Approach to Parenteral Nutrition

Module 9.3

Compounding, Drugs and Nutritional Admixtures in PN

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Learning Objectives

• To know the different systems for parenteral nutrition; their advantages and limits;
• To know the risks associated with the compounding/ready-to-use preparation of AiO PN admixtures (GMP and potential incompatibility reactions) and the pharmacist’s tasks and responsibility for an admixing service;
• To understand the general advice not to admix drugs to PN AiO admixtures, unless documented or of a vital need;
• To understand to apply a risk assessment for adding an i.v. drug to an AiO admixture for both the influence of a drug on a PN admixture and the influence of a PN admixture on the fate of a drug.

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2. PN compounding and admixing
   2.1. Good Manufacturing Practice (GMP)
   2.2. Aseptic preparation technique
   2.3. Compatibility and stability aspects of AiO admixtures
   2.4. Drug admixing to an AiO PN formulation
3. Summary

Key Messages

• The all-in-one concept is a milestone in the search for safe, efficient, and convenient PN in acute and (home) long-term treatment. It has stimulated technical and pharmaceutical developments;
• Standard AiO regimes are used in most cases for PN treatment of adult patients in hospital acute care. Nevertheless, individualised and tailor-made PN admixtures are also needed to meet the specific nutritional requirements of children (growth), those with severe illnesses including organ failures, and patients on a long-term (home) PN. Well designed cost-effectiveness studies are still lacking;
• The compounding of AiO admixtures or the final ready-to-use preparation of industrial AiO premixes are critical pharmaceutical issues. Good manufacture practice (GMP) rules have to be respected when compounding AiO PN or admixing nutritional components and drugs. The pharmacist as the manufacturing supervisor has to take specific responsibility to guarantee quality and stability of ready-to-use prepared admixtures. As a nutrition support team member he has to define and implement standards of correct storage and handling of AiO admixtures. These standards must reflect professional state of the art practice;
• Because of their complex composition and the character of o/w emulsions, PN AiO admixtures have high and potentially harmful instability risks. Instability reactions include physico-chemical
incompatibilities and microbial instability due to incorrect aseptic manipulation technique both of which represent avoidable medication errors. The most important incompatibility and instability reactions in AiO admixture can be classified according to their physico-chemical reaction type: emulsion deterioration, lipid peroxidation, oxidation of vitamins, and formation of insoluble precipitates. Measures to avoid them therefore need pharmaceutical expertise and advice and depend on the characteristics of the pharmaceutical nutrient or drug concerned;

- AiO admixtures are not suitable as drug vehicles due to their complex formulation and the high potential for interaction in vivo and in vitro. If admixture of a drug is necessary, it is helpful to have a simple and easy to understand procedure for risk assessment, based on the degree of need for the medication and on the physico-chemical profiles of the AiO admixture and the drug.
1. Introduction

1.1 PN: From Separate Nutrient Infusion to the All-In-One Admixture

From its early beginnings, parenteral nutrition (PN) encountered multiple (pharmaceutical) challenges (1), (Table 1). Over the last 40 years PN has evolved technically from a difficult to handle multi-bottle (MB) system to a partial PN admixture, and eventually to an all-in-one admixture system. Ideally, an AiO PN admixture is administered in a single container containing the whole daily nutritional requirements through a single central i.v. line (2), (Fig. 1).

Table 1 Challenges in PN

<table>
<thead>
<tr>
<th>Type</th>
<th>Issue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parenteral formulation of nutrients</td>
<td>Pharmaceutical</td>
</tr>
<tr>
<td>Need for hypertonic solutions for volume limitation</td>
<td>Pharmaceutical</td>
</tr>
<tr>
<td>Long-term (central) venous access (catheters)</td>
<td>Technical</td>
</tr>
<tr>
<td>Practicability, efficacy, and safety of (long-term) PN</td>
<td>Medical, nursing care-related, pharmaceutical</td>
</tr>
<tr>
<td>Strict asepsis during compounding and administration</td>
<td>Pharmaceutical</td>
</tr>
<tr>
<td>Prevent/correct metabolic, physico-chemical disturbances</td>
<td>Medical, pharmaceutical</td>
</tr>
</tbody>
</table>

The large number of dissolved components in AiO PN mixtures forms a complex pharmaceutical formula which, even in vitro, has an important number of potential physico-chemical interactions (incompatibilities), which may adversely affect the stability of the mixture and its individual components. These pharmaceutical aspects have a major impact on the quality, safety, and effectiveness of PN (3, 4, 5).

