

DGAFMS MEDICAL MEMORANDUM No-113

CARE IN MIXING DRUGS WITH INTRAVENOUS INFUSIONS

1. Drugs are frequently administered as additives to intravenous infusions. In many instances drugs are added to running infusions just as a matter of convenience without due regard to stability and therapeutic integrity. When drugs are added to infusion solutions a number of unwanted changes may occur e.g. an interaction between the drugs and infusion fluids, interaction between drugs itself, pH incompatibility, exposure to light etc. It is therefore essential to add drugs to infusions only if it is essential and with due regard to stability and therapeutic integrity of such combinations.

INDICATIONS FOR DRUG ADDITIVES TO IV INFUSIONS

2. Drugs should be added to infusion containers only under the following circumstances:-
- a) When constant drug concentrations in plasma are required.
 - b) When administration of a more concentrated solutions would be harmful.
 - c) When both oral and intra-muscular administration of drug are not feasible due to certain situations i.e. vomiting or unconsciousness in a patient on intensive anti-coagulant therapy.
 - a) When the number of veins available for drug administration are limited.

GENERAL GUIDELINES

3. Only one drug should be added to any infusion container and the components should be compatible. Details of compatibility are given in Appx. 'B'.
4. Drugs should not normally be added to blood products, mannitol, sodium bicarbonate, fat emulsions or amino-acid solutions. In general, isotonic saline is a suitable vehicle for most drugs except nor-adrenaline and some formulations of amphotericin B.
5. Before addition of drugs, the infusion fluid should be shaken and visually inspected for any particulate matter or haziness. If any of the latter are present, the fluid should be discarded. Likewise, after drug addition, the solution should be thoroughly mixed by shaking and checked for absence of particulate matter. Addition should not be made to an infusion container that has been connected to a giving set as mixing is hampered. If the solutions are not thoroughly mixed a concentrated layer of additive may form owing to differences in density. Potassium chloride is particularly prone to this 'layering effect' and such a non-uniform mixture may have serious cardiac effects.
6. Strict asepsis should be maintained throughout and in general a giving set should not be used for more than 24 hrs.

7. The infusion container should be labelled with the patient's name, the name and quantity of additives and the date and time of addition. This labelling should not interfere with the manufacturer label.
8. The infusion should be examined periodically while running. If any cloudiness, crystallisation, colour change or any other sign of interaction or contamination is observed the infusion should be discontinued.
9. Bactericides such as chlorocresol or phenyl mercuric nitrate are present in some injection solutions. The total volume of such solutions added to an infusion container should not exceed 15 ml.
10. Certain infusions must be protected from light to minimise oxidation, e.g. Amphotericin B, dacarbazine and Sodium nitroprusside.
11. Wherever available, the manufacturers' instructions regarding product reconstitution, vehicle, mixing and handling precautions should be strictly followed. Once reconstituted, addition to the infusion fluid should be made immediately to minimize microbial contamination or to prevent degradation, e.g. ampicillin injection degrades rapidly on standing and also may form polymers which can cause sensitivity reactions.
12. Ready prepared infusions should be used whenever available.
13. Addition via drip tubing is indicated for those drugs where extravasation is to be avoided e.g. several cytotoxic drugs. In these cases the preparation should be added aseptically via the rubber septum of a fast running infusion. In case a drug is intended for a bolus effect it should preferably be given directly into a separate vein.
14. The pH requirements, if any, should be kept in mind in case of certain drugs e.g. ampicillin and benzyl penicillin are unstable in the acidic pH of 5% dextrose.
15. Drugs may be administered by continuous infusion in a large volume of fluid or by intermittent infusion in a relatively small volume over a short period, e.g. 100 ml over 30 mins. The decision regarding this choice must be made separately for each drug and the drug infused accordingly, as this may have significant pharmacokinetic implications. For example, drugs such as dacarbazine, gentamicin and ticarcillin may not achieve adequate plasma concentrations by continuous infusion and hence should be administered by intermittent infusion. Penicillins and cephalosporins should not be given as continuous infusions due to problems of stability. Specific infusion guidelines are outlined in Appx 'C'.
16. Dilution with an appropriate vehicle and administration using a motorised infusion pump is advocated for preparations where a strict control over flow rate is required such as Oxytocin and Glyceryl trinitrate.

