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ABSTRACT. *Background:* The supply of high amounts of calcium (Ca) and phosphorus (P) during total parenteral nutrition (TPN) is matter of concern because of the risk associated with calcium phosphate precipitation. The *in vitro* Ca-P compatibility in ready-for-use TPN solutions after the addition of different concentrations of inorganic phosphate or d-fructose-1,6-diphosphate (FDP) and calcium chloride was evaluated. *Methods:* Four series of experiments for each Ca + P couple were carried out by varying amino acid concentrations (2% or 4%), temperature (25°C or 37°C), and pH. The extent of precipitation was estimated by visual inspection and particle count. The areas of maximal compatibility (ie, areas showing the complete absence of precipitates) were drawn from the precipitation curves. *Results:* The precipitation extent was considerably higher in conditions mimicking body environment for both Ca + P couples. The compatibility area at 37°C and 2% amino acid for $CaCl_2$ + Na_2HPO_4 admixtures was included within 2.50 mmol/L $CaCl_2$ and 2.22 mmol/L Na_2HPO_4, whereas that for $CaCl_2$ + FDP was within 33.3 mmol/L $CaCl_2$ and 10.0 mmol/L FDP (20 mEq/L of P). Unlike inorganic calcium phosphate, FDP dicalcium salt precipitation was kinetically delayed and was only minimally enhanced by decreasing amino acid concentration. *Conclusions:* Our data indicated that the use of FDP as the P source in parenteral nutrition solutions was effective in avoiding the life-threatening calcium phosphate precipitation. Thus, the addition of FDP to TPN admixtures represents a safe choice, allowing the simultaneous administration of high amounts of Ca and P in restricted fluid volumes, even at low amino acid concentrations. (*Journal of Parenteral and Enteral Nutrition* **23**:326–332, 1999)

The precipitation of calcium (Ca)-phosphorus (P) salts when calcium and phosphates are mixed in the same solution is a well-documented incompatibility.[1–3] The narrow solubility limits of inorganic calcium phosphates and the complex array of factors affecting their precipitation should therefore be taken into account in order to safely administer total parenteral nutrition (TPN) admixtures. However, calcium phosphate precipitation is not entirely predictable nor is easy to detect. For these reasons, providing the recommended high intake of both Ca and P, especially in pediatric parenteral nutrition,[4] continues to pose a significant physicochemical challenge in the preparation of TPN admixtures.

Attention was again drawn to this problem by a Safety Alert issued in 1994 by the US Food and Drug Administration (FDA).[5] It stressed the serious hazard to human health associated with parenteral nutrition when both P and Ca are supplied by addition of inorganic phosphates and calcium salts to three-in-one TPN admixtures. Two deadly events and two serious injuries occurred with diffuse pulmonary intravascular microemboli containing monohydrogen or dibasic calcium phosphate crystals.[6] The FDA document pointed out the number and complexity of parameters to be checked during the compounding and administration of the nutritional solutions to achieve a significant reduction of the risk for patients. However, there is still a need for alternative safety measures and it seems premature to envisage a resolution to the problem.

d-Fructose-1,6-diphosphate (FDP) is an important intracellular metabolite involved in the regulation of many biochemical pathways.[7] As a metabolizable phosphorus-rich compound, exogenous FDP is indicated, among others, for the treatment of either acute or chronic hypophosphatemic conditions such as those occurring during transfusion therapies, extracorporeal circulation, chronic alcoholism, prolonged malnutrition, and respiratory failure.[8] FDP has also been used in parenteral nutrition as a promptly available high-energy substrate,[9] because its IV administration results in a rapid bioconversion, mediated at least in part by the Embden-Meyerhoff pathway.[10] The drug has been marketed as sodium salt in several countries (including Italy, where it is part of the basic therapeutic armamentarium in hospitals and care units) for many years. The addition of FDP to TPN solutions has been envisaged as a solution to the problem of calcium phosphate precipitation, because the drug exhibits better compatibility with Ca in comparison to inorganic phosphates.[11] However, systematic and sound data

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TABLE I
$CaCl_2$ (mmol/L) and Na_2HPO_4/FDP (mEq/L of P) concentrations of the TPN admixtures examined (*)

