Module 9.3

Compounding and Ready-to-use Preparation of PN: Pharmaceutical Aspects. Compatibility and Stability Considerations; Drug Admixing

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Learning Objectives

- To know the different systems for parenteral nutrition (PN), tailor-made PN admixtures and ready-to-use industrial multi-chamber bag (MCB) PN admixtures and their advantages and limits;
- To know the risks associated with the compounding/ready-to-use preparation of All-in-One (AiO) PN admixtures (Good Manufacturing Practice (GMP) and potential incompatibility reactions, medication errors) and the pharmacist's tasks and responsibilities for an i.v. admixing service;
- To understand the general advice not to admix drugs to PN AiO admixtures, unless documented to be safe;
- To apply a risk benefit approach for adding i.v. drugs to an AiO admixture respecting both the influence of a drug on a PN admixture and the nutrient metabolism and the influence of the PN admixture on the fate of a drug.

Contents

Key Messages

- The all-in-one concept with an almost complete portion of daily i.v. nutrients represents a milestone achievement for safe, efficient, and convenient PN in acute and long-term (home) treatment. It resulted from pharmaceutical, technical and industrial development, as well as clinical research and development;
- Standard AiO regimens are used in most cases for adult patients in acute hospital care. Nevertheless, individualised and tailor-made PN admixtures are sometimes needed to meet the specific and changing nutritional requirements of particular patients, which may include some patients in intensive care, children (because of growth) and patients on long-term (home) PN. Well designed and current cost-effectiveness studies on PN, its formulation and positioning in nutrition management are scarce;
- 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 for compounding AiO PN or admixing components or drugs. The pharmacist as the manufacturing supervisor has specific responsibility to guarantee quality (stability) of ready-to-use prepared admixtures. As a nutrition support team member he has to define and implement standards for their correct labelling, storage, and handling to guarantee the safety and efficacy of PN through professional best practice**;**
- Because of their complex composition and the oil in water (o/w) emulsion character, AiO PN admixtures have high potential for interactions including potentially harmful stability risks. They include physicochemical incompatibilities and microbial instability due to incorrect aseptic manipulation. Such interactions represent avoidable medication errors. The most important incompatibility and instability reactions in AiO admixtures can be classified according to their physicochemical reaction type: emulsion deterioration, chemical degradation reactions like lipid peroxidation or oxidation of vitamins, and formation of insoluble precipitates. These reactions depend on the characteristics and composition of the PN admixture, on substrates added (nutrients, drugs), the container materials and specific ambient conditions like temperature, pH or light exposure. Measures to avoid them need pharmaceutical expertise and advice including specific laboratory analyses and data interpretation;
- AiO admixtures are not suitable drug vehicles due to their complex formulation and the high potential for interactions both in vitro and in vivo rendering it difficult to assess safety and efficacy of a therapeutic/nutritional treatment. If admixing of a drug to an AiO admixture is necessary, it is important to use a formalized risk assessment including an evaluation of the medical need for a co-medication with PN, and the pharmaceutical profile of the AiO admixture and the drug involved.

1. Introduction

1.1 PN: from Separate Nutrient Infusions to the All-in-one (AiO) Admixture

From its early beginnings in 1960, parenteral nutrition (PN) practice encountered numerous (pharmaceutical) challenges (1), (**Table 1**). The technical development of PN, the improved knowledge and monitoring of disease-specific metabolism together with the clinical evidence from studies showed the life saving or life supporting value of PN, if appropriately used, in a variety of indications.

Table 1
(Pharmaceutical) Challenges in PN (1, 5)

Type	Issue
Parenteral formulation of nutrients	Pharmaceutical
Need for hypertonic solutions for volume limitation	Pharmaceutical
Long-term (central) venous access (catheters)	Technical
Practicability, efficacy, and safety of (long-term) PN	Medical, nursing care-related, pharmaceutical
Strict asepsis during compounding, ready to use preparation and administration, compatibility issues of PN with other IV therapy	Pharmaceutical
Prevent/correct metabolic, physicochemical disturbances	Medical, pharmaceutical

PN allows gastrointestinal failure to be overcome or permits nutritional goals to be reached when enteral nutrition alone is not able to provide the necessary nutrients. From the difficult to handle multi-bottle (MB) system to a partial PN admixture, and eventually to an all-in-one admixture system, the latter is revealed as an almost universally applicable, easy to handle, safe, ergonomic and economic form of clinical nutrition; it is almost a prerequisite for home PN (2). Ideally, an AiO PN admixture is administered in a single container containing the whole daily nutritional requirements administered through a single (central) i.v. line over a sufficiently long period of time to be well tolerated. The high osmolality of $\geq$ 2000 mOsm/kg of a typical adult PN (**Fig. 1**) requires (sometimes long-term) central venous access. For specific, short-term supportive nutritional care, partial PN with less concentrated solutes and therefore lower osmolarity (850 mOsm/L at maximum) may be peripherally applied.

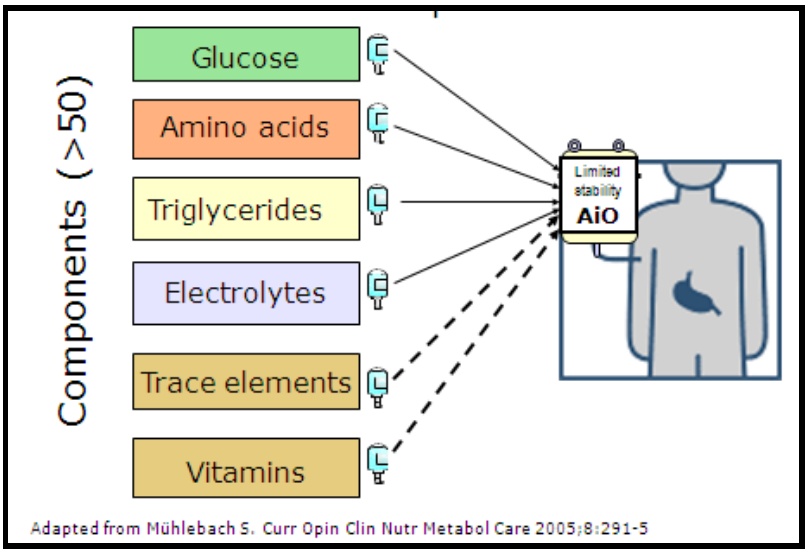

Fig.1 The AiO admixture concept

The osmolarity of peripheral PN has to be checked when adding electrolytes according to daily requirements (**Table 2**). The PN composition and administration rate have to be customized to incorporate the i.v. nutrients according to patients' individual nutritional needs. This could yield a patient-specific individually compounded formulation, e.g. in long-term PN use or when administering nutrients as pharmacological active ingredients (pharmaconutrients, nutraceuticals).