MAINTENANCE OF STERILITY

17. The accidental entry and subsequent growth of micro-organisms converts the infusion fluid into a potential vehicle for infection. This risk is increased if prepared solutions are stored before infusion, and is decreased if ready prepared infusions are used. Dextrose, blood

and electrolyte solutions are particularly prone to bacterial contamination. Hence it is essential to maintain strict asepsis while adding drugs to infusion fluids.

COMMON INCOMPATIBILITIES

18. Physical and chemical incompatibilities may occur with loss of potency, increase in toxicity or other adverse affects. This may occur as a result of pH, concentration changes and complexation or other chemical changes. The potential for incompatibilities is increased when more than one substance is added to the infusion fluids.

19. Avoiding precipitation is particularly important in case of drugs which have been implicated in thrombophlebitis (e.g. diazepam) or skin necrosis caused by extravasation (e.g. sodium bicarbonate) . The same applies to colloidal drugs whose precipitation may lead to a pyrogenic reaction e.g. colloidal amphotericin B.

20. In case blood or blood products have been administered earlier, the infusion set should be changed prior to further infusion.

21. Intravenous fat emulsions may break down if antibiotics or electrolytes are added, leading to the possibility of embolism.

22. Some drugs may exhibit clinically significant adsorption to plastic materials particularly polyvinyl chloride (PVC). In such cases, it is preferable to avoid plastic infusion containers, syringes and filters. Examples of such drugs include diazepam, glyceryl trinitrate, insulin, lignocaine, thiopentone sodium, chlorpromazine and promethazine.

23. Infusions which frequently give rise to incompatibility with a number of drugs include amino acids, mannitol and sodium bicarbonate.

Appendix 'A'

INFUSION FLUID CHARACTERISTICS AND COMMON INCOMPATIBILITIES

<u>Infusion Fluids</u>	<u>Characteristics</u>	<u>Incompatible with</u>
1. Dextrose	Acidic (pH may be as low as 3.5)	Benzyl Penicillin, aminophylline Barbiturates, Ampicillin, Vit B-12, Hydrocortisone, Heparin

2. Isotonic Saline	Neutral or slightly acidic. Suitable vehicle for most drugs.	Noradrenaline, Amphotericin B, Amiodarone.
3. Electrolytes (Na,K, Ca,Mg, Cl, Lactate.)	Slightly acidic or neutral	Ringer lactate incompatible with Amphotericin B, Tetracycline Succinyl Choline.
4. Dextrans	Consist of glucose polymers (dextrans) Slightly acidic pH.	Aminocaproic acid, ampicillin, ascorbic acid, chlorpromazine, barbiturates, promethazine, streptokinase.
5. Amino acids		DO NOT ADD ANY DRUG.
6. Fat emulsions		DO NOT ADD ANY DRUG.
7. Blood and blood products		DO NOT ADD ANY DRUG.
8. Mannitol	Hexahydric Alcohol	Add no drug or electrolyte to 20% solution. Not to be added to any strength : Barbiturates, Noradrenaline, Succinyl Choline, Tetracycline. Should never be given with blood or through an infusion set which has been used for transfusion.

Appendix 'B'

INCOMPATIBLE DRUG MIXTURES (in alphabetical order)

<u>Drug</u>	<u>Incompatible with</u>
1. Aminophylline	Adrenaline, Chlorpromazine, Phenobarbitone, Prochlorperazine, Pencillin G, Norepinephrine, Clindamycin, Dexamethasone, Dobutamine, Hydrocortisone, Opioid analgesics, Phenytoin, Promethazine, Vancomycin, Erythromycin, Vitamin C & B, & any strong acidic solution.
2. Amphotericin B	ALL ELECTROLYTES AND DRUGS (danger of precipitation)

