Chemical Incompatibility of Parenteral Drug Admixtures

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SUMMARY

Incompatibilty of parenteral drug admixtures is a subject with such wide ramifications that the problem of correlating all the factors will in future probably only be controlled by computer techniques. In the meantime, a knowledge of pH factors and a sound reference library, together with a pre-planned use of drug combinations wherever possible, will do much to alleviate the problem.

Useful reference articles and facets of pH are discussed. Consideration should be given to avoiding admixtures of undocumented drugs in infusion fluids, and use should be made of a single drug injection at a separate locus.

From the USA it is reported that an average of 18 - 20% of hospitalised patients suffer from adverse drug reactions, and a patient admitted with a minor injury like a broken leg stands a reasonable chance of dying from drug combinations administered to him. Predicting what will occur when several drugs are mixed is no easy matter, as can be seen from the following statistics of the number of unique combinations caused by mixing numbers of drugs.

Thus 20 drugs mixed 2 at a time, give 190 combinations;

20 drugs mixed 3 at a time, give 1 140 combinations;

24 drugs mixed 2, 3 and 4 at a time, give 11 000 combinations;

400 drugs mixed 5 at a time, give 84 million combinations.

Jacobs[1] interviewed 17 hospital departments and found that 56 drugs and 8 infusion solutions were in routine intravenous use. Patterson and Nordstrom[2] estimated that 86% of all infusions administered contained one or more additives.

Recently I lectured an anaesthetics department on some of the problems involved in chemical incompatibility occurring when injectables are mixed, and these problems are presented, not to discuss pharmacological or clinical incompatibility, but rather to assist housemen, anaesthetists and nursing staff with the difficulties of administering safe parenteral admixtures.

WHAT CONSTITUTES A SAFE ADMIXTURE?

A safe admixture is one that is free from micro-organisms, free from particulate matter, undecomposed and clinically

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compatible. One method of eliminating both microbial and particulate matter is to insert a Millipore filter between the needle and infusion bottle, but this practice is not common in South Africa. Particulate matter can cause granulomata (particularly pulmonary) and particles can cause a pyrogenic reaction—conceivably due to leucocytic damage with release of endogenous pyrogen.

Just how many particles constitute a haze would be difficult to define, but it may well be thousands, or even millions, of small particles per millilitre when one considers that the bacterial count comparator tubes equivalent to 750 million bacterial cells (1 - 2 μm in size) per millilitre are only a 'heavy haze'. Vacolitres containing 30 million glass particles per litre have been found on the market, and modern requirements demand not more than 10 000 (5 μm) particles per litre.

Particularly dangerous are those drugs which precipitate only slowly (e.g. Gantrisin 4 g in 5% aminosol, 1 - 6 hours, or diphenylhydantoin sodium in Ringer's with 5% dextrose, 6 - 24 hours). Tables concerning compatibilities of drugs used parenterally are freely available in chart form from both Abbott and Baxter Laboratories. The former lists 35 commonly used injectables and their reactions with the 59 available Abbott's infusion products, also indicating incompatibility, and where 'haze' occurs, the time when this may occur. Baxter's chart lists some 40 drugs in pairs in various infusions; thus aminophylline is incompatible with some 16 listed drugs in normal saline, with 18 in 5% dextrose solution, and with 24 in 3% sodium chloride solution. One cannot easily remember all these incompatibilities, but the charts should be available for ready consultation when intravenous therapy is being used.

In addition to these charts a number of papers have been published on such incompatibilities. Riley[3] has painstakingly taken 67 commonly used drugs and mixed each in turn with the other 66, using normal saline and also 5% dextrose (pH 4,3) as the vehicles. The phenothiazine family was one of the most active, and reacted with sodium and potassium salts of antibiotics and sodium salts of sulphonamides. Heparin formed immediate precipitates with a number of antibiotics, particularly those used in the treatment of tuberculosis. Sulphadiazine gave a visible reaction with a quarter of the substances under test, including retarded formation of a precipitate, which might not be noticed after some hours, particularly if it is in a plastic container. Antibiotics often interact owing to pH changes, possibly the largest single cause of incompatibility and potency loss in injectables. When the sodium salt of a weak acid such as penicillin is mixed with either an acid solution such as dextrose, or the hydrochloride of a tetracycline, stability loss or precipitation can occur.