Table 2
Osmolality increase by adding daily electrolyte portions in iv fluids (4)

Electrolite	Standard PN (mmol/day)	Salt form	Daily dosage mosmol (theopetical)
Na^+	80 – 100	NaCl	160 – 200
K^+	60 – 150	KH_2PO_4	180 – 450
		KCl	120 – 300
Ca^{++}	2.5 – 5	$CaCl_2$	7.5 – 15
		Ca (organ.)	2.5 – 5
Mg^{++}	8 – 12	$MgSO_4$	16 – 24

Therefore, the pharmaceutical characteristics of an intended ready to use AiO admixture may require support from the NST pharmacist to get the right preparation for the right patient, in the right form at the right time. PN is most often supplementary to enteral nutrition. PN guidelines exist in a disease/organ-specific approach (eg ESPEN (3)) and in a more form-related approach (eg German Society of Nutritional Medicine (4)) or CG32 guidelines from NICE (5).The large number of components in AiO PN admixtures creates a complex pharmaceutical formulation with only limited stability due to a number of different physicochemical interactions (incompatibilities), which may adversely affect the stability of the mixture and its individual components not only in vitro but also in the biodisposition in vivo. These pharmaceutical aspects have a major impact on the quality, safety, and effectiveness of PN and form a specific responsibility for the pharmacist in the multi-professional nutrition support team [NST] (6-10).

The interaction issue becomes even more complicated if drugs have to be added to an AiO formula (6) (**Fig.2**).

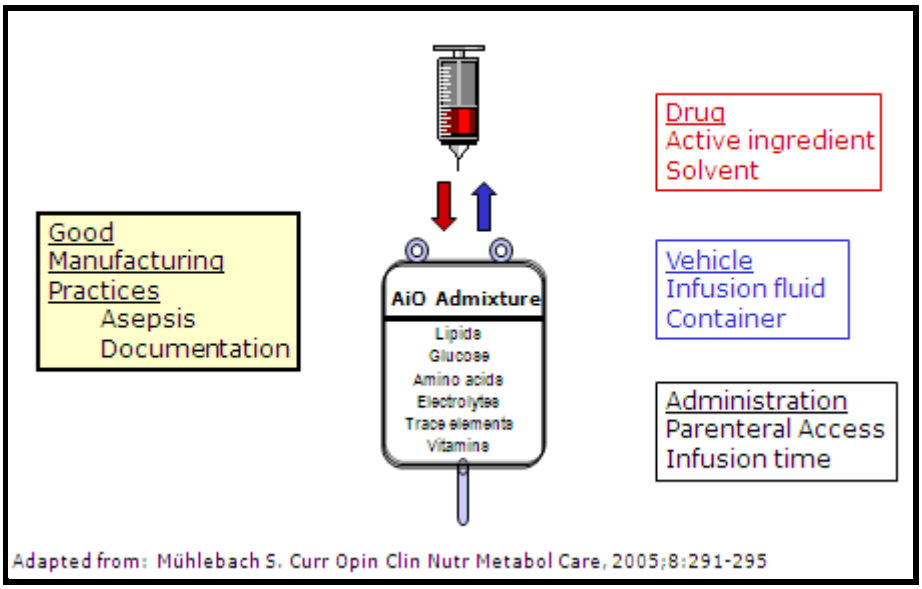

Fig. 2 Drug admixing to PN: Aspects of concern

Correct pharmaceutical advice is necessary to avoid incompatibilities occurring and being seen as preventable medical errors (11-14). In contrast to binary lipid-free PN admixtures or electrolyte-free lipid emulsions (15), ready-to-use AiO admixtures fulfil stability requirements only with restricted and specific conditions of storage and administration; the main limitation is imposed by their limited shelf life of only a very few days or less once all the components have been added. This does not allow the large scale industrial preparation of ready-to-use of AiO admixtures but allows us to have stable AiO premixes which are completed and prepared for administration immediately before use. The final ready-to-use product needs therefore the availability of a compounding or IV admixture service, e.g. in the hospital pharmacy, allowing delivery of the ready-to-use product on time to the right site of use, and with assurance of appropriate quality.

1.2 AiO Admixtures: Prerequisites, Benefits, and Limits

The specific needs for different nutrients in the individual patient vary according to the clinical state (intermediate metabolism), the overall nutritional intake and the potential side effects of PN. This leads to a rather small therapeutic index for an AiO nutrition formula in a given individual. Additionally different nutrients show pharmacological effects able to modulate the metabolic or the inflammatory status (pharmaconutrients, like certain amino acids (glutamine), ω-3 essential fatty acids or microelements like antioxidants) and can be used for therapeutic reasons. Therefore, standard regimens are mainly indicated for short periods of use but still have to be customized (**Table 3**). This highlights the importance of good monitoring of the patient and the experience of the NST to prevent or treat PN-related complications (3). For many patients, particularly those who are in unstable conditions (critically ill) or receiving long term care at home, the PN regimen has to be adapted. Then, the expertise of the pharmacist in the nutrition support team with access to an experienced admixture service is essential to provide more specific or tailor-made feeds (16-20) (**Fig. 3 and 4**).

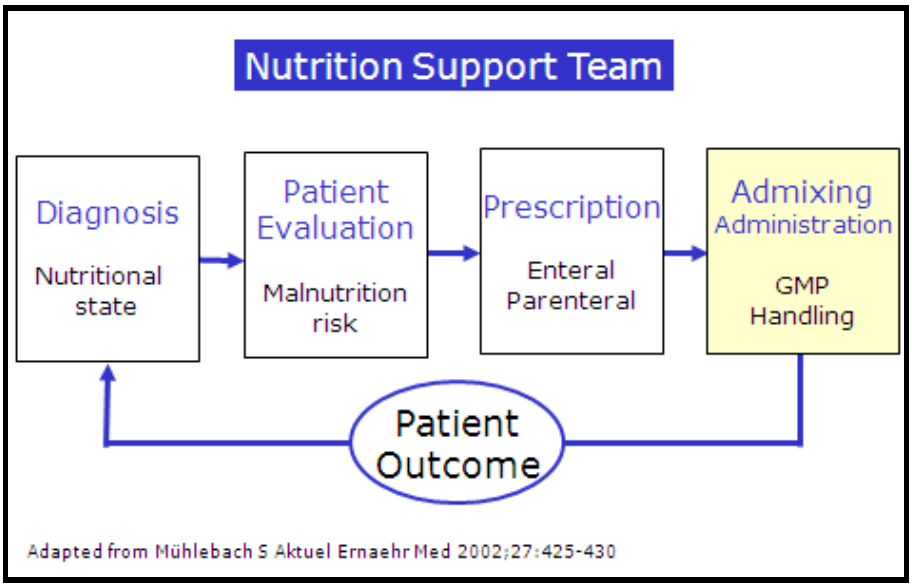

Fig.3 Clinical nutrition: a multi-professional process

Fig. 4 Aseptic PN compounding in a laminar air flow (LAF) cabinet using a (vacuum) filling machine