Ca£	0	1.11	2.22	3.34	4.45	5.56	6.67	8.89	11.1	13.3	20.0	33.3	40.0	60.0	66.7	80.0	100.0	120.0	133.3	166.7	200.0
0	§* $ &	*	§*	*	§*	*	§*	§	§	§	&	$	&	&	$	&	$ &	&	$	$	$
0.84	*	*	*	*	*	*	*														
1.67	§*	*	§*	*	§*	*	§*	§	§	§											
2.50	*	*	*	*	*	*	*														
3.34	§*	*	§*	*	§*	*	§*	§	§	§											
4.17	*	*	*	*	*	*	*														
5.00	§*	*	§*	*	§*	*	§*	§	§	§											
6.67	§		§		§		§	§	§	§											
8.34	§		§		§		§	§	§	§											
10.0	§		§		§		§	§	§	§											
16.7	&										&		&	&		&	&	&			
33.3	$ &										&	$	&	&	$	&	$ &	&	$	$	$
50.0	&										&		&	&		&	&	&			
66.7	$ &										&	$	&	&	$	&	$ &	&	$	$	$
83.3	&										&		&	&		&	&	&			
100.0	$ &										&	$	&	&	$	&	$ &	&	$	$	$
133.3	$											$			$		$		$	$	$
166.7	$											$			$		$		$	$	$
200.0	$											$			$		$		$	$	$

(*)The experiments were carried out with $CaCl_2$ and (§) P_i, 25°C, 2% amino acid; P_i, 25°C, 4% amino acid; P_i, 37°C, 4% amino acid; (*) P_i, 37°C, 2% amino acid; ($) FDP, 25°C, 2% amino acid; FDP, 25°C, 4% amino acid; (&) FDP, 37°C, 2% amino acid; FDP, 37°C, 4% amino acid.

assessing the therapeutic safety of FDP in TPN and quantifying the limiting doses that can be applied in order to simultaneously meet recommended Ca and P requirements are lacking.

Therefore, the aim of this study was to establish the highest concentrations of $CaCl_2$ and FDP or Na_2HPO_4 that can be added to a nutritional solution containing amino acids, glucose, and electrolytes (but not lipids, because a lipid emulsion may obscure the presence of turbidity) without formation of a precipitate. Although we are aware that calcium chloride is generally not recommended as a Ca supplement in multiple electrolyte admixtures, we chose this salt instead of calcium gluconate in order to assess the compatibility profile of FDP under conditions favoring precipitation and in a physicochemical environment in which the occurring ionic equilibriums would not be complicated by the presence of high fractions of undissociated calcium. Furthermore, the use of $CaCl_2$ has allowed us to examine admixtures containing very high Ca concentrations (up to 200 mmol/L) that could not have been reached with calcium gluconate due to its limited aqueous solubility (about 70 mmol/L). The results of this investigation support wider use of FDP in TPN as a safe alternative to inorganic phosphates.

MATERIALS AND METHODS

The following parenteral nutrition solution components were used in the preparation of test solutions: Freamine III 8.5% (Clintec, Montargis, France), magnesium chloride, potassium acetate, glucose, dibasic sodium phosphate, calcium chloride (Merck, Darmstadt, FRG), d-fructose-1,6-diphosphate sodium salt (Esafosfina, Biomedica Foscama, Ferentino, Italy).

All the solutions were filtered with 0.22 μm filter (Millex-SLGS, 025 BS, Millipore, Bedford, MA) before the addition of P and Ca sources. Each final admixture was thoroughly mixed utilizing a vortex mixer and then submitted to visual inspection at $t = 0$ and after 1 hour and 24 hours under good illumination conditions and against a dark background to detect gross turbidity and precipitation. For the experiments assaying FDP, the solutions not obviously precipitated were submitted to particle counting (light blockage method, from 2 μm to 50 μm) using a C1000 Particle Analyzer (Climet, Redlands, CA).

The pH of the solutions was determined with a 682 Titroprocessor (Metrohm, Herisau, Switzerland) before and after the addition of P and Ca.