The incompatibility issue becomes even more complicated if drugs have to be added to an AiO formula (6), (Fig. 2). Correct pharmaceutical advice is necessary to avoid incompatibilities to be seen as preventable medical errors.
Figure 2 Drug admixing to PN: Aspects of concern

Ready-to-use AIO admixtures fulfil stability requirements only under restricted and specific conditions of storage and administration; the main restriction is imposed by their limited shelf life of only a few days once all the ingredients have been added. This does not allow the large scale industrial preparation of fully ready to use AIO admixtures. The final ready to use product depends therefore upon the availability of a specialist compounding service, in hospital or centrally, with the capability of delivering the freshly compounded product to its site of use.

1.2 AIO Admixtures: Prerequisites, Benefits, and Limits

The specific needs of different nutrients in each patient lead to a small therapeutic index of a clinical nutrition formula in a given individual (Table 2).

<table>
<thead>
<tr>
<th>Table 2 PN Nutrient requirements</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Neonate</strong></td>
</tr>
<tr>
<td>Non protein energy</td>
</tr>
<tr>
<td>Basic metabolic rate</td>
</tr>
<tr>
<td>Growth</td>
</tr>
<tr>
<td><strong>Macronutrients [g/kg]</strong></td>
</tr>
<tr>
<td>Glucose</td>
</tr>
<tr>
<td>Triglycerides</td>
</tr>
<tr>
<td>Essential FA (C18:2)</td>
</tr>
<tr>
<td>Protein (aa pattern!)</td>
</tr>
<tr>
<td><strong>Electrolytes [mmoles/kg]</strong></td>
</tr>
<tr>
<td>Na</td>
</tr>
<tr>
<td>K</td>
</tr>
<tr>
<td>Ca</td>
</tr>
<tr>
<td>Mg</td>
</tr>
<tr>
<td>Phosphate</td>
</tr>
<tr>
<td>Water [ml/kg]</td>
</tr>
<tr>
<td><strong>Micronutrients (RDA) Vitamins</strong></td>
</tr>
<tr>
<td>Vit. A (retinol)</td>
</tr>
<tr>
<td>Vit D (cholecalciferol)</td>
</tr>
</tbody>
</table>
Vit. E (α-tocopherol) 10-15 μg
Vit. K 100-200 μg 10 mg (once a month)
Vit B1 (thiamine) 2-3 mg 3.5*
Vit B2 (riboflavin) 2-4 mg 5.7*
Vit B6 (pyridoxine) 3-4 mg 5.5*
Niacin 40 mg 46*
Vit B12 3-6 μg 6.0*
Folate 400 μg 400*
Biotin 60-75 μg 69*
Vit. C 100-150 mg 125*

Trace elements [μmol]

<table>
<thead>
<tr>
<th>Element</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iron</td>
<td>20-40</td>
</tr>
<tr>
<td>Zinc</td>
<td>50-100</td>
</tr>
<tr>
<td>Copper</td>
<td>5-20</td>
</tr>
<tr>
<td>Mangenese</td>
<td>3-5</td>
</tr>
<tr>
<td>Selenium</td>
<td>0.5 (-2.5)</td>
</tr>
<tr>
<td>Jodine</td>
<td>1</td>
</tr>
<tr>
<td>Chromium</td>
<td>0.2-0.5</td>
</tr>
<tr>
<td>Molybdenium</td>
<td>0.1-0.2</td>
</tr>
</tbody>
</table>

* given as Cernevit® in a separate piggy bag infusion

DGEM PN Guidelines in paediatrics (ESPGHAN) J Ped Gastro Nutr 2005;41:S1
NN in: Basics in clinical nutrition, 3rd edition, Galen/ESPEN, Prague 2004
Guidelines clinical nutrition, 3rd edition, Kantonsspital Aarau (Switzerland), 2005

For many patients, particularly those who are critically ill or receiving long term care at home (7, 8), the expertise of the pharmacist is therefore essential in order to provide tailor-made feeds appropriate to their clinical condition (9, 10), (Fig. 3).