The i.v. admixture service runs with pharmaceutical supervision and must comply with legal, technical and professional aspects for manufacturing (authority license and regular inspections in most countries). It has to ensure the delivery of PN admixtures on time with

the necessary quality assurance, the correct labelling, and with provision of the important instructions for prescription, storage, and administration (4, 21).
Ready-to-use AiO PN prepared in compliance with Good Manufacturing Practice (see below) is a cornerstone in reducing the major complications that were common in the early days of PN (MB systems) (**Fig. 5**):

- infectious complications
- metabolic complications and reduced tolerance
- mechanical complications (catheter occlusion)
- deteriorated admixtures (instabilities): toxicity
- medication errors: incorrect handling, erroneous administration of components (22)
- inconvenience and low quality of life (multiple i.v. accesses and stop-cock care, mobility)
- costs (product costs (PN admixture), morbidity, mortality)

• Infective	Microbial contamination *aseptic compounding/admixing: GMP*
• Metabolic	Nutrient administration / tolerance *PN-associated hyperglycaemia, refeeding syndrome, bone loss*
• Mechanical	catheter occlusions *Compounding/admixing incompatibilities: precipitations*
• Toxicity	Harmful (reactions) products: *lipid (PUFA) and liver dysfunction* *emulsion deterioration; lipid peroxidation*
• Errors	wrong products/dosing/timing *incorrect ready-to-use preparation*
• QoL	Manipulations, patient care *number of i. v. accesses, stop cocks management, mobility, Home PN (QoL)*
• Costs	Cost effectiveness *Standards, multi-chamber bags*

Fig. 5 Risks associated with PN

Therefore, complete AiO admixtures provide the ideal and most feasible form of PN. Neonates with their need for high and incompatible amounts of nutrients (electrolytes etc.) are notable exceptions.

1.3 Industrial PN Admixtures: the Multi-chamber Bag, Its Use Customization (Labelling!) and Limits

The high capital cost of compounding equipment (aseptic manufacture) and the labour-intensive nature of the work (**Fig. 4**) has stimulated technical development in PN. This included new delivery systems, and a need for industrial production to get more stable, safe and easy to handle PN admixtures. Plastic materials for PN containers such as ethyl-vinyl-acetate (EVA) foils were, in contrast to extractable PVC-containing bag materials, suited for lipid-containing AiO PN admixtures, but permeable to air and therefore unable to protect the content from oxidation (a stability issue, see below). Compounding machines facilitating the filling of bags from individual starting solutions, documenting the composition, and also labelling the compounded AiO bag were introduced in compounding centres (**Fig. 4**).

Stable 2 in 1 PN admixtures containing amino acids, glucose, and electrolytes have been produced commercially. Such concentrated aqueous solutions were often infused in parallel with a bottle of lipid, representing progress compared to the multi-bottle PN system and reducing also the risks of less effective PN by better parallel infusion of energy (carbohydrate) together with amino acids for protein synthesis (**Fig. 6**).

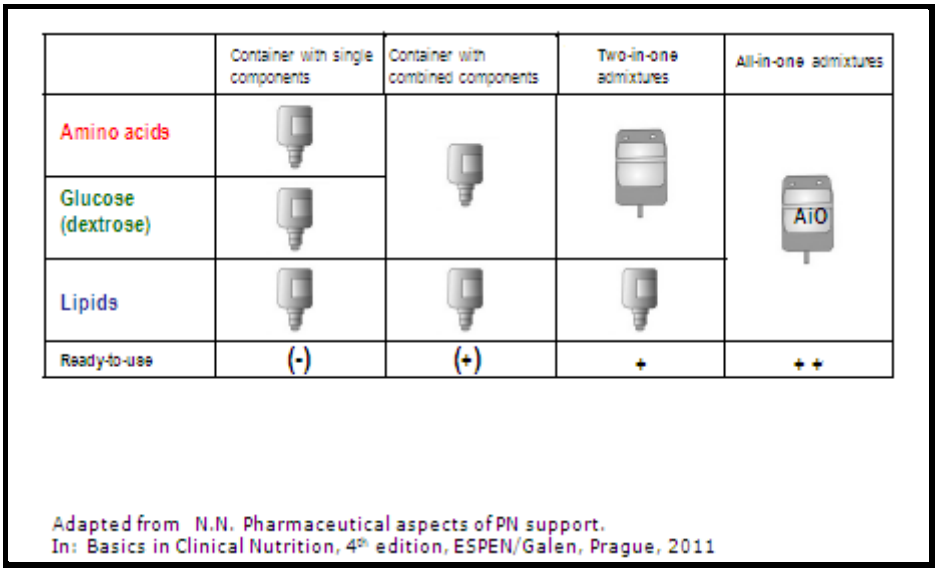

Fig. 6 PN delivery systems

The next major advance was the industrial multi-chamber bag system with each of the macro-nutrients separated from the other in its own compartment and also containing a basic profile of electrolytes. Multi-chamber bags with new multilayered bag materials allowed steam sterilisation and extended microbial stability (23). Protective wrapping with air-tight plastic foils contributes to the extended shelf life of these AiO premixes over many months through excluding oxidation by ambient air. Industrial production of near complete standard AiO admixtures or premixes (**Fig. 7**) was therefore achieved. To make them ready for use, the seal between the chambers has to be broken mechanically and the components are then mixed together in a closed bag system (asepsis).

