TOTAL PARENTERAL NUTRITION SOLUTIONS

Issued 6/98

NOTE: Because of the complexity of these solutions, the customary format of the "Guide" cannot be used. The double entry system is impractical. However, the "see also under" notation will be used to direct attention to this section wherever possible.

Hazards of Precipitation with Total Parenteral Nutrition

Total parenteral nutrition solutions present unique stability and compatibility problems due to the complexity of these formulations (1542, 1543, 1545, 1546, 1547, 1548, 1549, 1550, 1551, 1552, 1553, 1554, 1555, 1557, 1558). The following are important considerations in the preparation and administration of TPN solutions:

• Extra caution should be exercised in compounding TPN fluids that contain lipid emulsions, since the emulsion may obscure the visibility of precipitates;

• Pharmacists should ensure that the prescribed amounts of calcium and phosphate will not precipitate (also, see below);

• When adding calcium and phosphate to a TPN solution, the phosphate should be added first, and the line should be flushed between the addition of any potentially incompatible components;

• When compounding or administering TPN solutions, the admixture should be closely observed for signs of precipitation or other evidence of ingredient incompatibility;

• A filter should be used when infusing either central or peripheral admixtures;

• TPN admixtures should be administered within the following time frames: if stored at room temperature, start infusion within 24 hours after mixing; if stored at refrigerated temperatures, within 24 hours of rewarming;

• Calcium chloride leads to precipitation to a greater extent than calcium gluconate whenever the amounts of calcium and phosphate in the formulation approach the maximum solubility limits of these components. 15 mEq of calcium ion and 30 mEq of phosphate ion per liter are generally considered the limits of solubility (1542). Solubility limits should be calculated from the volume at the time calcium is added. However, due to the diverse physical and chemical conditions of TPN solutions, it is not reasonable to guarantee maximum single volumes of 10% calcium gluconate and 3 mMole/ml inorganic phosphates injection that would be compatible in all TPN (1562).

FACTORS AFFECTING SOLUBILITY OR PRECIPITATION OF CALCIUM PHOSPHATE (1552)

Factor	Comment
Salt form of calcium	CaCl has a greater chance of precipitation than Ca Gluconate.
Concentration of phosphate	The higher the phosphate, the higher the chances of ppt.
Concentration of amino acids	AA form soluble complexes with Ca and phosphate, decreasing the available Ca and phosphate that can form precipitates.
Amino acid composition	Some brands inherently contain Ca and phosphate.
Dextrose concentration	The higher the concentration, the lower the pH and hence the more Ca and phosphate that can be solubilized.
Lipid concentration	The lipids increase pH of TPN, potentiating the possibility of calcium phosphate ppt.
Temperature of solution	The incidence of precipitation increases with higher temperatures.
pH of solution	The power the pH, the more Ca and phosphate that can be solubilized.
Presence of other additives	Increased number of additives and increased quantities of these additives result in increased likelihood of ppt.
Order of mixing	Add the Ca salt to dextrose and phosphate to the AA solution before mixing.
Standing times of solution	Lengthy standing increases precipitation formation.
Infusion rates	Slow infusion rates may result in the formation of precipitates.

The above table was originally published by Maswoswe, et al. "An old nemesis; calcium and phosphate interaction in TPN admixtures," HOSP. PHARM., 30, (7), page 580, 1995. Copyright 1995 Lippencott-Raven Publishers, New York.

SEE also the tabulations on the following pages under Total Parenteral Nutrition Solutions, especially Total Parenteral Nutrition Solutions (cont'd-4), as well as the specific drug entries to be admixed listed in this monograph.