Figure 3 Clinical Nutrition a multi-professional process

An experienced and flexible admixture service can cope with all the technical and administrative problems, since it runs under pharmaceutical supervision and has to comply with legal and technical requirements for manufacture (authority license in most countries). It can ensure the delivery of PN admixtures on time, and can provide the necessary quality assurance with documentation, correct labelling, and instruction for prescription, storage, and administration, all of which are mandatory (11-14).
A ready-to-use AiO PN system reduces major complications common in the early MB systems (Fig. 4):
- infectious complications;
- metabolic complications and reduced tolerance;
- mechanical complications;
- incorrect handling, erroneous administration of components (15);
- inconvenience and quality of life (multiple i.v. accesses and stop cock care, mobility);
- costs (morbidity, mortality).

![Figure 4 Risks associated with PN](Image)

Therefore, with few exceptions, AiO admixtures provide the ideal form of PN. Neonates with their need for incompatible amounts of nutrients (electrolytes etc.) are a notable exception.

### 1.3 Industrial PN Admixtures: The Multi-Chamber Bag
The high capital cost of equipment and the labour intensive nature of the work have stimulated technical developments in PN, including new delivery systems, in the search for higher efficiency. New plastic materials for containers like ethyl-vinyl-acetate (EVA), suited for lipid-containing AiO PN admixtures, have replaced extractable-containing PVC for PN bags. Compounding machines facilitating the filling of bags, and systems for the documentation and labelling of individual AiO admixtures have all been developed and used in compounding centres (Fig. 5).

![Figure 5 PN compounding with a filling machine](Image)
Stable 2:1 PN admixtures containing amino acids, glucose, and electrolytes have been produced commercially. These concentrated aqueous solutions were infused in parallel with a bottle of lipid, representing the first advance from the multi-bottle system, reducing the risks of PN (Fig. 6).

<table>
<thead>
<tr>
<th>Amino acids</th>
<th>Glucose</th>
<th>Lipid</th>
<th>Two in one Admixtures</th>
<th>All-in-one (3 in 1) admixtures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bottles with single components</td>
<td>Bottles with combined components</td>
<td>+</td>
<td>++</td>
<td></td>
</tr>
</tbody>
</table>

Ready-to-use: (-) (+) + ++

Figure 6 PN delivery systems

The next advance was the sterilised multi-chamber bag system with each of the macro-nutrients in its own compartment with a basic profile of electrolytes (16). Protective wrapping with air-tight plastic foils allowed an extended shelf life of these AiO premixes over many months. Industrial production of near complete standard AiO admixtures or premixes (Fig. 7) was therefore possible. Before use, the seal between the chambers is broken and the components are mixed together mechanically within the outer bag container in a closed system (asepsis).

Figure 7 PN multi-chamber bag

Additional nutrients, electrolytes, or oligo-elements may be added according to defined aseptic admixing procedures. Compatibility and stability data have then to be provided during the final storage and administration periods, relying on appropriate physico-chemical analyses to guarantee the safe use of these admixtures.

In hospitals, such standard PN regimes are used in most adult patients (17). Comparing the use of individually compounded or commercial PN multi-chamber admixtures, only small differences in the amount of nutrients administered were seen; both systems respecting current recommendations.

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However, patients with specific and changing nutritional requirements, such as children or patients on long-term home-PN (8) (Table 2), are dependent on tailor-made and individualised PN admixtures (18). A PN compounding/admixing service is still needed to treat such patients and for the final preparation for use of AiO premixes. Economical and ergonomic studies to evaluate cost effectiveness of the different PN systems and their overall benefits and limits are few (19), (Fig. 8).