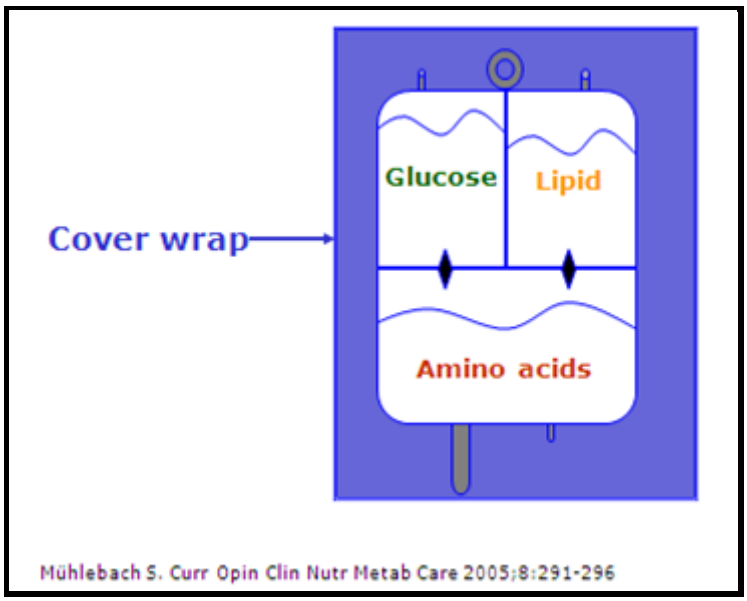

Fig.7 The PN multi-chamber bag

Additional nutrients, electrolytes or oligo-elements may be added to selected compartments according to defined aseptic admixing procedures which respect compatibility. This allows individualization of the final ready-to-use AiO PN with limited but guaranteed hanging time for administration. Physicochemical stability data, also delivered from the product supplier, assist in the preparation of safe ready-to-use admixtures with selected and tested additives (see below).

In hospitals standard PN regimens are mainly used for adult patients (24, 25). Therefore, the use of commercial AiO pre-admixtures instead of fully compounded AiO admixtures is common. Industrial PN multi chamber bags, with a final prior-to-use adaptation, cover patients' PN needs and follow PN recommendations for timely, limited PN use together with EN in a general adult acute care hospital population (26). However, patients with specific and changing nutritional requirements due to their underlying disease and/or growth (paediatric patients) (**Table 3**) or patients on long-term PN (18, 20), are still dependent on tailor-made individualised PN admixtures. Therefore, an experienced i.v. compounding/admixing service is still needed (27).

Table 3
TPN requirements (slow increase; ICU over 3-5 days)

DGEM PN Guidelines in paediatrics (ESPGHAN) J Ped Gastro Nutr 2005;41:S1
NN in: Basics in clinical nutrition, 4th edition, Galén/ESPEN, Prague 2011
NN in: Harrison's Principles of Internal Medicine 16th edition, McGraw-Hill, 2006
Specific hospital guidelines on clinical nutrition: Kantonsspital Aarau (Switzerland), 3rd edition 2005; Inselspital Bern (Switzerland) 3rd edition 2010

	Neonate	Adult	AIO PN admixture "1800-16" Mean for a 75 kg patient [total dose over 24 hrs]
Energy requirements [kcal/kg]			
Non protein energy	90-110	(20-)25-30(-35)	1800
Basic metabolic rate	35-50	15-20	
Growth	45	-	
Macronutrients [g/kg]			
Glucose	16-20	3-5	250 (1000 kcal)
Triglycerides	1(-2-3)	1	75 (680 kcal)
Essential FA ($C_{18:2\omega3}$)	0.1-0.25	0.02-0.04	~5 g
Protein (aa pattern!)	2.0-3,5	(0.8-)1.2(-1.8)	100g (16 g N)
Electrolytes [mmol/kg)			
Na	2.5	1	100
K	1-3	1	60
Ca	1-2	0.05	4
Mg	0.5	0.15	5
Phosphate	2	0.2	25 (5 from lipid)
Water [ml/kg]	60-130	30	1950
Micronutrients (RDA)			
Vitamins			
Vit. A (retinol)		1000 μg	1000*
Vit D		10-15(-20) μg	5.5*
Vit. E (α-tocopherol)		10-15μg	10.1*
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 (vit. B_3)		40 mg	46*

Vit. B12		3-6 μg	6.0*
Folic acid (vit. B_9)		400 μg	400*
Biotin (vit. B_7)		60-75 μg	69*
Vit. C		40-100 mg	125*
Trace elements [μmol]			
Iron		20-40	50
Zinc		50-100	50
Copper		5-20	5
Manganese		3-5	5
Selenium		0.5 (-2.5)	0.3
Iodine		1	1
Chromium		0.2-0.5	0.5
Molybdenum		0.1-0.2	0.2

Also, the final aseptic ready-to-use preparation and the final correct labelling, remain important pharmaceutical tasks to avoid errors and improper handling (4, 14, 22, 26). The label should include standard information such as the patient's name, the day of administration, the appropriate rate and duration of infusion [ml/hr], a detailed composition (concentration and dose of components in well-defined units), a lot (batch) identification, the expiry date and the appropriate storage conditions (21).

Pharmacoeconomic and ergonomic studies to evaluate cost effectiveness of the different PN systems and their overall benefits are few and more are needed (2, 26) (**Fig. 8**).

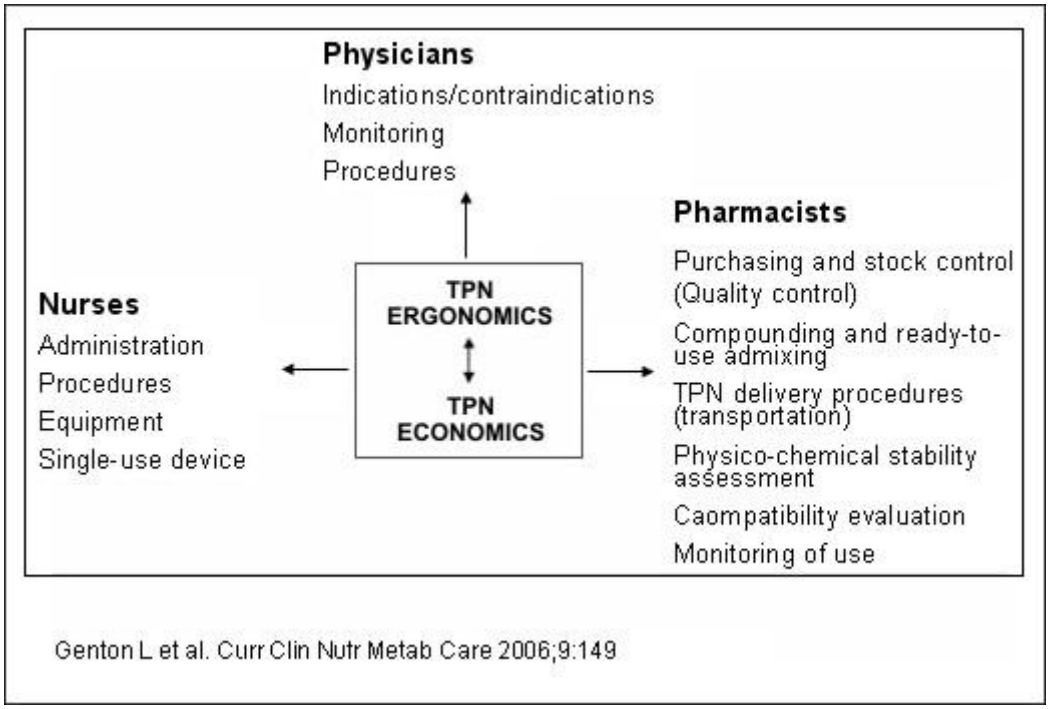

Fig. 8 Workload related to PN

Such investigations should also evaluate the NST support and workload, including the comparison of pharmaceutical compounding **(Fig. 9)** with ready-to-use preparation of industrial premixes and advice/control of appropriate use and handling of PN in clinical nutrition care (2, 25-27).

