbenicillin sodium	Unstable in alkaline solutions. Given in saline, dextrose or dextrose-saline during 6 hours or less.
Heparin	Rapidly inactivated in solutions with a *p*H below 6.0 Should not be infused in dextrose or dextrose-saline over a long period.
Methicillin sodium	Acid solutions may cause cloudiness or precipitation. Check dextrose solutions frequently for clarity during infusion. Administer during 6-8 hours.
Novobiocin sodium	Must not be added to dextrose infusions. Administer in saline or Ringers solution.
Sulphadiazine sodium	Incompatible with laevulose and very acid dextrose infusions may cause precipitation. May be administered in normal saline.

***p*H of common infusion fluids (B.P.* or U.S.P.** limits)**

Ammonium chloride	4.0 - 6.0**
Dextran 40 in 5% dextrose (Rheomacrodex in dextrose)	3.5 - 6.5*
Dextran 40 in Normal saline (Rheomacrodex in saline)	4.0 - 7.0*
Dextrose 5%	3.5 - 6.5*
Hartmann's solution	5.0 - 7.0*
	6.0 - 7.5**
Mannitol 10%	4.5 - 7.0*
Protein hydrolysate	5.0 - 7.0**
Sodium chloride	4.5 - 7.0**
Sodium chloride 0.18% with Dextrose 4.3%	3.5 - 6.5*
Sodium lactate 1/6 molar	5.0 - 7.0*

indiscriminately. The makers recommend that apart from the cautious addition of heparin no other drug be added to infusion bottles of fat emulsions. These emulsions may however be given concurrently with saline or dextrose solutions provided that they are administered through a Y—tube placed just before the needle.

Drug reaction with containers, closures or the infusion set: A few drugs may be absorbed by rubber stoppers, e.g. those containing phenolic groupings, and glass itself has been reported to adsorb insulin from solution.[2] Mercaptomerin must be injected through rustless needles and must not come into contact with aluminium fittings.[3] The use of non-neutral glass containers, or surface-treated glass containers in which the film has become worn or scratched, may liberate alkali into

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