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TOTAL PARENTERAL NUTRITION SOLUTIONS (cont'd-1)

Issued 6/01

Table 2. Compatibility[a] of Calcium (as Acetate) and Phosphate (as Potassium Salt) in Formulations 1-5

Formulation 1			Formulation 2			Formulation 3			Formulation 4			Formulation 5		
Sample [b]	37 °C	23 °C	Sample [b]	37 °C	23 °C	Sample [b]	37 °C	23 °C	Sample [b]	37 °C	23 °C	Sample [b]	37 °C	23 °C
1-C40P4	C	C	2-C40P5	C	C	3-C40P7	C	C	4-C40P9	C	C	5-C40P5	C	C
1-C40P5	C	C	2-C40P6	C	C	3-C40P8	C	C	4-C40P10	C	C	5-C40P10	C	C
1-C40P6	X	X	2-C40P7	C	C	3-C40P9	C	C	4-C40P11	X	X	5-C40P11	X	C
1-C40P7	X	X	2-C40P8	X	X	3-C40P10	X	C	4-C40P12	X	C	5-C40P12	X	X
1-C40P8	X	X	2-C40P9	X	X	3-C40P11	X	X	4-C40P13	X	X	5-C40P13	X	X
1-C26.9P5	C	C	2-C26P6.5	C	C	3-C28.5P9.3	C	C	4-C40P14	X	X	5-C28.5P9.3	C	C
1-C27.3P6	C	C	2-C27P7.5	C	C	3-C28.9P10.3	C	C	4-C26P11	C	C	5-C28.9P10.3	C	C
1-C27.5P6.8	X	X	2-C28P8.5	X	C	3-C29.3P11.3	X	C	4-C27P12	C	C	5-C29.3P11.3	X	C
1-C27.9P7.8	X	X	2-C29P9.5	X	X	3-C29.5P12	X	X	4-C27.5P12.5	C	C	5-C29.5P12	X	C
1-C28.3P8.8	X	X	2-C30P10.5	X	X	3-C29.9P13	X	X	4-C28P13	X	C	5-C29.8P13	X	X
1-C8P8	C	C	2-C11P11	C	C	3-C13P13	C	C	4-C29P14	X	X	5-C14P14	C	C
1-C9P9	C	C	2-C12P12	C	C	3-C14P14	C	C	4-C30P15	X	X	5-C16P16	C	C
1-C10P10	C	C	2-C13P13	C	C	3-C15P15	C	C	4-C31P16	X	X	5-C17P17	C	C
1-C11P11	C	C	2-C14P14	X	C	3-C16P16	X	C	4-C16P16	C	C	5-C18P18	C	C
1-C12P12	X	C	2-C15P15	X	X	3-C17P17	X	X	4-C17P17	C	C	5-C19P19	X	C
1-C13P13	X	X	2-C16P16	X	X	3-C18P18	X	X	4-C18P18	C	C	5-C20P20	X	X
1-C14P14	X	X	2-C5.5P23	C	C	3-C19P19	X	X	4-C19P19	X	C	5-C22P22	X	X
1-C4P26.5	C	C	2-C6.5P24	C	C	3-C7.0P27.6	C	C	4-C19.5P19.5	X	X	5-C7.5P27.9	C	C
1-C4.8P26.8	C	C	2-C7.5P25	X	C	3-C7.8P27.9	C	C	4-C20P20	X	X	5-C8.5P28.3	C	C
1-C5.4P27	X	C	2-C8.5P26	X	X	3-C8.5P28.2	X	C	4-C21P21	X	X	5-C9.3P28.5	C	C
1-C6.5P27.4	X	X	2-C9.5P27	X	X	3-C9.3P28.5	X	X	4-C10P25	C	C	5-C10P28.8	X	C
1-C7.5P27.8	X	X	2-C30P40	C	C	3-C10P28.8	X	X	4-C11P26	C	C	5-C11P29.1	X	X
1-C2P40	C	C	2-C40P40	C	C	3-C10.8P29.1	X	X	4-C12P27	X	C	5-C6P40	C	C
1-C3P40	C	C	2-C50P40	C	C	3-C5P40	C	C	4-C13P28	X	X	5-C7P40	C	C
1-C4P40	X	C	2-C60P40	X	C	3-C6P40	C	C	4-C14P29	X	X	5-C8P40	C	C
1-C5P40	X	X	2-C70P40	X	X	3-C7P40	X	X	4-C15P30	X	X	5-C9P40	C	C
1-C6P40	X	X	2-C80P40	X	X	3-C8P40	X	X	4-C7P40	C	C	5-C10P40	X	C
						3-C9P40	X	X	4-C8P40	C	C	5-C11P40	X	X
						3-C10P40	X	X	4-C9P40	C	C			
									4-C10P40	X	C			
									4-C11P40	X	X			
									4-C12P40	X	X			

a. C=compatible; X=incompatible

b. The number following the "C" indicates the concentration of calcium in milliequivalents per liter; the number following the "P" indicates the concentration of phosphates in millimoles per liter.