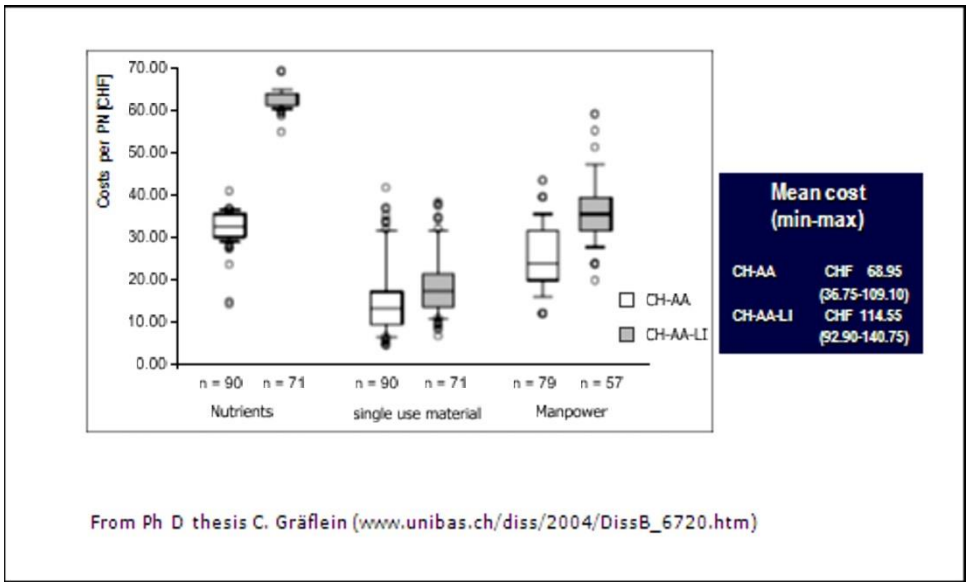

Fig. 9 Compounding cost of PN in neonatology

2. PN Compounding and Admixing (the i.v. Admixing Service)

2.1 Good Manufacturing Practice (GMP)

Ready-to-use AiO PN admixtures are complex pharmaceutical formulations with limited stability and shelf life. After aseptic compounding or admixing for a ready-to-use AiO PN, a final specific analytical quality testing is difficult to realize before release, because of mostly immediate use. Therefore, process documentation, validation, and in-process checks are key for GMP and the quality assurance of the finished preparation (site master file) (28-30) (**Fig. 10**).

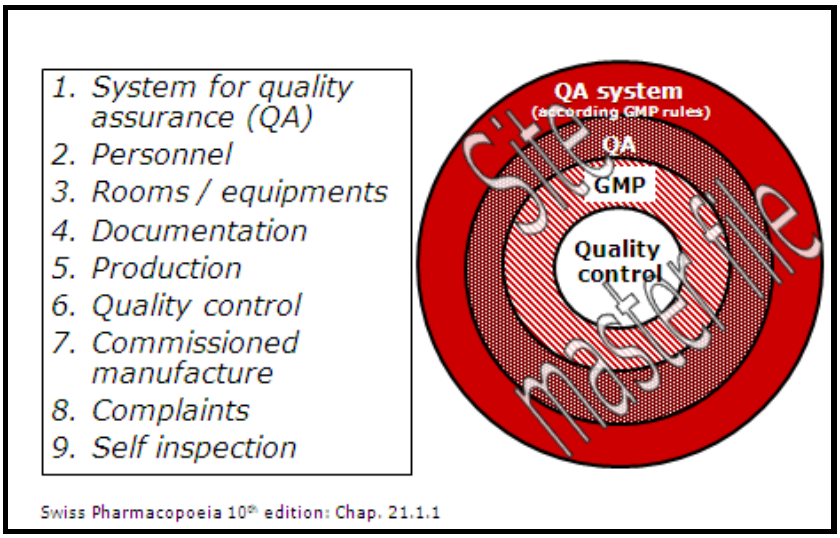

Fig.10 GMP rules and chapters of content

To run a compounding and admixing central i.v. admixture service (CIVAS), the responsible pharmacist has to adhere to the legal requirements for manufacturing and distribution. Proper organisation, documentation (protocols), technical measures, experienced staff, and user guidance are the key for good quality products and their safe use. The need to implement suitable GMP for pharmaceutical compounding of PN is an important factor when working within a NST. For example, the Swiss Pharmacopoeia has established GMP rules

for pharmaceutical small scale production (30) which have been legally enforced in the country since 2005. The monograph as well as the requirements in the UK helped when the international guidelines of the Pharmaceutical Inspection Convention (PIC) were compiled. The site master file is the main document of reference for quality assurance including GMP. The USP includes a specific chapter on pharmaceutical compounding (31). Different professional healthcare bodies have issued guidelines defining the pharmaceutical tasks in PN compounding (21). Self-assessments, critical incidence and error reporting, 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) staff in charge is mandatory to keep expertise and practical knowledge at the required level.

2.2 Aseptic Preparation Technique

A ready-to-use PN (AiO) admixture is a large formulation intended for parenteral use, which has to be sterile and pyrogen-free. Because of the reactivity of heat-labile components in ready-to-use PN admixtures – essential fatty acids, vitamins, different amino acids etc. – and due to emulsion characteristics, a final steam sterilisation of the ready-to-use AiO PN admixture is not possible. A strict aseptic procedure must therefore be applied 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 (aseptic) operation procedures (SOP)
- for the compounding/admixing activities: strictly controlled, defined and validated procedures

A clean room area type A or class 100 is needed (per m^3 incoming air: max. 3500 particles $\geq 0.5\mu m$ and max. 20 $\geq 5\mu m$ are accepted). The clean room environment can be granted by using a suitable laminar airflow (LAF) cabinet (**Fig. 5**) or an isolator. Cleaning and disinfection of the working surface and of the starting materials must be carried out, and correct working procedures (SOP) 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 process has to be checked and validated by media fills based on a defined risk plan. Also the qualification and the performance of the operating personnel have to be assessed and documented regularly. Individualised practical training sessions have to be scheduled and documented, including instruction measures to prevent contamination such as impeccable personal hygiene, special clothing, and wearing of sterile gloves (30-31).
The drastic reduction of microbial risks by these pharmaceutical standards was a cornerstone to guarantee survival of patients requiring PN and for the safe long-term use of central venous access. This clearly demonstrates the need for specifically educated (pharmaceutical) staff in an i.v. compounding/admixing unit and their supervision by an experienced pharmacist. Aseptic preparation at the ward level by non-specifically educated healthcare professionals such as nurses and clinicians mostly does not reach pharmaceutical standards and should be replaced by central services (27).