Aqueous solubilities of $FDPCa_2$ and $CaHPO_4$ were measured in saturated solutions at equilibrium by assaying FDP (ion-exchange HPLC with electrochemical detection) and inorganic phosphate (phosphomolybdate method with spectrophotometric reading at 660 nm), respectively, in the supernatant after centrifugation.

General Procedure

Eight separate sets of experiments were performed, each one including the assay of 49 test solutions disposed in a 7 × 7 matrix. Six different concentrations of $CaCl_2$ (obtained by the Latin square progression) and a blank containing no Ca were mixed with each of six similarly obtained concentrations of Na_2HPO_4 or FDP and a blank containing no P (Table I).

Both combinations of $CaCl_2$ + Na_2HPO_4 and $CaCl_2$ + FDP were assayed at the following conditions: (a) T = 25°C, 2% amino acid; (b) T = 25°C, 4% amino acid; (c) T = 37°C, 2% amino acid; and (d) T = 37°C, 4% amino acid. Every solution contained defined amounts of glucose (10% w/v), magnesium chloride (10 mmol/L), and potassium acetate (40 mmol/L).

In order to examine the effects of the dissociation status of both P sources on Ca-P salts precipitation, the initial pH of the solutions was adjusted to 6.50 for each experiment (a) and (b) and to 7.40 for each experiment

TABLE II
Maximum allowed concentrations of FDP or Na_2HPO_4 (visual inspection after 24 hours) in TPN solutions containing increasing amounts of $CaCl_2$ under different experimental conditions

	(a) T = 25°C, 2% amino acid, pH_{in} 6.5 (*)					(b) T = 25°C, 4% amino acid, pH_{in} 6.5 (*)					(c) T = 37°C, 2% amino acid, pH_{in} 7.4 (*)				(d) T = 37°C, 4% amino acid, pH_{in} 7.4 (*)			
FDP (mEq/L of P)	>200	>200	200	100	66.7	>200	>200	200	66.7	33.3	>60	>60	60.0	20.0	>120	>120	120.0	20.0
$CaCl_2$ (mmol/L)	5.00	6.67	33.3	66.7	100	5.00	10.0	33.3	100	200	2.50	5.00	16.7	33.3	1.67	5.00	16.7	33.3
Na_2HPO_4 (mEq/L of P)	4.45	2.22	<2.2	<2.2	<2.2	6.67	4.45	<4.4	<4.4	<4.4	2.22	1.11	<1.1	<1.1	6.67	2.22	<2.2	<2.2

(*) pH_{in} is the pH of solutions before the addition of P and Ca sources.

(c) and (d). Phosphorus and calcium solutions were then added, in that order,[12] and the resulting admixtures were finally brought to constant volume (16 mL) with filtered bidistilled water.

Statistical analysis was performed by fitting the precipitation curves against a simple mathematical model, ie, $[Ca] = K [P]^{-1}$, by assuming that for each [P] value the exact [Ca] threshold value for precipitation was between the highest [Ca] assayed with no visible precipitation after 24 hours and the lowest [Ca] with visible precipitation. These two concentrations were therefore entered as duplicate values, except for those threshold situations where a precipitate was judged to be present on the basis of particle count analysis but not from visual inspection: in that case a single [Ca] value was entered, as that point was assumed to be the closest to the actual threshold value. Due to the likely formation of soluble FDP complexes with Ca^{2+} at very high FDP concentration, the highest [P] values were not considered for the curve fitting. The calculated K values, which were taken as a quantitative measure of Ca-P compatibility in the different experimental conditions examined, are expressed as mean values and their 95% confidence intervals are reported.