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TOTAL PARENTERAL NUTRITION SOLUTIONS (cont'd-2)

Issued 6/01

(see also under Amino Acids solution, Aminosyn 3.5% M and 7%, Freamine II and III, Intralipid)

Changes in Antimicrobial Activity of Antibiotics in Hyperalimentation Solutions (Ref. 182)

	Solution 1 Containing FreAmine 8.5% pH 6.20				**Solution 2** Containing McGaw Essential Amino Acid Mixture 5.25% pH 5.92				**Solution 3** Containing Amigen 5% pH 5.81			
	25ºC		37ºC		25ºC		37ºC		25ºC		37ºC	
	Time	Percent Initial Concentration (pH)	Time	Percent Initial Concentration (pH)	Time	Percent Initial Concentration (pH)	Time	Percent Initial Concentration (pH)	Time	Percent Initial Concentration (pH)	Time	Percent Initial Concentration (pH)
Ampicillin 1-mg/ml	0 min	100 (6.42)	0 min	100 (6.42)	0 min	100 (6.18)	0 min	100 (6.18)	0 min	100 (5.93)	0 min	100 (5.93)
	6 hr	90	6 hr	75	4 hr	88	2 hr	89	24 hr	88	12 hr	87
	12 hr	85	12 hr	65	6 hr	88	4 hr	81			24 hr	84
	24 hr	75	24 hr	60	12 hr	75	6 hr	82				
					24 hr	83	12 hr	72				
							24 hr	60				
Kanamycin 0.25 mg/ml	0 min	100 (6.20)	0 min	100 (6.20)	0 min	100 (5.89)	0 min	100 (5.89)	0 min	100 (5.82)	0 min	100 (5.82)
	24 hr	87	6 hr	88	24 hr	82	6 hr	74	24 hr	89	12 hr	86
			12 hr	82			12 hr	66			24 hr	64
			24 hr	61			24 hr	48				
Methicillin 1 mg/ml	NC* (6.23)		0 min	100 (6.23)	NC (5.95)		0 min	100 (5.95)	NC (5.85)		NC (5.85)	
			24 hr	80			24 hr	86				
Cephalothin 1 mg/ml	NC (6.13)		0 min	100 (6.20)	NC (5.92)		0 min	100 (5.94)	NC (5.84)		0 min	100 (5.84)
			24 hr	87			24 hr	80			24 hr	83

*NC = No change during 24-hour period

COMPOSITION OF BASIC SOLUTIONS ABOVE:

Solution 1	**Amount of Mixture**
FreAmine (McGaw) (Crystalline essential amino acid mixture)	200 ml
50% Dextrose in water	400 ml
Potassium phosphate (Travenol)	15 mEq (5 ml)
Potassium acetate (McGaw)	15 mEq (5 ml)
Calcium gluconate 10% (Vitarine)	20 ml
M.V.I. (Multi-vitamin infusion) (USV Pharm.)	10 ml
Magnesium sulfate	8.1 mEq (2 ml)
Sodium chloride	40 mEq (1).5 ml)
Water for injection	1000 ml
Solution 2	
Essential amino acid solution* 5.25% (McGaw) investigational drug	200 ml
Additional ingredients as recorded for solution 1	
Solution 3	
Amigen 5% (Baxter) (Protein hydrolysate)	200 ml
Additional ingredients as recorded for solution 1	

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TOTAL PARENTERAL NUTRITION SOLUTIONS (cont'd-3)

Issued 6/01

(see also under AMINO ACIDS SOLUTION, AMINOSYN 3.5%M and 7%, FREAMINE II and III, INTRALIPID)

Compatibility of TPN mixtures and Secondary Antibiotic Infusions

The following basic TPN mixture was challenged by the introduction of a secondary infusion of antibiotics (758).