To minimise infectious complications in patients at risk, the use of inline filters for PN administration is recommended but in selected cases only (4). To eliminate bacteria from

a contaminated PN admixture mechanically, a pore size of 0.22 μm has to be used for lipid-free 2 in 1 admixtures and filters of 1.22 μm for lipid-containing preparations since fat droplets exceed the 0.2 μm filtration size (see 2.3.1). Although, both pore sizes are effective in removing precipitates (see 2.3.3), they are not equally effective against bacteria.

2.3 Compatibility and Stability Aspects of AiO Admixtures

2.3.1 Oil in Water (o/w) Emulsion (Physical Stability)

A typical AiO PN admixture contains some 40-50 dissolved components **(Table 4);** it is an oil-in-water emulsion due to the lipid content.

Table 4
Guide for drug therapy in PN patients (adapted from (6))

Order	Questions	Comment
1st step: need for i.v. medication	Is there a need for this medication and for the i.v. route to be used?	
2nd step: need for concomitant i.v. medication administration, consider possibility of admixing medication in AiO PN (including safety)		Alternative formulations may be used.
3rd step: profile of the drug	Is there alternative i.v. access possible and/or an intermittent administration possible?	Multi-lumen catheters should be advised in patients on PN with several i.v. medications (acute care PN patients). Evidence for Y-site medication compatibility and stability with PN.
4th step: documentation and inspection of the admixture	Patient on long-term (home) cyclic PN allows intermittent drug administration with sufficient flushing.	

Safe and well tolerated i.v. fat emulsions show a fat droplet size distribution of 0.25 - 0.5μm, which is similar to chylomicrons that have a physiological upper limit of particle size of about 5μm (small blood vessel diameter). The emulsion has to be labile to allow plasma lipid clearing (lipase) and tissue uptake of triglyceride after administration. There is a high potential for incompatibilities causing 'oiling out' **(Fig. 11),** which is an important safety issue.

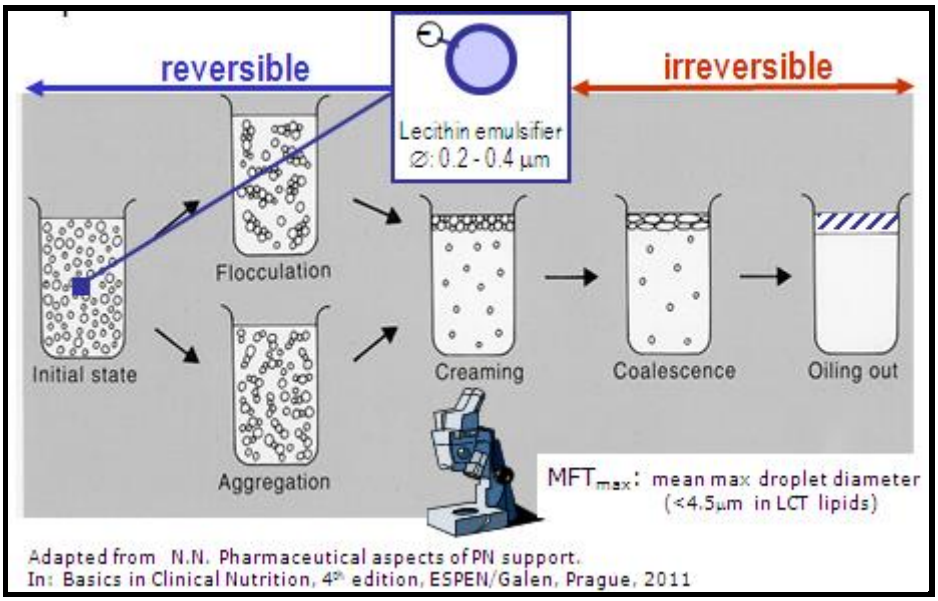

Fig. 11. Lipid emulsion destabilisation

Parenteral lipid emulsions contents (fat percentage by weight)								
		Intralipid	Lipofundin Medialipid	Structolipid	Clinoleic	Omegaven	Lipoplus Lipidem	SMOF Lipid
C8:0	Caprylic acid	-	29.6	24.3	-	-	26.2	16.2
C10:0	Capric acid	-	19.1	9.9	-	-	19.8	11.4
C12:0	Lauric acid	-	0.3	0.2	-	0.7	-	-
C14:0	Myristic acid	0.1	0.1	0.1	-	5.5	1.0	1.0
C16:0	Palmitic acid	11.0	6.5	7.6	13.0	10.4	6.1	9.1
C16:1ω7	Palmitoleic acid	0.1	-	0.1	0.8	9.4	0.2	1.7
C18:0	Stearic acid	4.3	2.0	3.0	3.6	1.2	2.6	2.8
C18:1ω9	Oleic acid	22.5	1.3	15.7	56.6	8.5	11.4	27.7
C18:2ω6	Linoleic acid	53.8	35.0	33.7	17.2	1.8	21.9	18.6
C18:3ω3	α-linolenic acid	6.9	5.8	4.2	2.4	1.2	3.1	2.4
C18:4ω3	Stearidonic acid	-	-	-	-	6.2	-	-
C20:4ω6	Arachidonic acid	0.1	-	0.1	0.6	1.6	0.4	0.5
C20:5ω3	Eicosapentaenoic acid	-	-	-	-	23.7	3.3	2.4
C22:6ω3	Docosahexaenoic acid	0.3	-	0.3	0.1	27.7	3.0	2.6

Intralipid: 100% soybean oil
Lipofundin/Medialipid: 50% soybean oil, 50% medium-chain triglycerides
Structolipid: 100% structured triglycerides
Clinolei: 20% soybean oil, 80% olive oil
Omegaven: 100% fish oil
Lipoplus/Lipidem: 40% soybean oil, 50% medium-chain triglycerides, 10% fish oil
SMOF Lipid: 30% soybean oil, 30% medium-chain triglycerides, 25% olive oil, 15% fish oil

Fig. 12 Lipids currently used in PN and their composition

In the presence of high concentrations of di- and tri-valent cations (electrolytes, trace elements) bridges with the negatively charged emulsifier (lecithin) are formed and decrease the negative surface potential (zeta potential) of the lipid droplets (retracting forces) coated by a (charged) monolayer film of the emulsifier. As a consequence and according to their thermodynamic tendency, 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 the proportion of

large diameter oil droplets impairs the dispersion of the chylomicron-like lipid emulsion (32). Therefore the admixing of trace elements into an AiO also matters and has a high impact on emulsion stability. Large diameter oil droplets (>5μm) may harm the patient by causing occlusion (embolisation) of small blood vessels but also by causing oxidative stress and tissue injury (33).