3.	Ampicillin	Adrenaline, Atropine, Calcium, Chloramphenicol, Chlorpromazine, Dopamine, Aminoglycosides, Hydrocortisone, Oxytetracycline, Phenebarbitone, Succinyl choline, Thiopentone, Vitamin-B and C.
4.	Ascorbic Acid	Aminophylline, Dextran, Penicillin G, Sodium Bicarbonate, Vancomycin, Carbonates, Phosphates, Sulfates, Tartrates.
5.	Benzyl Penicillin	Chlorpromazine, Oxytetracycline, Phenytoin, Promethazine, Thiopentone, Vancomycin, Vit-B&C.
6.	Calcium Gluconate	Oxytetracycline, Phenytoin, Promethazine, Sodium Bicarbonate, Vancomycin.
7.	Chloramphenicol Sodium Succinate	Hydrocortisone, Phenytoin, Promethazine, Vancomycin, Chlorpromazine.
8.	Chlorpromazine	Aminophylline, Ampicillin, Benzyl Penicilline, Chloramphenicol, Cloxacillin.
9.	Cloxacillin	Chlorpromazine, Aminoglycosides, Vit-C, Lactate solutions, Carbohydrate solutions with pH less than 4, Bicarbonates
10.	Diazepam	PVC containers
11.	Dobutamine HCl	Alkaline solutions, Calcium Gluconate, Diazepam, Frusemide, Regular Insulin, Phenytoin sodium, Verapamil
12.	Frusemide	All drugs. Preferably administered by direct injection only. However, if required to be diluted only with isotonic saline.
13.	Gentamicin	Chloramphenicol, Heparin, all penicillins.
14.	Heparin	Rapidly inactivated below pH 6. Benzyl penicillin, Chlorpromazine, Gentamicin, Hydrocortisone, Promethazine, Vancomycin, Tetracycline, Morphine.
15.	Hydrocortisone	Add only to pH neutral solutions. Ampicillin, Calcium, Chloramphenicol, Chlorpromazine, Heparin, Vancomycin, Tetracyclines.
16.	Lignocaine	Ampicillin.
17.	Morphine Sulphate	Aminophylline, Heparin, Phenytoin Sodium, Sodium Bicarbonate, Promethazine, Barbiturates.
18.	Nafcillin	Aminophylline, Gentamicin, Hydrocortisone, Vit-B&C, Sympathomimetics.

19.	Nitroglycerin	PVC containers
20.	Phenobarbitone	Chlorpromazine, Hydrocortisone, Opioid analgesics.
21.	Promethazine	Aminophylline, Barbiturates, Benzyl penicillin, chloramphenicol, Heparin, Dextran, Hydrocortisone, Morphine, Phenytoin.
22.	Thiopentone	All acidic solutions (such as chlorpromazine, morphine). Amikacin, Benzyl penicillin, insulin, Ringer lactate, Pentazocine, Pethidine, Sodium bicarbonate, Succinyl Choline.
23.	Vancomycin	Penicillin G, Ticarcillin
24.	Verapamil	Dobutamine HCl, albumin, hydralizsic, septran, Amphotericine B & PH greater than 6
25.	Vit-B&C	Aminophylline, Barbiturates, Chloramphenicol, Chlorpromazine, Hydrocortisone Penicillin G, carbonate, citrate, barbiturates, Solution containing sodium bisulphates.

Appendix 'C'

GUIDELINES FOR INFUSION OF INDIVIDUAL DRUGS

<u>Drug</u>	<u>Infusion Guidelines</u>
1. Abciximab	Continuous in 5% dextrose or 0.9% Sodium Chloride through 0.2 or 0.22 Micron Filter.
2. Acetylcysteine	Continuous in 5% dextrose
3. Acyclovir	Initially reconstitute to 25 mg/ml in water for injection or isotonic saline. Now dilute to 5 mg/ml with isotonic saline or isotonic glucose saline or Ringer lactate and administer over one hour.
4. Alfentanil	Continuous or intermittent in 5% glucose, isotonic saline or Ringer lactate.
5. Alprostadil	Continuous in glucose or saline. Add directly to solutions avoiding contact with walls of plastic containers.
6. Alteplase	Continuous or intermittent in saline. <u>Not to be infused in glucose.</u>