RESULTS

The aqueous solubilities of calcium monohydrogen phosphate ($CaHPO_4$) and d-fructose-1,6-diphosphate dicalcium salt ($FDPCa_2$) were preliminarly checked at 25°C by conventional chemical analysis (assay of inorganic P and FDP, respectively, in the supernatant from a saturated solution), obtaining the values of 2.2 mmol/L and 2.4 mmol/L, respectively. However, due to the complexity of physicochemical interactions in solutions containing other electrolytes and different organic compounds,[13] these values cannot be taken as predictive of the behavior of Ca, inorganic phosphates, and FDP in TPN admixtures. Thus in the subsequent series of experiments, the pattern of precipitation of Ca-P salts as a function of $CaCl_2$ and Na_2HPO_4 or FDP concentrations was evaluated in simplified TPN solutions. Some parameters (ie, concentrations of glucose, magnesium ion,[14] and potassium acetate) were kept constant, whereas those recognized as being critical in promoting precipitation of calcium phosphates, such as amino acid concentration, temperature, and pH, were appropriately varied.[13]

The initial pH of solutions containing neither of the two minerals was adjusted to 6.50 for each experiment of the series (a) and (b) and to 7.40 for each one of the series (c) and (d) (see "Materials and Methods"). After addition of P and Ca sources and final dilution, the pH of the admixtures ranged from 5.04 to 7.04 and from 5.13 to 6.97 for the experiments of the series (a) and (b), respectively. It ranged from 5.34 to 7.21 and from 5.42 to 7.54 for those of the series (c) and (d), respectively. These pH changes were due to the different ionic equilibriums occurring after $CaHPO_4$ and $FDPCa_2$ precipitation (1 mol of HCl per mole of $FDPCa_2$ is produced, as $FDPNa_3H$ is the predominant species existing at pH near to neutrality; in contrast, no net hydrogen ion production occurs with $CaHPO_4$ formation) and to the intrinsic limited buffering capacity of the starting TPN admixtures.

Table II indicates the maximum concentrations of FDP and Na_2HPO_4 that can be mixed with different amounts of $CaCl_2$ without visible precipitation in the four sets of experiments. Compatibility of FDP greatly exceeds that of inorganic phosphate, as the ratios between the maximum allowed concentrations of the two P sources are always higher than 45, in terms of phosphate equivalents.

Figure 1 shows the Ca-P precipitation curves obtained for the two sources of P in the different experimental conditions examined. The areas to the right of each curve represent visual precipitation after 24 hours of incubation. The compatibility areas have been graphically exemplified for each P source by drawing rectangles having the upper right-hand corner in the correspondence with the maximal comparable concentrations of both minerals causing no turbidity in the worst-case scenario conditions, ie, for experiments carried out at 37°C and 2% amino acid. The compatibility area under such conditions for the admixtures containing $CaCl_2$ + Na_2HPO_4 is included within 2.50 mmol/L $CaCl_2$ and 2.22 mmol/L Na_2HPO_4 (area B). Two different areas were drawn for $CaCl_2$ + FDP, which are included within 33.3 mmol/L $CaCl_2$ and 10.0 mmol/L FDP (corresponding to 20.0 mEq/L of phosphate; area A_1), or within 16.7 mmol/L $CaCl_2$ and 30.0 mmol/L FDP (corresponding to 60.0 mEq/L of phosphate; area A_2).

Due to the formation of soluble complexes of amino acids with Ca and P, precipitation of inorganic calcium phosphate can be avoided to some extent by increasing amino acid concentration, thereby confirming previous findings.[13] In contrast, the pattern of precipitation of