An emulsion stability assessment of i.v. lipids has been included in the USP (34). The optical sensing method (light obscuration) is mainly used by manufacturers and is not a routine testing when checking for admixture stability. Other, less elaborate, low-cost, but still sensitive checks like a standardised, microscopic method, are able to detect early deterioration of a lipid emulsion at the critical upper tail of the droplet distribution curve. Such a method is useful for stability control of AiO admixtures, e.g. in a pharmacy-based compounding unit (35). Different lipids (**Fig. 12**) and amino acids may have a profound influence on the emulsion stability of AiO admixtures and have to be tested individually (**Fig. 13**) which demonstrates the difficulty in any theoretical extrapolation of data.

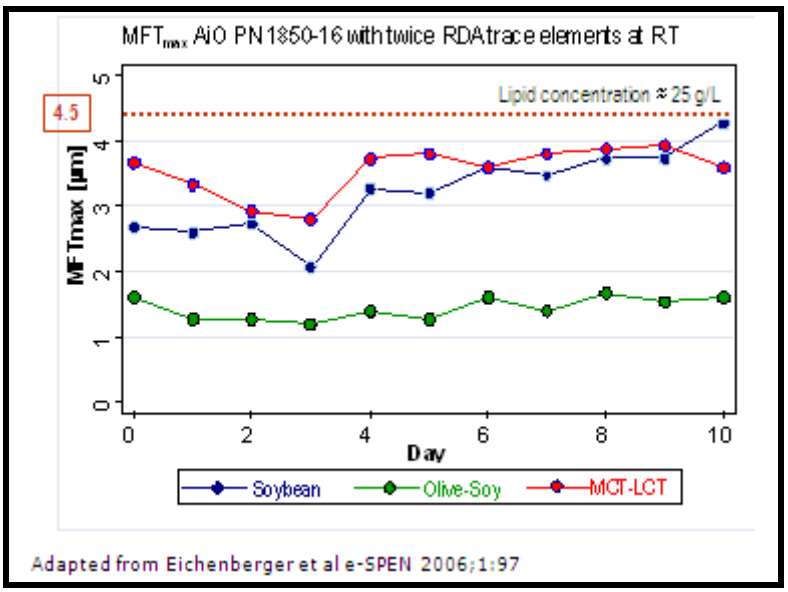

Fig. 13 AIO Emulsion Stability: Type of Fat

Other factors affecting the emulsion stability include pH (≤ 5), increased temperature, and local (high) concentrations of admixed electrolytes as a result of an incorrect sequence of component admixing! Lipids should always be added last to an AiO admixture to protect the emulsion from higher destabilizing electrolyte concentrations. Therefore, electrolyte and trace elements should never be admixed directly into a lipid emulsion, neither when using starting materials for compounding nor when applying additives in a compartment of multi-chamber bags. Divalent cations added to amino acid solutions may be partially masked by complexation and increase the compatibility and stability of AiO admixtures. Again the type of amino acid solution might have an even higher influence than the type of i.v. fat emulsion (**Fig. 14**).

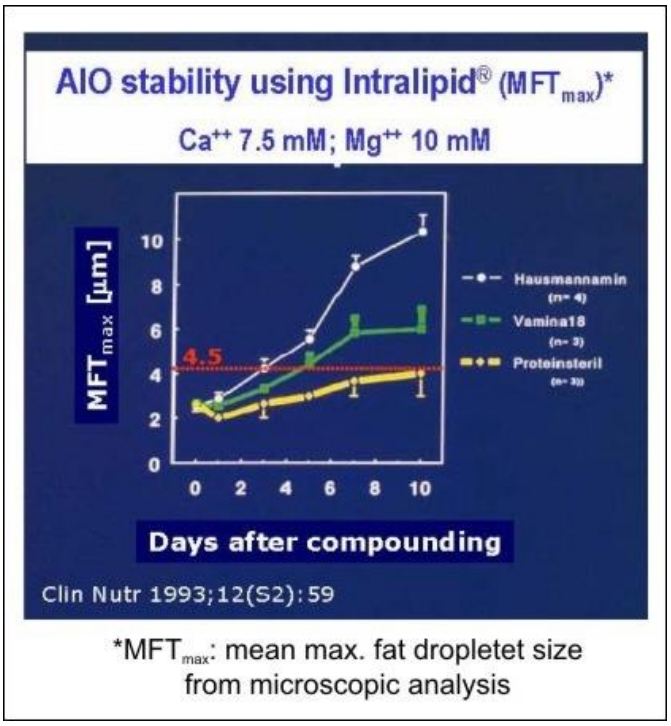

Fig. 14 Influence of amino acids on LCT lipid emulsion stability

2.3.2 Lipid Peroxidation and Oxidative Loss of Vitamins (Chemical Stability)

In the presence of oxygen, lipid peroxidation (LPO) occurs as a chemical instability (chain) reaction with potentially harmful reaction products (reactive oxidative species (ROS) like radicals). This also happens in lipid-containing PN admixtures with polyunsaturated fatty acids (PUFA) (**Fig. 15**).

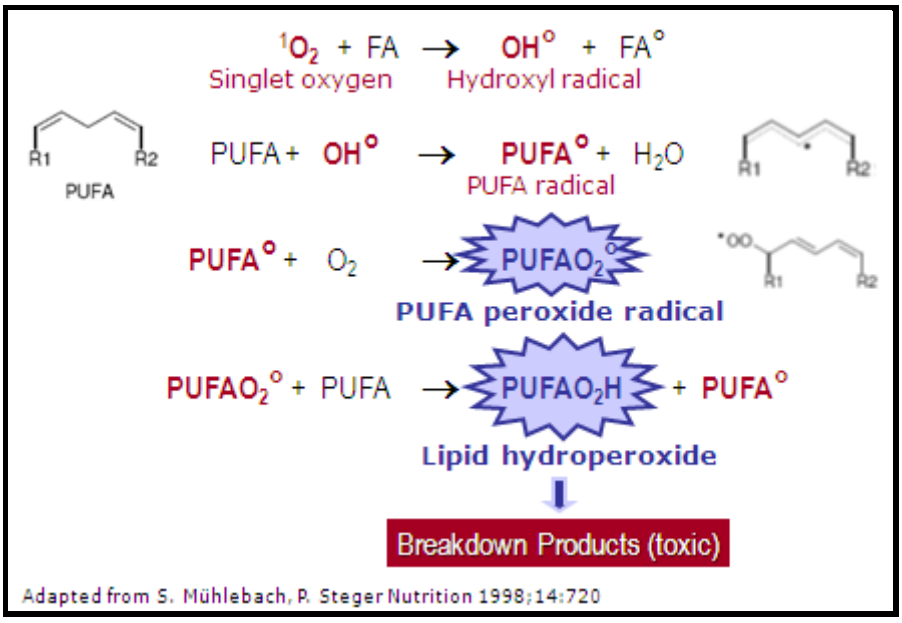

Fig. 15 Lipid peroxidation (LPO)

