DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

FDA SAFETY ALERT:

Hazards of Precipitation Associated with Parenteral Nutrition

To: Hospital Pharmacists
Hospital Risk Managers
Hospital Nutritional Support Teams
Home Health Care Nutrition Support Services
Hospital Directors of Nursing
Home Care Pharmacists
Home Care Nurses
Physicians

April 18, 1994

This is to alert you of a concern that precipitate formation in total parenteral nutrition (TPN) admixtures may present a life-threatening hazard to your patients.

The Food and Drug Administration has received a report from one institution of 2 deaths and at least 2 cases of respiratory distress, which developed during peripheral infusion of a three-in-one (amino acids, carbohydrate and lipids) TPN admixture. The admixture contained 10% FreAmine III, dextrose, calcium gluconate, potassium phosphate, other minerals, and a lipid emulsion all of which were combined using an automated compounder. The solution may have contained a *precipitate of calcium phosphate. Autopsies revealed diffuse microvascular pulmonary emboli* containing calcium phosphate. One literature report cites an adult case of subacute interstitial pneumonitis associated with calcium phosphate precipitates.[1]

TPN solutions are made according to a variety of formulations and compounding protocols. Thus, there are possibilities of calcium phosphate precipitates and many other chemical incompatibilities. Precipitates could develop because of a number of factors such as: the concentration, pH, and phosphate content of the amino acid solutions; the calcium and phosphorous additives; the order of mixing; the mixing process; or the compounder. The presence of a lipid emulsion in the TPN admixture would obscure the presence of any precipitate.

Because of the potential for life threatening events, caution should be taken to ensure that precipitates have not formed in any parenteral nutrition admixtures.

There is a medical need for the use of parenteral nutrition in some patients. Until data can be developed and validated to support specific recommendations for TPN preparation, the FDA suggests the following steps to decrease the risk of additional injuries:

1. The amounts of phosphorous and of calcium added to the admixture are critical. The solubility of the added calcium should be calculated from the volume at the time the calcium is added. It should not be based upon the final volume.

   Some amino acid injections for TPN admixtures contain phosphate ions (as a phosphoric acid buffer). These phosphate ions and the volume at the time the phosphate is added should be considered when calculating the concentration of phosphate additives. Also, when adding calcium and phosphate to an admixture, the phosphate should be added first.

   The line should be flushed between the addition of any potentially incompatible components.

2. A lipid emulsion in a three-in-one admixture obscures the presence of a precipitate. Therefore, if a lipid emulsion is needed, either: (1) use a two-in-one admixture with the lipid infused separately, or (2) if a three-in-one admixture is medically necessary, then add the calcium before the lipid emulsion and according to the recommendations in number 1 above.

   If the amount of calcium or phosphate which must be added is likely to cause a precipitate, some or all of the calcium should be administered separately. Such separate infusions must be properly diluted and slowly infused to avoid serious adverse events related to the calcium.

3. When using an automated compounding device, the above steps should be considered when programming the device. In addition, automated compounders should be maintained and operated according to the manufacturer's recommendations. Any printout should be checked against the programmed admixture and weight of components.

4. During the mixing process, pharmacists who mix parenteral nutrition admixtures should periodically agitate the admixture and check for precipitates. Medical or home care personnel who start and monitor these infusions should carefully inspect for the presence of precipitates both before and during the infusion. Patients and caregivers should be trained to visually inspect for signs of precipitation. They also should be advised to stop the infusion and seek medical assistance if precipitates are noted.

5. A filter should be used when infusing either central or peripheral parenteral nutrition admixtures. At this time, data has not been submitted to document which size filter is most effective in trapping precipitates.

   Standards of practice vary, but the following is suggested: a 1.2 micron air eliminating filter for lipid containing admixtures, and a 0.22 micron air eliminating filter for nonlipid containing admixtures.

6. Parenteral nutrition admixtures should be administered within the following time frames: if stored at room temperature, the infusion should be started within 24 hours after mixing, if stored at refrigerated temperatures, the infusion should be started within 24 hours of rewarming. Because warming parenteral nutrition admixtures may contribute to the formation of precipitates, once administration begins, care should be taken to avoid excessive warming of the admixture.

   Persons administering home care parenteral nutrition admixtures may need to deviate from these time frames. Pharmacists who initially prepare these admixtures should check a reserve sample for precipitates over the duration and under the conditions of storage.

7. If symptoms of acute respiratory distress, pulmonary embolus, or interstitial pneumonitis develop, the infusion should be stopped immediately and thoroughly checked for precipitates. Appropriate medical intervention should be instituted. Home care personnel and patients should immediately seek medical assistance.

These recommendations represent the best advice that the FDA can provide at this time. The FDA recognizes there may be alternative safety measures which could be taken to prevent the infusion of precipitates in TPN admixtures. The FDA has requested that industry develop and submit data that will be used to revise relevant labeling (instructions for use) to clarify these issues.

Practitioners who become aware of similar or other drug or device related deaths, serious illnesses and/or serious injuries are asked to notify the FDA. Please submit your reports to MedWatch, Medical Product Reporting Program, by phone at 1-800-FDA-1088 (also call for MedWatch information); by FAX at 1-800-FDA-0178; by modem at 1-800-FDA-7737; or by mail to MedWatch, HF-2, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857.

The Safe Medical Devices Act of 1990 (SMDA) requires hospitals and other facilities to report death, serious illness and injury associated with the use of medical devices. You should follow the procedures established by your facility for such mandatory reporting. Practitioners who become aware of any medical device related adverse event or product problem/malfunction should report to their Medical Device User Facility Reporting person. If it is not reportable under the SMDA, it may be reported directly to MedWatch.

If you have any questions regarding this Safety Alert, please contact Thomas J. McGinnis, RPH, Office of Health Affairs, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857; by phone 1-800-238-7332, or by FAX at 1-800-344-3332.

Sincerely yours,

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[1]Knowles, JB, et al, Pulmonary Deposition of Calcium Phosphate Crystals as a Complication of Home Total Parenteral Nutrition. JPEN, 13 (2), 209-213, 1989.