Basic TPN Mixture	Qty
Amino Acids 10%	750 ml
Dextrose 70%	429 ml
Lipid Emulsion 20%	225 ml
Sterile Water	15 ml
Sodium Phosphate (3mM Phos)	5 ml
Calcium Gluconate 10%	20 ml
Magnesium Sulfate 50%	2 ml
Sodium Chloride 4 mEq/ml	15 ml
Potassium Chloride 2 mEq/ml	20 ml
Trace Minerals	3 ml
Multivitamins-12	10 ml

All of the TPN - antibiotic mixtures appeared to be physically stable EXCEPT for those prepared with TETRACYCLINE. Addition of tetracycline disrupted the lipid emulsion, probably because of its highly acidic pH due to the large amount of ascorbic acid in the formulation. There were no signs of creaming or broken emulsion with the other antibiotics (758).

Antibiotics Tested
Ampicillin Sod., 2 Gm in NS
Cefamandole Naf., 2 Gm in D5W
Cefazolin Sod., 1 Gm in D5W
Cefoxitin Sod., 1 Gm in D5W
Cephapirin Sod., 1 Gm in D5W
Clindamycin Phos., 600 mg in D5W
Erythromycin Lac., 1 Gm in NS
Gentamicin Sulf., 80 mg in D5W
Kanamycin Sulf., 500 mg in D5W
Oxacillin Sod., 1 Gm in D5W
Penicillin G Pot., 2 mil u in D5W
Tetracycline HCl, 500 mg in D5W
Ticarcillin Disod., 3 Gm in D5W
Tobramycin Sulf., 80 mg in D5W

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TOTAL PARENTERAL NUTRITION SOLUTIONS (cont'd-4)

Issued 6/01

(see also under AMINO ACIDS SOLUTION, AMINOSYN 3.5%M and 7%, FREAMINE II and III, INTRALIPID)

Compatibility of TPN mixtures and Secondary Cardiovascular Medications

The following basic TPN mixture was challenged with solutions of the cardiovascular agents listed, using equal volumes of the two solutions (1:1) ratio, to simulate Y-site administration (763).

Basic TPN Mixture	Qty
Amino Acids 10%	750 ml
Dextrose 70%	429 ml
Lipid Emulsion 20%	225 ml
Sterile Water	15 ml
Sodium Phosphate (3mM Phos)	15 ml
Calcium Gluconate 10%	20 ml
Magnesium Sulfate 50%	2 ml
Heparin Sodium	6000 u
Sodium Chloride 4 mEq/ml	60 ml
Potassium Chloride 2 mEq/ml	40 ml
Trace Minerals	3 ml
Multivitamins-12	10 ml

All of the 1:1 mixtures of the TPN solution with the cardiovascular agent appeared to be physically compatible (i.e. no disruption of the emulsion) for up to 4 hours EXCEPT in the case of METHYLDOPATE in D5W. The solution of methyldopate in D5W cracked the emulsion upon testing and retesting. Methyldopate appears acceptable for infusion with the TPN when diluted with 0.9% sodium chloride (763).

Cardiovascular Agents Tested (using both 50 ml D5W and 50 ml NS)	Test Dose (mg)
Digoxin	0.625
Dopamine Hydrochloride	80
Furosemide	165
Isoproterenol Hydrochloride	0.2
Lidocaine Hydrochloride	200
Methyldopate Hydrochloride	250
Norepinephrine Bitartrate	0.4

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TOTAL PARENTERAL NUTRITION SOLUTIONS (cont'd-5)

Issued 6/01

(see also under AMINO ACIDS SOLUTION, AMINOSYN 3.5%M and 7%, FREAMINE II and III, INTRALIPID)

Table 1. Physical Compatibility of Calcium Gluconate and Potassium Phosphate Admixed In Protein Hydrolysate/Dextrose Solution [a]