INTRAVENOUS ADDITIVES

An excellent review of intravenous additives is that of Grayson,[4] which runs to 7 pages and obviously cannot be reproduced in full here. A few examples have been chosen to show the reactivity of certain drugs, and these appear in Table I.

TABLE I. DRUG INTERACTIONS IN INTRAVENOUS INFUSION FLUIDS (AFTER GRAYSON[4])

First drug	Incompatible with
Adrenaline (pH 3)	Alkaline solutions, ascorbic acid, cardiac glycosides, chlorpromazine, Darrow's solution, heavy metal salts, hyaluronidase, magnesium salts, mephentermine, novobiocin, pheniramine, sodium chloride solution, tetracycline, Warfarin in 5% dextrose.
Aminophylline (pH 7-9,5)	Anileridine, ascorbic acid, barbiturates, calcium and magnesium salts, chlorpromazine, codeine phosphate, dimenhydrinate, hydralazine, hydroxyzine, levorphanol, methadone, morphine sulphate, oxytetracycline, papaverine, pethidine, phenytoin, procaine HCl, prochlorperazine, promazine HCl, promethazine HCl, strongly acid solutions, vancomycin, vitamin B compounds and preparations.
Levallorphen (Lorfan) (pH 4,3)	Methicillin sodium, morphine derivatives, phenytoin, sulphafurazole.
Noradrenaline (Levophed) (pH 3-4,5)	Alkalis and oxidising agents, barbiturates, chlorpheniramine, chlorothiazide, nitrofurantoin, novobiocin, phenytoin, sodium bicarbonate, sodium iodide, streptomycin, sulphadiazine, sulphafurazole.
Oxytocin (Syntocinon, Pitocin) (pH 3-4)	Fibrinolysin, Warfarin sodium.

Other highly reactive drugs are antibiotics, phenothiazine derivatives, ascorbic acid, morphine derivatives, hydrocortisone, sodium succinate, heparin, dimenhydrinate and barbiturates.

DRUGS TO BE USED IMMEDIATELY AFTER RECONSTITUTION

Jacobs[1] also lists several drugs, particularly the antibiotics, with notes regarding their stability. A far more comprehensive document is that of Latiolais et al.,[5] which covers hundreds of drugs, their stability, recommended diluent, etc. They instituted a drug reconstitution service in the Ohio State Hospital where all parenteral drugs are reconstituted aseptically (using laminar screens) in the hospital pharmacy. This removes the tremendous onus of responsibility for error from the nursing staff, who, unlike the pharmacist, have not had the benefit of 4 years of chemistry, not that a knowledge of chemistry can anticipate all the reactions that may occur when one or more drugs are mixed. Thus a list of drugs which must be used immediately after reconstitution has been summarised as follows: [5]Amytal sodium, antivenin (Crotalidal) polyvalent vial, Ascorbin B (3 hours), Aureomycin intravenous, Betolake with C (3 hours), Cathomycin lyovac vial, Cosmegen lyovac, coumadin, Cytoxan (3 hours), Dilantin (few hours), Dornavac, dried human fibrinogen, fibro-AHF, Folbesyn, Furadantin sodium, Librium, Luminal sodium, Manibec-C, Miochol intra-ocular, Mustagen HCl, novocain, Novogran, Orinase diagnostic (1 hour), Parenogen (1 hour), Parlite vitamins B with C, Penbritin-S (1 hour), phenobarbital sodium ($\frac{1}{2}$ hour), Polycillin-N (1 hour), pontocaine HCl niphanoid, Regitine methanesulphonate, Solu-B with ascorbic acid, Solu-zyme with ascorbic acid, Tham-E (few hours), thrombolysin (2 hours), Urevert, Vicert C, Viron No. 1.

To these may be added the following from Jacobs[1] — ampicillin sodium, Ampiclox neonatal, Crystapen, crystamycin, Pyopen, Orbenin and Hyalase Celbenin.