Figure 8 Workload related to PN

2. PN Compounding and Admixing

2.1 Good Manufacturing Practice (GMP)

Ready-to-use AiO PN admixtures are complex pharmaceutical formulations with only limited stability and shelf life. After compounding or admixing any ready-to-use AiO feed, a final analytical quality testing is difficult to carry out, because they are often used immediately after prescription and ordering. Process documentation and validation are, therefore, most important for quality assurance of an admixture service (site master file). Standardisation of feeds using a small range of tried and tested formulae is helpful and meets the needs of most patients safely and effectively. Feeds may be administered flexibly for varying lengths of time, depending on circumstances, e.g. 12 hours overnight for home TPN. Electronic support for prescription, preparation (Fig. 5), administration, and monitoring reduces errors, facilitates documentation and monitoring, and saves time.

To run a compounding and admixing unit, the responsible pharmacist has to adhere to the legal requirements for manufacture and distribution. Proper organisation, protocols and technical measures are the key to the manufacture of good quality products and to their safety of use. The Swiss Pharmacopoeia has established rules for GMP in pharmaceutical small scale production (13) which has been legally enforced since 2005. Different professional bodies of hospital pharmacists have issued similar guidelines defining pharmaceutical tasks in PN compounding (14). An international guideline of the Pharmaceutical Inspection Convention has drafted, based on the relevant chapter of the Swiss pharmacopoeia. The main features of GMP are presented in (Fig. 9).
The site master file is the main document of reference. Self assessments, critical incidence and error analyses, and inspections by authorities allow the maintenance of a high safety level and help to prevent errors in pharmaceutical manufacture. Regular training and updating of the pharmaceutical personnel in charge is mandatory to keep expertise and practical knowledge at the required level.

2.1 Aseptic Preparation Technique

A ready-to-use PN AIO admixture is a large and complex formulation, which has to be sterile and pyrogen-free. Because of the reactivity of heat-labile components in ready-to-use PN - fat emulsion, vitamins, different amino acids etc. - final sterilisation by heating is not possible a strict aseptic procedure must therefore be followed throughout the whole PN compounding/admixing process to avoid any microbial contamination. The use of sterile components and devices for admixing and compounding, protection of the working area from contamination, and special training and qualifications of the operators are essential. Measures include:

- for the preparation zone: clean room type A requirements;
- for the operators: compliance with operation procedures (SOP);
- for the compounding/admixing activities: defined and validated processes.

A clean room area type A or class 100 is needed (max. 3500 particles $\geq 0.5 \mu m$, max. $20 \geq 5 \mu m$ per m$^3$ air). This can be achieved using a suitable laminar airflow (LAF) cabinet (Fig. 5) or isolator. Cleaning and disinfection of the working surface and of the materials must be carried out and correct working procedures have to be defined and validated. The function of the LAF or isolator has to be monitored and tested at regular intervals.

The performance of the aseptic admixing processes has to be validated by media fills based on a risk plan. The qualification and the performance of the operating personnel have to be checked and documented. Regular and individualised practical training sessions with assessments, have to be scheduled and documented, including instruction in measures to prevent contamination, such as personal hygiene, special clothing, and wearing of sterile gloves (13), (Fig. 5).

This clearly demonstrates the need for specifically educated (pharmaceutical) staff in a compounding unit, and their supervision by an experienced pharmacist.

To minimise infectious complications in patients at risk, the use of inline filters for PN administration is recommended in some cases (2). To eliminate bacteria from a contaminated PN admixture, a pore size of 0.22 $\mu m$ should be used for lipid-free 2:1 admixtures and one of 1.2 $\mu m$ for lipid-containing preparations since fat droplets exceed the 0.2 $\mu m$ filtration size (2.3.1). Although, therefore, both pore sizes are effective in removing precipitates, they are not equally effective against bacteria. (2.3.3). Additional problems may occur like filter adsorption of admixed
low dosed components or filter occlusion interfering with the administration of the feed. The use of filters should therefore be restricted to high risk patients.

2.1 Compatibility and Stability Aspects of AiO Admixtures

2.1.1 O/W Emulsion (Physical Stability)
A typical AiO PN admixture contains some 40-50 dissolved components (Table 2); it is an oil-in-water emulsion due to its lipid content.