Calcium Gluconate (mEq/liter)	Potassium Phosphate (mEq/liter)											
	0	4	6	8	10	15	20	25	30	35	40	50
0												
4		C										
6			C									
8				C	C[b]							
10					C							
15					C[b]	C	C[b]	C[b]				
20					C[b]	C	C	X	X	X	X	
25					C[b]	C	X b	X	X[b]	X	X[b]	
30						X	X	X[b]	X	X[b]	X[b]	
35						X	X b	X	X[b]	X	X[b]	
40						X	X b	X[b]	X[b]	X[b]	X	
50							X		X		X	X

[a] Calcium gluconate was added first, followed by potassium phosphate.

[b] Readings were taken at one and four hours only.

Table 2. Physical Compatibility of Calcium Gluconate and Magnesium Sulfate Admixed in Protein Hydrolysate/Dextrose Solution [a]

Calcium Gluconate (mEq/liter)	Magnesium Sulfate (mEq)/liter)									
	0	4	6	8	10	20	30	40	50	100
0										
4		C								
6			C							
8				C						
10					C					
20						C				
30							C			
40								C		
50									C	
100										C

[a] Calcium gluconate was added first, followed by magnesium sulfate.

Table 3. Physical Compatibility of Potassium Phosphate and Magnesium Sulfate Admixed in Protein Hydrolysate/Dextrose Solution [a]

Potassium Phosphate (mEq/liter)	Magnesium Sulfate (mEq/liter)									
	0	4	6	8	10	20	30	40	50	100
0										
4		C								
6			C							
8				C						
10					C					
20						C[b]				
30							C[b]			
40								C		
50									C	
100										C

[a] potassium phosphate was added first, followed by magnesium sulfate.

[b] Readings were taken at one and four hours only.

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TOTAL PARENTERAL NUTRITION SOLUTIONS (cont'd-6)

Issued 6/01

(see also under AMINO ACIDS SOLUTION, AMINOSYN 3.5%M and 7%, FREAMINE II and III, INTRALIPID)

Table 4. Physical Compatibility of Potassium Phosphate and Calcium Gluconate Admixed in Protein Hydrolysate/Dextrose Solution [a]

Potassium Phosphate (mEq/liter)	Calcium Gluconate (mEq/liter)				
	0	25	35	40	50
0	C				
25		C	C		
35		C	C		
40				C	
50					X[b]

[a] Potassium phosphate was added first, followed by calcium gluconate (order of mixing reverse of that in Table 1). Precipitate was not observed until 24th hour.

Table 5. Physical Compatibility of Calcium Gluconate and Magnesium Sulfate with the Addition of Potassium Phosphate Admixed in Protein Hydrolysate/ Dextrose Solution [a]

Calcium Gluconate and Magnesium Sulfate (mEq/liter each)	Potassium Phosphate (mEq/liter)								
	0	4	6	8	10	20	30	40	50
0									
4		C							
6			C						
8				C					
10					C				
20						C			
30							X		
40								X	
50									X

a Calcium gluconate and magnesium sulfate were added first, followed by potassium phosphate.

Table 6. Physical Compatibility of Selected Vitamins in the Presence of Calcium Gluconate, Magnesium Sulfate or Potassium Phosphate, or All Three, Admixed in Protein Hydrolysate/Dextrose Solution [a]

A=Calcium Gluconate (5 mEq/Liter)
B=Calcium Gluconate (100 mEq/Liter)
C=Potassium Phosphate (10 mEq/Liter)
D=Potassium Phosphate (100 mEq/Liter)
E=Magnesium Sulfate (5 mEq/Liter)
F=Magnesium Sulfate (100 mEq/Liter)
G=Calcium Gluconate and Potassium Phosphate (20 mEq/Liter each)
H=Calcium Gluconate, Magnesium Sulfate and Potassium Phosphate (20mEq/Liter each)
I=Calcium Gluconate and Potassium Phosphate (30 mEq/Liter each)