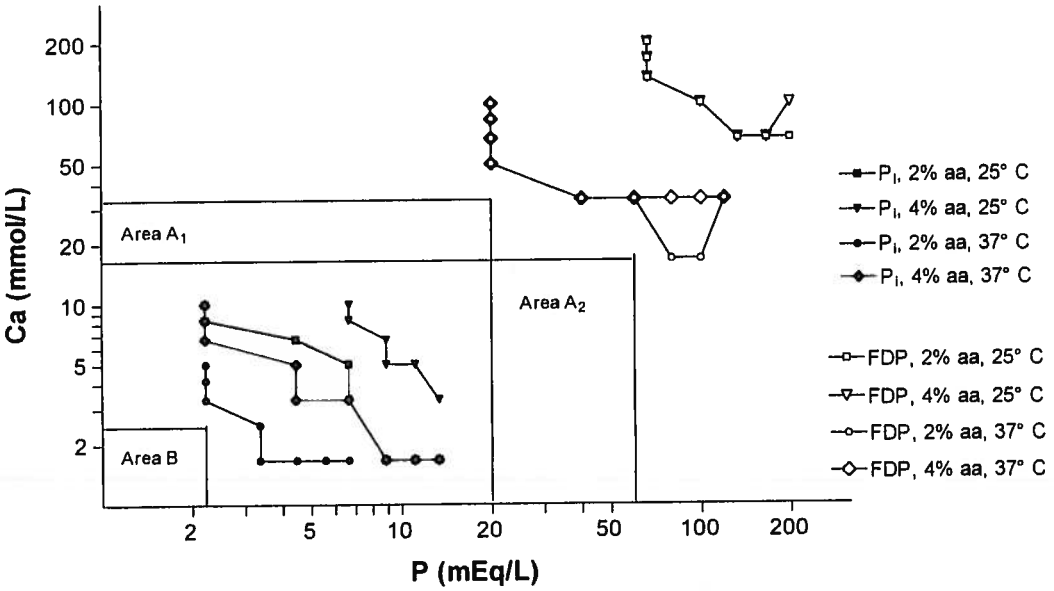

FIG. 1. Calcium (Ca)-phosphorus (P) precipitation curves and compatibility areas for TPN admixtures containing Na_2HPO_4 (P_i) + $CaCl_2$ or FDP + $CaCl_2$ (visual inspection). Areas A_1 and A_2: FDP/$CaCl_2$ compatibility areas; area B: P_i/$CaCl_2$ compatibility area. FDP, d-fructose-1,6-diphosphate; aa, amino acids.

$FDPCa_2$ at 4% amino acid was not much different from that at 2% amino acid, as evidenced by the extensive superimposition of the corresponding precipitation curves. For both P sources, precipitation was enhanced by the increase of temperature (as well as by pH increase, as $H_2PO_4^-/HPO_4^{2-}$ and tribasic/tetrabasic FDP equilibriums shifted toward the more ionized forms).

The kinetics of the precipitate formation were also examined. Visual inspection performed immediately after the addition of $CaCl_2$ and at 1 hour revealed that precipitation of $FDPCa_2$ is remarkably delayed in respect to that of $CaHPO_4$ (Fig. 2). This is an important finding from the physicochemical perspective that is likely to have *in vivo* relevance due to the short half-life of IV-administered FDP.

A limited number of solutions near the concentrations of FDP and Ca critical for precipitation were assessed again after adjusting pH toward the physiologic value. Thus admixtures containing 60 mmol/L FDP + 16.7 mmol/L $CaCl_2$ or 10 mmol/L FDP + 33.3 mmol/L $CaCl_2$ (4% amino acid, 37°C) remained stable for a minimum of 1 hour up to pH 7.40 (visual inspection). On the other hand, opalescence from solutions containing 30.0 mmol/L FDP + 16.7 mmol/L $CaCl_2$ or 10.0 mmol/L FDP + 33.3 mmol/L $CaCl_2$ (at 2% amino acid and 37°C; 1 hour of observation) was noticed from pH 6.75.

The determination of subvisible particles in FDP-containing solutions was carried out in the range 2 μm to 50 μm by an automated particle counting device. This was calibrated before use according to a certified electronic method using four spheric particle size standards of known mean diameter within the above range. The number of particles ≥ 10 μm and ≥ 25 μm in solutions containing FDP + $CaCl_2$ with no visible turbidity or opalescence was determined after 24 hours in comparison with the proper blank containing no Ca. With the exception of solutions containing 50.0 mmol/L FDP + 66.7 mmol/L $CaCl_2$ (2% amino acid, 25°C), 33.3 mmol/L FDP + 100.0 mmol/L $CaCl_2$ (4% amino acid, 25°C), and 30.0 mmol/L FDP + 16.7 mmol/L $CaCl_2$ (2% amino acid, 37°C), the difference between the number of particles ≥ 10 μm and ≥ 25 μm in the examined solutions and that in the blank was not greater than 50/mL and 5/mL, respectively. This indicating that no detectable precipitation of Ca-P salts occurred.