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| 7. | Amikacin | Intermittent in glucose, saline or Ringer lactate over 30 minutes or IV Push. |
| 8. | Aminophylline
(Theophylline) | Continuous in glucose, saline or Ringer lactate.
Concentration 800 mg/500 ml = 1.6g/m infusion rate 0.2-0.6 mg/kg/hr. |
| 9. | Amiodarone | Continuous or intermittent in glucose.
<u>Incompatible with saline.</u> (glass or polyolefin. Containers for maintenance infusion)
<ul style="list-style-type: none"> - Loading dose: 150 mg over 10 mts, then 1mg/mt for 6 hrs - Maintenance concentration: 450mg/250ml = 1.8mg/ml. - Infusion rate .5mg/mt (=17ml/hr) |
| 10. | Amoxycillin | Intermittent in glucose or saline or IV push..
Reconstituted solutions to be diluted and given without delay as 100 ml over 30-60 minutes.
Continuous infusion not recommended. |
| 11. | Amphotericin B | <u>Incompatible with saline or other electrolytes</u> |
| | a) Colloidal | Intermittent in glucose 5%. Initially reconstitute with water for injection 50 mg in 10 ml, then dilute to a concentration of 625 microgram per ml. Initial test dose 2 mg of 100 microgram per ml over 10 minutes. If tolerated give at 1 to 2 mg/kg/ over 2-3 hrs after pre-medication with Inj hydrocortisone, Inj Avil & Tab Crocin
<u>Incompatible with saline or other electrolytes.</u> |
| | b) Lipid complex | Intermittent in glucose 5%. Allow suspension to reach room temperature, shake gently and withdraw required dose into 20 ml syringe. Now replace needle with 5 micron filter needle and dilute to 1 mg/ml. Initial test dose 1 mg over 10 minutes. Now administer at 2.5 mg/kg/hour using in-line filter of atleast 15 microns. |
| | b) Liposomal | <u>Incompatible with saline and electrolytes.</u>
Intermittent in 5% glucose. Reconstitute with 12 ml water for injection and shake vigorously to produce a concentration of 4 mg/ml. Now withdraw required dose and introduce to infusion fluid through 5 micron filter provided to produce a final concentration of 0.2 –2 mg/ml.
Initial test dose 1 mg over 10 minutes. Now infuse total dose over 30 to 60 minutes. |
| | d) Deoxycholate complex | <u>Incompatible with saline or other electrolytes.</u>
Intermittent in 5% glucose. Reconstitute vial with 10 ml water for injection and shake immediately to produce 5 mg/ml colloidal solutions. Dilute further to 100 microgram per ml. pH of glucose must not be below 4.2. Initial test dose 1 mg over 20 to 30 minutes.
Protect from light. |

12.	Ampicillin	Intermittent in glucose or saline. Suggested volume 100 ml over 30 to 60 minutes. Continuous infusion is not recommended. May be injected directly into the drip tubing.
13.	Atracurium	Continuous in glucose or saline or Ringer lactate.
14.	Benzyl Sodium Penicillin	As for Amoxicillin
15.	Bleomycin Sulphate	.As IV push after sensitivity test with 2 units s/c.
16.	Calcium gluconate.	Continuous in glucose or saline. Avoid bicarbonates, phosphates or sulphates.
17.	Carboplatin	In glucose, give over 15 to 60 minutes.
18.	Cefazolin	Intermittent or directly into tubing in glucose or saline or Ringer lactate.
19.	Cefotaxime	IV Push
20.	Ceftazidime	As IV Push.
21.	Ceftriaxone	As IV Push.
22.	Chloramphenicol Sodium Succinate	Intermittent or via drip tubing in glucose or saline. Or IV push
23.	Chloroquine	Continuous in saline.
24.	Cidofovir	Intermittent in saline. Dilute required dose with 100 ml fluid and infuse over 1 hour.
25.	Cisplatin	Intermittent in saline. Reconstitute with water for injection to produce 1 mg/ml, now dilute in 2 ltr infusion fluid and give over 6 to 8 hours.
26.	Clindamycin	Continuous or intermittent in glucose or saline.
27.	Co-amoxiclav (amoxycillin with clavulanic acid)	Intermittent in saline or via drip tubing in glucose or saline as 50 to 100 ml and given over 30 to 40 minutes.
28.	Cyclophosphamide	Intermittent or via drip tubing in glucose or saline as 50 to 100 ml given over 5 to 15 minutes.
29.	Cytarabine	Continuous or intermittent or in drip tubing in glucose or saline.