Vitamins	A	B	C	D	E	F	G	H	I
Solu B Forte									
5 ml/liter	C	C	C	C	C	C	C	C	X
10 ml/liter	C	C	C	C	C	C	C	C	X
Folic Acid									
0.5 mg1liter	C	C	C	C	C	C	C	C	X
5 mg/liter	C	C	C	C	C	C	C	C	X
Cyanocobalamin									
300 microgram/liter	C	C	C	C	C	C	C	C	X
1000 microgram/liter	C	C	C	C	C	C	C	C	X
Phytonadione									
10 mg/liter	C	C	C	C	C	C	C	C	X
50 mg/liter	C	C	C	C	C	C	C	C	X
M.V.I.									
10 ml/liter	C	C	C	C	C	C	C	C	X
20 ml/liter	C	C	C	C	C	C	C	C	X

[a] The calcium gluconate was added first, then potassium phosphate, magnesium sulfate and the vitamin.

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TOTAL PARENTERAL NUTRITION SOLUTIONS (cont'd-7)
Issued 6/01

(see also under AMINO ACIDS SOLUTION, AMINOSYN 3.5%M and 7%, FREAMINE II and III, INTRALIPID)

Table 7. Physical Compatibility and pH of Protein Hydrolysate/Dextrose Solution Admixed with All Selected Vitamins in the Presence of Calcium Gluconate, Magnesium Sulfate or Potassium Phosphate, or All Three [a]

A=Calcium Gluconate (5 mEq/Liter)
B=Calcium Gluconate (100 mEq/Liter)
C=Potassium Phosphate (10 mEq/Liter)
D=Potassium Phosphate (100 mEq/Liter)
E=Magnesium Sulfate (5 mEq/Liter)
F=Magnesium Sulfate (100 mEq/Liter)
G=Calcium Gluconate and Potassium Phosphate (20 mEq/Liter each)
H=Calcium Gluconate, Magnesium Sulfate and Potassium Phosphate (20mEq/Liter each)

PH/D-Vitamin Admixture Plus:	A	B	C	D	E	F	G	H
M.V.I								
10 ml/liter	C	C	C	C	C	C	C	C
pH	5.22	5.22	6.50	5.67	5.10	5.62	5.67	5.80
Solu B Forte								
10 ml/liter	C	C	C	C	C	C	C	C
pH	5.00	5.05	5.25	6.4	4.95	4.85	5.32	5.42

a The calcium gluconate was added first, then potassium phosphate, magnesium sulfate and the vitamin.
b Protein Hyd rolysate/Dext rose Solution with: Folic Acid 5 mg/liter, B-12-1000 microgram/liter, K-1-10 mg/liter.

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D70W	500 ml	FreAmine III 8.5%	500 ml
FreAmine II	500 ml	D50W	500 ml
NaCl	40 mEq	Hyperlyte	1 vial
MVI	1 amp	Sodium Phosphate	10 mEq/l
Insulin, reg	5 units	Insulin, regular	15 u/L
Heparin	1000 units	Cimetidine	200 mg/l
Solu-Cortef	500 mg	Claforan	1 g/L
No evidence of precipitation within 8 hours (519).		No apparent physical or chemical incompatibility on several such solutions which ran over 8 hours. Patient response thought to be good to all components (598).	

It has been noted that TPN solutions being administered by IMED 922 infusion pumps, using either Venoset-78 with 0.22 micron IVEX 0.2 filter or solution administration set #2CO210 with inline 0.22 micron filter solution sets between the TPN bottles and pumps had blood "backing up" into the tubing from the administration site. It was found that by replacing the filter set with a standard solution set (Travenol Laboratories, Inc. #2CO017) between the bottle and pump, the back-up problem ceased. Placement of a 0.22 micron filter (Abbott Laboratories Hospital Products, IVEX-HP, #4524) down flow from the pump did not result in any apparent impediment to solution flow (511).

When frozen and thawed 30 or 60 days later by microwave technique, the individual amino acids electrolytes, and dextrose remain unchanged and suitable for patient administration. Levels of dihexylethylphthalate (DEHP) were monitored throughout the study and did not change significantly (548).

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