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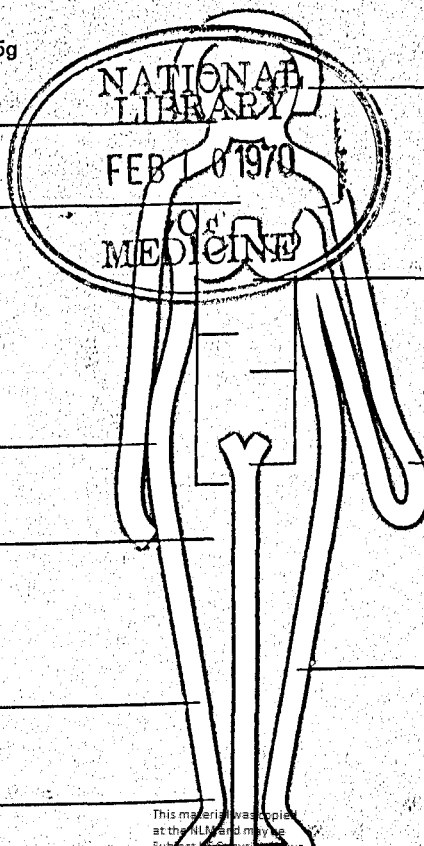
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Factors Influencing Drug Stability in Intravenous Infusions

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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.

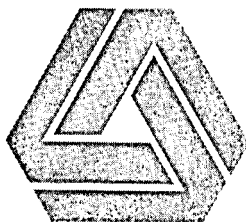
There is an important area of investigational work to be covered in the determination of stability of intravenous solutions

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.

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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 $\frac{1}{2}$ 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 pH. (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 pH 3.5. In solutions of very low pH, 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 pH of about 10.5. When this is added to dextrose solutions of pH 4.4, the pH 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 pH

<i>Drug</i>	<i>Stability characteristics</i>
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 pH 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 pH 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.

pH 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

Table 2

EFFECT OF ELECTROLYTES ON DRUG STABILITY

<i>Drug</i>	<i>Electrolyte</i>	<i>Result</i>
Amphotericin-B	Sodium chloride	Colloidal suspension broken, and coarse precipitate produced
Mannitol 20% (or higher concentrations)	Potassium chloride or sodium chloride	Crystallisation of mannitol due to "salting out" process
Sodium bicarbonate	Calcium ions	Insoluble calcium salt precipitated
Tetracycline or oxytetracycline	Calcium (in neutral or alkaline solution) in alkaline Ringers or Ringer-Lactate solution	Insoluble calcium complex precipitated

the solution. Citrates and phosphates readily produce glass spicules in these bottles and the problem of preparing and storing sodium bicarbonate solutions in has been suspected of dissolving small quantities of electrolytes from solution.

Reaction with oxygen or carbon dioxide:

The bubbling of air through an infusion over a long period may cause a reaction with carbon dioxide or oxygen. Phenytoin sodium reacts with carbon dioxide liberating the free base and producing a cloudy solution, and ascorbic acid, sodium *p*-amino hippurate and riboflavine are glass bottles without the deposition of a fine white precipitate is still largely unsolved. Doubts have also been raised about the inertness of plastic containers which may liberate plasticiser into solutions stored in them and polypropylene sensitive to oxidation. Such solutions must be checked during the infusion for clarity and possible colour change.

Light sensitivity: A few drugs are unstable to light and infusion bottles should not be exposed for prolonged periods to direct sunlight or strong artificial light. (See table 3) It is recommended that bottles of amphotericin—B infusion be covered with black paper to prevent decomposition during administration.

Microbiological contamination: Growth of micro-organisms within the infusion fluid may occur, particularly in warm climates and where the infusion is continued for a long period. This may produce either a febrile pyrogen reaction or infection. It may be preferable to use two half-litre flasks in place of a single litre bottle.

Care should be exercised when adding drugs to the infusion bottle. Although completely aseptic conditions are unlikely to be attainable in the normal ward atmosphere, nursing personnel preparing infusions must wash their hands, work with a no-touch technique, preferably use a mask, and swab all rubber caps, etc., with disinfectant before puncturing them with a needle.

Table 3

DRUGS SENSITIVE TO LIGHT

Amphotericin-B
Nitrofurantoin-Sodium
Sulphadiazine sodium
Riboflavine
Tetracyclines
Oestrogenic substances
(Premarin ®)

Contamination is a special risk with blood and deaths have been reported when faulty technique has resulted in gross contamination of these infusions. It seems advisable that no drugs whatsoever be added to blood prior to transfusion. Antihistamines and steroids are best administered separately to the patient and not added to the transfusion as is common practice in many hospitals.