		Check container for cloudiness or precipitates during administration.
30.	Dacarbazine	Intermittent in glucose or saline.
31.	Dactinomycin	Intermittent in or via tubing in glucose or saline.
32.	Daunorubicin HCl	Via tubing in saline. Reconstitute with water for injection to make 5 mg/ml dilute required dose with infusion fluid to 1 mg/ml, give over 20 minutes.
33.	Desferrioxamine	Continuous or intermittent in glucose or saline. Dissolve initially in water for injection make 500 mg in 5 ml. Now dilute with infusion fluid.
34.	Diazepam	Continuous in glucose or saline. Dilute to not more than 40 mg/ 500 ml. Infusion must be completed within a maximum of 6 hours. <u>Plastic containers may adsorb drug.</u>
35.	Dobutamine HCl	Continuous in glucose or saline. Dilute to 0.5 to 1 mg/ml and give by a controlled infusion device. - Concentration :- 250mg/250ml = 1000 mcg/ml – infusion rate :- 3mcg/kg/mt.titrate up to 20mcg/kg/mt. Incompatible with bicarbonates.
36.	Docetaxel	Intermittent in glucose or saline. Infuse over 1 hour. Pre-medicate and Post-medicate with steroids
37	Dopamine Hydrochloride	Continuous in glucose or saline or Ringer lactate as 1.6 mg/ml. <u>Incompatible with bicarbonates.</u> -concentration :-800mg/500ml=1600ug/ml - injection rate :- 3ug/kg/mtn titrate to effect.
38.	Doxorubicin HCl	Via drip tubing in glucose or saline. Reconstitute with water for injection or saline to make 10 mg/5 ml, give over 2 to 3 minutes.
39.	Epoetin Beta	Intermittent in saline. Reconstitute with water for injection and dilute with 100 ml infusion fluid. Infusion must be completed within 2 hours of preparation. <u>Only plastic material is to be used for infusion.</u>
40.	Esmolol HCl	Continuous or intermittent in glucose or saline as 10 mg/ml. Loading dose :- 500 mcg/kg over 1mt. Infusion rate :- 50 mcg/kg/min. <u>Incompatible with bicarbonates.</u>

41. Ethanol	Continuous in glucose or saline or Ringer Lactate after dilution to 5to 10%.
42. Etoposide	Intermittent in saline. Over 1 hour Check container for haziness or precipitate during infusion.
43. Filgrastim	Given s/c 5 mcg/kg/day.
44. Fludarabine Phosphate	Intermittent in saline as 100 ml over 30 minutes.
45. Flumazenil	Continuous in glucose or saline.
46. Fluorouracil	IV bolus or IV infusion over 15 minutes or Continuous or via drip tubing in glucose for continuous infusion .
47. Fomepizole	Intermittent in glucose or saline over 30 minutes as 100 ml infusion.
48. Furosemide	Continuous in saline.or IV push pH must be above 5.5. Rate must not exceed 4 mg/minute. <u>Incompatible with glucose.</u>
49. Ganciclovir	Intermittent in glucose or saline or Ringer lactate over 1 hour.
50. Gemcitabine	Intermittent in saline over 30 minutes.
51. Gentamicin	Intermittent IV push or via drip tubing in saline or glucose as 50 to 100 ml over 20 minutes.
52. Glyceryl trinitrate (Nitroglycerine)	Continuous in glucose or saline.(glass or polyolefin container) <u>Incompatible with PVC infusion containers.</u> Concentration - 50 mg/250ml =200mcg/ml Infusion rate – 10mcg/min titrate to effect
53. Heparin Sodium	Bolus or continuous in glucose or saline.14-18 units/kg/hour
54. Imipenam with cilastatin.	Intermittent in glucose or saline. Continuous infusion not recommended.
55. Insulin (soluble)	Continuous in saline or Ringer lactate as 1 unit per ml. <u>Adsorbed by plastics.</u> 100 units in 500ml of normal saline Infusion rate(50 ml/hr) = 10 units/hr
56. Ketamine HCl	Continuous in glucose or saline as 1 mg/ml solutions.