INTERACTIONS BETWEEN INFUSION FLUIDS AND DRUGS

Generalisations that can be made on such interactions include:

Direct interaction: Tetracycline interacting with calcium salts to form the insoluble salt which precipitates;

Salting out by electrolytes: Amphotericin B, being colloidal, is salted out by electrolytes and furthermore is sensitive to light, losing activity with time of infusion;

Polymerisation: Cephaloridine tends to polymerise at acid pH and these polymers have been implicated in the development of hypersensitivity;

Conjugation: Some drugs, e.g. the penicillins, can conjugate with the proteins of infusion fluids to form potential allergens;

pH: Decomposition may occur if a salt of a weak acid is added to an acidic infusion (e.g. dextrose) or the hydrochloride of a weak base is added to an alkaline fluid (sodium bicarbonate infusion). Epinephrine loses 60% of its activity immediately on addition to a 5% sodium bicarbonate solution.[6]

The importance of pH is so great that it warrants further attention. Both pH and concentration are related by the well-known Henderson equation.

$$\text{Thus pH} = pKa + \log \frac{[\text{Salt}]}{[\text{acid}]}$$

Let us consider sodium sulphadiazine 10% solution as an example. Reference to tables gives the dissociation of sulphadiazine (pKa) as 6,3. The solubility of sulphadiazine is only 1 - 1 300 of water, but sodium sulphadiazine is soluble 1 - 2 of water.

Thus at pH 7,3

$$(7,3)\ pH = pKa\ (6,3) + \log \frac{[100]\ (Salt,\ Sod.\ sulphadiazine)}{[\ 10]\ (Acid,\ sulphadiazine)}$$

while at pH 8,3

$$(8,3)\ pH = 6,3 + \log \frac{[100]}{[\ 1\ ]}$$

and at pH 9,3 $pH = 6,3 + \log \dfrac{[100]}{[0,1]}$

At pH 7,3 there are 10 g/litre of acid present and since the solubility of the free acid (sulphadiazine) is only 1 - 1 300, some remains undissolved. At pH 8,3 only 1 g remains, and will probably just dissolve, and certainly at a more alkaline pH. It should thus be obvious that if sodium sulphadiazine solution 10% is added to a solution which brings its pH below 8,3 it will precipitate. We see similarly that pheno-barbital has a solubility of only 0,11% between pH 2 - 6, but is soluble 0,41% at pH 8 and 2,9% at pH 10.

However, if we mix two simple unbuffered solutions in equal volumes, the result is not a simple arithmetic mean of the two pH values. Thus mixing equal volumes of un-buffered solutions of pH 4 and 8 produces a pH of 4,3. Similarly mixing pH 3 and 6 produces 3,3, while pH 8 and 10 produces 9,7. Unfortunately, to complicate matters, in-jectables, other than infusion fluids, are seldom simple solutions and can contain preservatives, buffers, stabilisers, chelating agents like EDTA, and other adjuvants. Unless these are listed on the injection label one has little hope of anticipating what will occur on admixture, which in itself is a strong case against making a potentially harmful chemical soup in the infusion bottle.

Where possible, a separate locus of injection should be used. This may inconvenience the patient, but better a temporarily inconvenienced patient than a permanently dead one. As Baker[7] pointed out, it is only in certain cases that continuous intravenous infusion is required to main-tain a constant drug level (heparin, lignocaine, potassium chloride). Where a drip is running, direct intravenous in-jection via the tubing is preferable for many antibiotics or vitamins, although concentrated penicillin solutions, being alkaline, can cause vein damage. However, should imme-diate precipitation occur, there could be dangerous con-sequences to the patient, hence the preference for an en-tirely separate injection site.

CONCLUSION

It is apparent that with the multiplicity of drugs available only computer techniques will enable a rapid information retrieval to predict compatibility and stability. Where a set pattern of drugs is used, then a good reference library becomes imperative, a good basis for which would be the references mentioned here. It is felt that the pharmacist's knowledge could be better used in this connection, parti-cularly that of the new trainee pharmacist who wishes to become more clinically orientated, and who has 4 years of chemistry, 3 years of pharmaceutics and 2 years of pharmacology in his curriculum. If invited to ward rounds, a suitable *quid pro quo* could surely be arranged?

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