Dissociation constants of the drug: If the time taken for a certain percentage of a drug to react or break down under certain conditions is known, estimates can be made of the optimal and maximum time during which infusion can take place. Carlin and Perkins⁴ have published the T_{10} per cent values for several penicillins using the reaction data from chemical stability studies. The T_{10} per cent represents the time it takes for ten per cent of the drug to react, and has been taken as a reasonable standard for the time to measure the 10 per cent loss in drug potency which is acceptable during an infusion. At pH 5.0 the T_{10} per cent of potassium penicillin-G is about 12 hours at 25°C. If ascorbic acid and vitamin B complex are added to a 5% dextrose solution of the antibiotic and this infusion has a pH of 3.65, the resulting T_{10} per cent is only 1.2 hours. The importance of these values is obvious since in the latter case the concentration of the penicillin in the vitamins—dextrose infusion during the last hour of an 8-hour infusion period would be about half that of the initial concentration, and after 12 hours only about one third of the original percentage would be left in the solution.

Drug additives: The addition of a second, third or any additional drug to an infusion may seriously reduce the stability of the mixture and sometimes results in gross incompatibility. A great many charts reporting such drug incompatibilities have been published^{5, 6, 7, 8, 9, 10}, and even a computerised compatibility-incompatibility

print-out of mixtures of two drugs has been described.¹¹

Many of these schemes utilise information obtained from other charts since little basic data of the actual mechanism of drug instability and interaction has been published. Obvious visible incompatibilities have been noted where evolution of gas, change of colour or pH or precipitation occur, but many decomposition mechanisms result in no such obvious phenomena. The mixture is then reported as 'not incompatible' or 'not known', neither of which statement helps either the compounder or the patient. These charts may be useful but suspect. More charts documenting substantiated drug compatibilities are urgently needed.

Manufacturers' Information: It should be axiomatic that every drug firm should be able to provide full information on its own products, yet when letters were despatched to 26 international and local firms asking for details on the stability of their products under varying conditions, only four manufacturers were able to provide comprehensive replies and of these only two producers gave actual percentage assay figures. Some firms did not reply. Some replies were ambiguous or unhelpful. One firm stated that their product, a corticosteroid, should not be mixed with other drugs in the infusion flask, and that the pH of the infusion should be greater than 7.4, despite the fact that almost every common infusion fluid has a pH below 7.0. Another firm stated that to determine the stability of their anticoagulant would be a matter of trial and error, and that they could be of no further service!

Previous surveys of commercial drug literature^{12, 13} have shown deficiencies in the information published in manufacturers' standard reference booklets and package leaflets. It is obvious that a very unsatisfactory situation exists if data are not available in reference books, have not been the subject of pharmaceutical

research, and cannot be supplied by the manufacturers of the drug itself.

As almost every large hospital routinely uses I. V. infusions containing added drugs, it would seem essential that this neglected field of drug research should be explored with vigour and in depth.

Successful therapy is dependent upon a consideration of the causes of drug instability and the correct application of knowledge to preserve the full activity of the drug and the vehicle during the period of the infusion.

Acknowledgement

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Patients and their Hospitals

KING Edward's Hospital Fund for London has recently published a report on a survey intended to discover to what extent the customers (i.e. hospital patients) were satisfied with their experiences in hospital. Questionnaires were distributed to be answered in some cases just prior to leaving hospital in others at home immediately afterwards. A response rate of 62% was achieved. No attempt was made to evaluate medical treatment. The questions related to the experiences of patients with regard to the ward and its equipment, sanitary accommodation and facilities, meals, activities, care of patients and overall contentment.

The answers reflected grateful satisfaction in nearly all aspects but some criticisms stood out painfully—inadequate sanitary facilities, early waking, lack of information and so on. The overall picture pointed to the fact that patient satisfaction depends primarily on human or organisational factors rather than physical factors.

Many complaints could be cured by imaginative organisation and good management. At a press conference held to launch the report it was stated that there appeared to be a close correlation between staff contentment and patient contentment and the report will surely underline to hospital authorities the need for enlightened policies in the field of staff recruitment and training. The report gives no support to those who would restrict the numbers of "visitors" to patients on wards (such as the various technicians and the ward pharmacist) since 111 out of 131 patients commenting on one question complained of boredom! I wonder if those who have visited the wards in this capacity would support the contention that most patients welcome a friendly word with the ward pharmacist as he or she examines the prescription at the foot of the bed.

(*Patients and their Hospitals*—A King's Fund Report. 12/6d. King Edward's Hospital Fund for London.)