57.	Magnesium Sulphate	Continuous in glucose or saline as 200 mg/ml solution.
58.	Melphalan	Intermittent or directly in tubing in saline. Maximum 90 minutes between addition and completion of administration. <u>Incompatible with glucose.</u>
59.	Mesna	Continuous or directly by tubing in glucose or saline.
60.	Methotrexate	Continuous or in tubing in glucose or saline or Ringer lactate or IV push.
61.	Metoclopramide HCl	Continuous or intermittent in glucose or saline or Ringer lactate. To be administered over at least 15 minutes.
62.	Naloxone.	Continuous in glucose or saline as 4 microgram per ml solution.
63.	Netilmicin	Intermittent or via tubing in glucose or saline.
64.	Nimodipine	Directly via drip tubing in glucose or saline. <u>Incompatible with PVC.</u> <u>Protect from light.</u>
65.	Noradrenaline	Continuous in glucose or IGS. Incompatible with alkalis.
66.	Oxytocin	Continuous in glucose 5%. For induction or enhancement of labour dilute 5 units in 500 ml of infusion fluid. For postpartum haemorrhage, dilute 5 to 20 units in 500 ml.
67.	Paclitaxel	Continuous in glucose or saline. Incompatible with PVC infusion container/equipment. Administer as 0.3 to 1.2 mg per ml and infuse over 3 hours.
68.	Pentamidine	Intermittent in glucose or saline. Dilute in 50 to 200 ml and give over at least 60 minutes.
69.	Phenytoin Sodium	Intermittent in saline. Flush IV line with saline before and after infusion. Infusion concentrations not to exceed 10 mg per ml. Rate of administration not more than 50 mg/minute.
70.	Piperacillin	Intermittent in glucose or saline.as IV infusion
71.	Potassium Chloride	Continuous in glucose or saline.

Mix thoroughly to avoid 'layering'.

Maximum concentration - 40 m mol/ltr

Infusion rate – 20 m mol/hr

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| 72. | Quinine dihydrochloride | Continuous in saline, to be given over 4 hours. |
| 73. | Ritodrine HCl | Continuous in glucose. |
| 74. | Sodium Nitroprusside | Continuous in glucose. Reconstitute 50 mg with 2 to 3 ml glucose and then dilute immediately with 250-1000 ml infusion fluid /glucose.
<u>Protect from light.</u>
_Concentration – 50mg/250 ml = 200 mcg/ml
_Infusion rate – initially 0.25 mcg/kg/mt.titrate to effect |
| 75. | Streptokinase | Continuous or intermittent in glucose or saline.
Infuse over at least 60 mins. |
| 76. | Teicoplanin | Intermittent in glucose saline or Ringer lactate. Infuse over 30 minutes.
Continuous infusion not recommended. |
| 77. | Vancomycin | Intermittent in glucose or saline.
Reconstitute each 500 mg with 10 ml water for injection and dilute to make 5 mg/ml.
Give over at least 60 minutes. |
| 78. | Vinblastine Sulphate | Via drip tubing in saline over 1 minute. |
| 79. | Vincristine | Via drip tubing in glucose or saline.or IV push |
| 80. | Vit -B&C | Intermittent or via drip tubing in glucose or saline.
Administration should be immediate after dilution.
Give over at least 10 minutes. |

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