Safe and well tolerated i.v. fat emulsions have a fat droplet size distribution similar to chylomicrons with a physiological upper limit of particles size at about 5\( \mu \)m (small blood vessel diameter). The emulsion stability is labile and has a high potential for incompatibilities causing ‘oiling out’ (Fig. 10), an important safety issue. In the presence of high concentrations of di- and tri-valent cations (electrolytes, trace elements) bridges with the negatively charged emulsifiers (lecithin) are formed and decrease the negative surface potential of the lipid droplets (retracting forces).

![Figure 10 Lipid emulsion destabilisation](image)

As a consequence, oil droplets can aggregate and fuse (coalescence). It should be remembered that a divalent cation e.g. Ca++ has 60 times the destabilising effect of a monovalent cation e.g. Na+. An increase in proportion of the large diameter oil droplets occurs and impairs the dispersion of the chylomicron-like lipid emulsion (20). Large diameter oil droplets (>5\( \mu \)m) may harm the patient by causing occlusion (embolisation) of small blood vessels.

As well as optical sensing methods (light obscuration), even standardised microscopic methods are able to detect early deterioration of a lipid emulsion even at the upper tail of the droplet distribution curve and are useful low-cost stability control methods in a pharmacy-based compounding unit (21). Different lipids (22) and amino acids (Fig. 11) may have a profound influence on the emulsion stability of all-in-one admixtures and have to be tested individually. Other factors affecting the emulsion stability include pH, increased temperature, and local (high) concentrations of admixed electrolytes (correct sequence of component admixing!). Therefore, lipid should always be added last to an AiO admixture. Electrolyte and trace elements should never be admixed directly into a lipid emulsion (as starting material for compounding or as a compartment of multi-chamber bags). Divalent cations are added to amino acid solutions for possible complexation and have less incompatibility effect on maximal dilution.
2.1.2 Lipid Peroxidation and Oxidative Loss of Vitamins (Chemical Stability)

Lipid peroxidation (LPO) is a chemical instability reaction with potentially harmful reaction products (radicals) which occurs in lipid-containing PN admixtures (Fig. 12). LPO has to be assessed when testing the stability of AiO admixtures during storage or the addition of trace elements (23). Appropriate storage conditions (2-8°C, light protection) and the admixing of trace elements (catalytic action) just prior to administration reduces the extent of LPO considerably.

The extent of LPO correlates with the fatty acid profile; the higher the polyunsaturated fatty acids (PUFA) content, the higher the likelihood of peroxidation: soybean oil / fish oil (>60% PUFA) > LCT/MCT (∼40%) > olive oil (∼20%) (22). Antioxidants (vitamin E and C) in appropriate concentrations have a protective effect (24).

LPO and the formation of reactive radicals are dependent on the presence of oxygen containing air in the admixture. Cover wrapping with air-tight plastic foils or oxygen absorber during storage or the use of poly-laminated container material with better gas barrier resistance compared to EVA reduces considerably losses of nutrients prone to be degraded by oxidation (PUFA, vitamin C and E) (16, 25).
In the absence of stability data and because of mutual interactions the oligo-elements i.e. vitamins and trace elements should be injected separately into the feed bag; they should not be combined before being added because of mutual vitamin and or trace element interaction and inactivation e.g. between Fe and vitamin C (2).

2.1.3 Electrolyte Precipitations (Physical Stability)
Beside incompatibilities influencing the emulsion stability of an AiO admixture, precipitates of electrolytes, trace elements or drugs dissolved as salts may be formed when incompatible concentrations of cations and anions are present. This is crucial, for example, with calcium and (inorganic) phosphate. The formation of low soluble Ca-monohydrogen-phosphate ($pK = 7.2$) depends on the pH. Even small changes of an AiO admixture’s pH or a slight increase in temperature may trigger precipitation (Fig. 13). In such cases an inline filter may not prevent infusion of precipitates, because the precipitate may be formed on the patient side of the inline filter as the admixture is warmed by the patient’s body. The lipid component of an AiO admixture will conceal this form of precipitation.