Except for FDP + $CaCl_2$ assayed at 4% amino acid and 37°C, each set of experiments resulted in a precipitation curve (as described in "Materials and Methods") fitting the equation $[Ca] = K\,[P]^{-1}$, where K may be taken either as the solubility product or as a measure of the compatibility area in those conditions. Calculated K values for the couple P_i + $CaCl_2$ under the experimental conditions (a), (b), (c), and (d) were 17.65 (95% confidence intervals: 13.48 to 21.83; $R^2 = 0.774$), 46.23 (40.37 to 52.08; $R^2 = 0.875$), 5.97 (5.19 to 6.74; $R^2 = 0.912$), and 12.59 (9.68 to 15.51; $R^2 = 0.780$), respectively. Whereas K values for FDP + $CaCl_2$ under the conditions (a), (b), and (c) were 7300.7 (6490.9 to 8110.5; $R^2 = 0.939$), 7264.4 (6408.3 to 8120.5; $R^2 = 0.933$), and 862.0 (623.7 to 1100.3; $R^2 = 0.713$).

Table III shows a comparison between maximal concentrations allowed for each combination of Ca and P sources and an estimate of the concentrations of both minerals needed to meet the daily requirements of premature infants, adults, and hypophosphatemic adults. The values for premature infants were calculated from the reported fetal accretion rates for Ca and P[15] by assuming 1 kg body weight and a daily fluid requirement of 120 mL/kg per day. The required mineral concentrations for adults were obtained from the appropriate parenteral Recommended Dietary Allowances (RDA)[16,17] by assuming 70 kg body weight and a daily fluid requirement of 35 mL/kg per day.

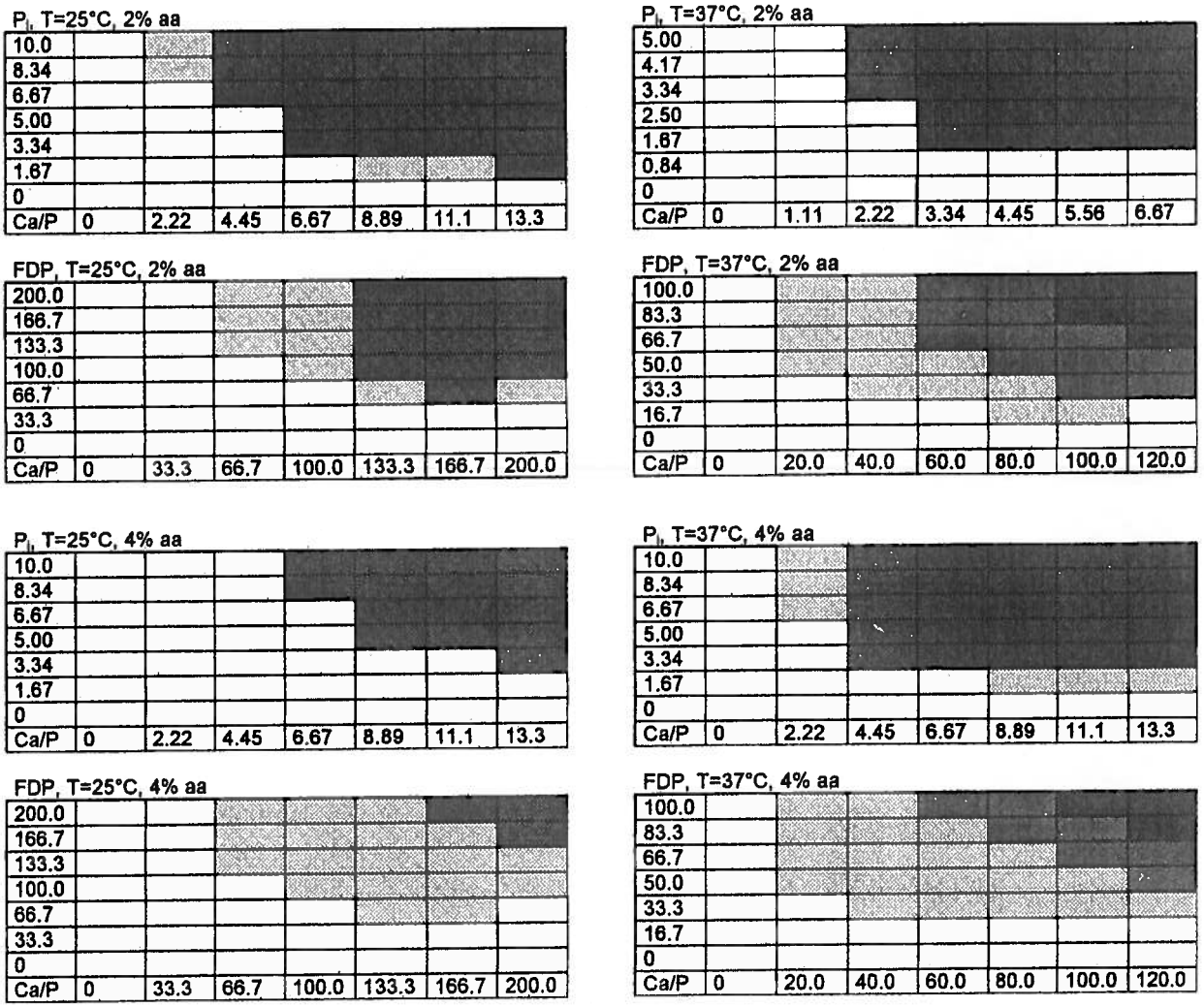

FIG. 2. Kinetics of calcium (Ca)-phosphorus (P) salts precipitation (visual inspection) for admixtures containing the couples Na_2HPO_4 + $CaCl_2$ and FDP + $CaCl_2$ under different experimental conditions. Turbidity was noticed from t = 0 (deep gray cells), t = 1 hour (gray cells), or t = 24 hours (light gray cells); Ca and P concentrations are expressed as mmol/L and mEq/L of P, respectively. FDP, d-fructose-1,6-diphosphate; T, temperature; aa, amino acids.

DISCUSSION

Due to the critical situation of patients requiring TPN therapy, avoidance of the risk of calcium phosphate precipitation and minimization of traumatic approaches is highly advisable. The Ca-P compatibility problem in TPN solutions is especially important in pediatric parenteral nutrition, because low-volume solutions containing relatively low concentrations of amino acids and high amounts of Ca and phosphates are a favorable environment for Ca-P salts precipitation. In addition, a number of complications seen in very-preterm infants (especially oliguria) need further fluid restriction in the presence of unaltered Ca and P needs. Although to a lesser extent, the same risk occurs in adult congestive heart failure patients necessitating a restricted fluid volume.

Different strategies have been proposed in order to avoid the danger of calcium phosphate precipitation.

TABLE III

Maximum allowed concentrations for the couples Na_2HPO_4 + $CaCl_2$ and FDP + $CaCl_2$ in TPN solutions and comparison with the approximate concentrations needed to meet the recommended daily intakes for different sets of patients (^)

	Max. conc. for Na_2HPO_4 + $CaCl_2$	Max. conc. for FDP + $CaCl_2$		Premature infant (§)	Adult (°)	Hypophosphatemic adult (°)
Ca (mmol/L)	2.50	33.3	16.7	29	2.0	4–6
P (mEq/L)	2.22	20.0	40.0	20	12.2	17–29

(^)The reported values for admixtures containing FDP are those where the number of subvisible particles found after 24 hours was within the limits specified in the text (see "Results"); for both P sources the values are drawn from the worst-case scenario conditions. (§) 1 kg body weight and a daily fluid requirement of 120 mL/kg have been assumed. (°) 70 kg body weight and a daily fluid requirement of 35 mL/kg have been assumed. conc., concentration.