![Figure 13 Calcium phosphate precipitation](image)

The use of organic phosphate may be an alternative way of avoiding solubility problems with Ca and phosphate, especially in neonates with their high requirements for these elements (26) (Fig. 13). As emphasised above, a well defined admixing sequence is mandatory to avoid precipitation due to incorrect dilution of nutrients during compounding (preventable medical error).

2.2 Drug Admixing to AiO PN Formulation
Due to the complex composition and formulation of AiO admixtures, they are not really suitable vehicles for drug administration. Numerous incompatibility reactions can occur between a large numbers of potential candidates (Fig. 2). In addition there is an increased risk of contamination from any additional manipulations (Fig. 4).

During acute illness most patients need additional i.v. infusions, apart from PN, for the administration of substrates and drugs. For these purposes, a multi-lumen catheter, for the separate administration of drugs and nutrients, should be inserted, reserving one lumen for the feed.

In chronic and long-term PN it may be necessary to add an essential drug to the mixture in order to avoid repeated and separate infusions with their associated risks. In such situations specific stability and compatibility testing are mandatory. Even drugs with apparently identical active ingredients may differ in pH or other characteristics between different manufacturers and this may have important effects on compatibility. A literature analysis alone can therefore be misleading and practical lab analyses are mandatory in each case.
For drugs with small therapeutic indices (critical dose drugs) bioavailability of the drug admixed may be critical and should be determined (6).

Lipophilic drugs may distribute into the lipid moiety of the AiO admixture, affecting their bioavailability. Interactions with solubilizers have also to be considered. I Interactions e.g. with lecithin may modify drug release and give different drug kinetics, thereby influencing pharmacological dose-response.

Metabolism of the nutrients themselves, e.g. lipid clearance, may also be affected by such interactions. An investigation made with Cremophor-solubilized cyclosporin showed reduced hydrolysis of LCT in a lipase in vitro model (Fig. 14). Although physico-chemical analyses of both cyclosporin and the AiO fat emulsion, respectively, showed no pharmaceutical instability, there were interactions on free fatty acid release with potentially important effects in vivo (6, 27).

Figure 14 Drug nutrient interaction

A practical approach to risk evaluation of mixing drugs with AiO PN feeds is given in Table 3 (6).

<table>
<thead>
<tr>
<th>Order</th>
<th>Questions</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1&lt;sup&gt;st&lt;/sup&gt; step: need for i.v. medication</td>
<td>Need for this medication and for the i.v. route?</td>
<td>Alternative formulations may be used</td>
</tr>
<tr>
<td>2&lt;sup&gt;nd&lt;/sup&gt; step: need for concomitant administration (admixing in AiO PN)</td>
<td>Alternative i.v. access or an intermittent administration? Multi-lumen catheters should be advised in acute care PN patients. Patient on long-term (home) cyclic PN allows intermittent drug administration with sufficient rinsing fluid</td>
<td></td>
</tr>
<tr>
<td>3&lt;sup&gt;rd&lt;/sup&gt; step: profile of the drug</td>
<td>Therapeutic index of the active ingredient? (critical dose drugs)</td>
<td>No admixing in absence of evidence (documentation, own lab data) for compatibility and stability</td>
</tr>
</tbody>
</table>

Physico-chemical characterisation of the drug product (4)? (solution type, pH, pK, excipients, osmolality) cave low or high pK
Incompatibility to be expected?
(cation interacting with lipid emulsifier, e.g. heparin)

Questions 1-3 no obstacle?
No obvious incompatibility or interaction with the PN component reported?
Easy testing possible? (pH changes, visual examination, lipid droplet assessment)

Aseptic admixing in the appropriate starting solution.
Appropriate sequence of admixing and dilution.
Protective measures: light protection, inline filter, instruction and labelling.

Summary

All-in-one admixtures are safe, efficient, and convenient. The mixture of tailor made feeds or the pre-use preparation of commercially available multi-chamber All-in One bags needs expert pharmaceutical input and supervision; GMP rules apply. Good storage/handling practices prevent instabilities/incompatibilities. Admixing drugs is risky and should only be carried out when absolutely necessary and by expert pharmacy staff.

References


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