Some clinicians suggested an alternate administration of calcium and inorganic phosphate in pediatric patients. However, this idea has been abandoned, because mineral retention and balance are better achieved with simultaneous administration of Ca and phosphates.[18] Other measures, such as lowering the pH or the temperature of TPN solutions, resulted in an enhancement of Ca-P solubility, but again with considerable drawbacks in terms of overall safety and poor clinical acceptance. In particular, concern has been expressed on the limited capacity for a metabolic compensation of an excessive acid load in immature infants.[15] The use of a 1.2 μm in-line filter was recommended by the FDA and the American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.)[19] as a protective measure against precipitation into the catheter during infusion. However, even the filters might be ineffective in preventing body heat–mediated catheter occlusion if they are distal to the site for TPN administration.[20]

An alternative approach based on replacing inorganic phosphate with a bioavailable organic P compound is being pursued, particularly in Europe and Canada.[21] Calcium glycerophosphate was positively assessed in a clinical trial in low-birth-weight infants in comparison with the conventional calcium gluconate plus inorganic phosphate mixture.[22] However, Ca and P could only be provided in a 1:1 molar ratio, thus hindering the design of tailored regimens.

Raupp et al[23] evaluated the Ca-P compatibility of sodium glycerophosphate and glucose phosphate in TPN solutions. They used calcium gluconate and relatively low magnesium concentrations, and these are the major differences from the experimental conditions adopted in the present study. Their data suggested that the use of these organic phosphates is a convenient and safe solution to the Ca-P compatibility problem in neonatal TPN. The *in vitro* Ca-P compatibility profile of FDP emerging from the present study is comparable with that of sodium glycerophosphate and glucose phosphate assessed by Raupp et al,[23] although the use of the less dissociable calcium gluconate in place of $CaCl_2$ would have resulted in further improved Ca-P solubilities for FDP.

It is well known that FDP is a high-energy glycolytic intermediate that bypasses the critical, adenosine triphosphate (ATP)–requiring step catalyzed by phosphofructokinase. Although the ability of exogenous FDP to cross cellular membranes has been questioned, *in vivo* animal and human studies indicated that FDP administration enhanced energy production and ATP generation in a number of severe pathologic conditions such as ischemia and shock (reviewed in ref. 10). Thus, unlike other sources of P, FDP might be of additional benefit in several debilitating clinical conditions requiring TPN support, provided that it can to some extent gain access into cells (as firmly suggested by a ^{13}C-nuclear magnetic resonance study in hog carotid artery showing ^{13}C-lactate production from exogenously applied [1,6-^{13}C]FDP).[24]

A high phosphate bioavailability and a positive P balance after IV administration of FDP during TPN in surgical patients have been observed.[25] This is in agreement with an *in vitro* study showing that the release of inorganic P after incubation of red blood cells with FDP is accompanied by a parallel increase of the intracellular P uptake.[26] However, further detailed studies examining phosphate intake and retention after FDP administration to specific subsets of patients are needed.

The data show that substitution of inorganic phosphates with FDP may overcome the safety issue of Ca-P salts precipitation in TPN admixtures, particularly when it is necessary to supply Ca and phosphate combinations at high concentrations and in the presence of a low amino acid content. Data reported in Table III show that differently modulated high requests of Ca and P can safely be satisfied using a TPN solution containing FDP (Fig. 1).

The use of FDP as a source of phosphate may simplify TPN handling of the solutions, save time, and provide a safe delivery. Furthermore, it prevents the Ca-P salts precipitation both at room temperature and in the critical step of body heating, when the check of the nutrient solution flowing into the vein is unfeasible. Additional advantages of FDP include its molar P content, which is twice that of inorganic phosphate, and the chemical stability of its neutral or mildly acidic solutions. Reconstituted FDP sodium salt 10% solution, pH 5.5 to 5.7, loses on average 0.28% of its content in active ingredient after 24 hours at 25°C in the dark.

Although FDP and other organic phosphates in TPN are approved and have been in clinical use in TPN in several countries, the use of inorganic phosphate is often recommended because of lower cost.[27] Today the ratio between the selling price of FDP *vs.* potassium phosphate in Italy is 4.4 (in terms of phosphate equivalents). Although the major cost of FDP is significant in absolute terms, its actual weight in relation to the overall cost of TPN therapies seems rather low. Furthermore, a wider use of FDP would most probably result in a reduced cost of the product and would obviate the need of frequently monitoring potassium plasma levels.

The results of this study therefore encourage a critical reevaluation of the above information, at least for those clinical situations where Ca-P incompatibility problems are suspected or foreseen.

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