The resulting oxidative stress which also induces inflammation and/or apoptosis (32) may impact finally on morbidity and mortality in PN patients. LPO needs to be tested for in the stability assessment of AiO admixtures during storage and administration (36,37), and for compatibility reasons such as the addition of trace elements (38). 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 PUFA content, the higher the likelihood of peroxidation: soybean oil / fish oil (>60% PUFA) > LCT/MCT (~ 40%) > olive oil (~ 20%) (35) (**Fig. 12**). Antioxidants (vitamin E and C) in appropriate concentrations have a protective effect (39).

Cover wrapping with airtight plastic foils or oxygen absorber during storage, or the use of poly-laminated container material with better gas barrier resistance than EVA, considerably reduces losses of nutrients prone to be degraded by oxidation (PUFA, vitamin C and E) (39,40). In the absence of stability data and due to potential mutual interactions, vitamins and trace elements (oligo-elements) should be injected separately into the PN bag; they should not be combined before being added because of mutual vitamin and/or trace element interaction and inactivation, e.g. between iron and vitamin C (4,5).

2.3.3 Electrolyte Precipitations (Physical Stability)

Beside incompatibilities influencing the emulsion stability of an AiO admixture, precipitates of electrolytes, trace elements or drugs dissolved as salts are of concern when incompatible concentrations of cations and anions are present, as for calcium and (inorganic) phosphate. The formation of poorly soluble calcium-monohydrogen-phosphate (pK = 7.2) depends on the pH and temperature. Even small changes of an AiO admixture's pH or a slight change in temperature can trigger precipitation (**Fig. 16**).

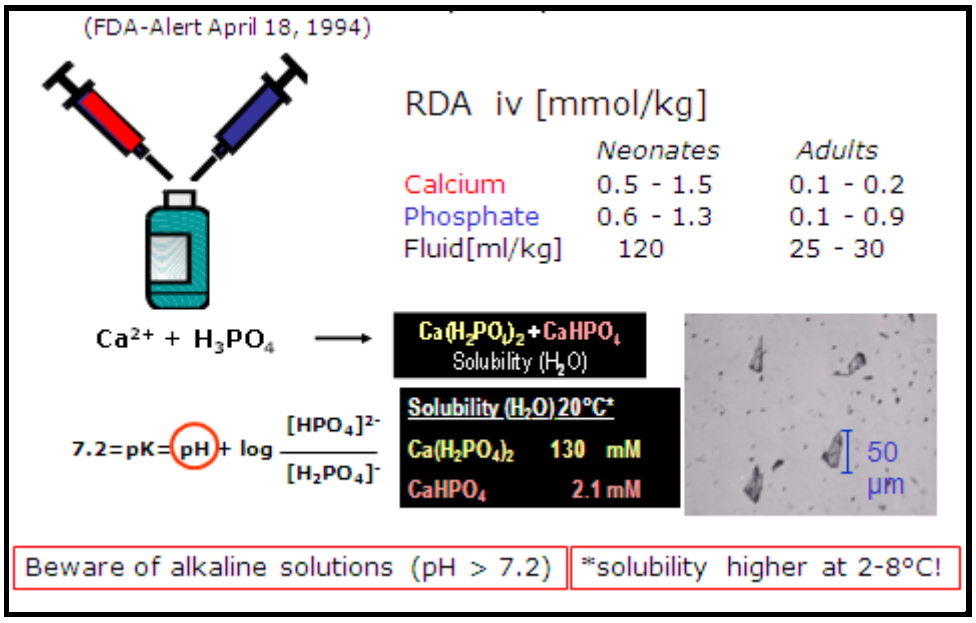

Fig. 16 Calcium phosphate precipitation

In the case of calcium phosphate an inline filter may not prevent infusion of precipitates formed on the patient side of the filter upon warming of the AiO admixture by the patient's body temperature. The lipid component of an AiO admixture will moreover conceal this form of precipitation.
The use of organic phosphate is an alternative way to avoid solubility problems with calcium and phosphate, especially in neonates with their high requirements for these components (41). As emphasised above, a well-defined admixing sequence is mandatory to avoid precipitation due to incorrect dilution of nutrients during compounding (preventable medical error) (13).

2.4 PN Regimen Selection and Nutrition Management

Standardisation of PN regimens using a small range of established and tested formulae is helpful to prevent such instability problems. They meet the needs of most patients in the initial PN period safely and effectively, even in neonates (15). An AiO PN bag can be administered flexibly over varying time periods or during cyclic infusion for home PN (21) taking into account metabolic tolerance and hanging stability. A slow initiation of clinical nutrition and avoidance of overfeeding is especially important in the ICU patient (16, 19, 20, 42) and should be included in prescribing and administration guidelines and in product labelling. For documentation, control and management of PN electronic support for prescription, preparation administration, and monitoring is advised and helps to reduce medication errors (**Fig. 3**).

2.5 Drug Admixing to AiO PN Formulation

Due to the complexity of AiO PN formulations, such admixtures are not suitable vehicles for parenteral drug administration. Numerous interactions can occur between a large number of potentially interacting substrates or materials (**Fig. 2**) leading to incompatibilities or sorption and permeability phenomena *in vitro*, or occlusion of catheters, but also to interactions between nutrients and drug *in vivo*. There is also an increased risk of microbial contamination from the additional manipulations (**Fig. 5**).

During acute illness and after surgery most patients with PN need supplementary i.v. parenteral support to treat the underlying disease, discomfort and to correct fluid, electrolyte, and substrate imbalances. For these purposes, a multi-lumen catheter for a separate administration of drugs and PN is often advised, reserving one lumen for the often continuous PN administration.

In chronic and stable long-term treatment it may be necessary to add essential drugs to the PN admixture in order to avoid repeated and separate infusions with their associated risks, and to guarantee the patient's well-being and QoL. In such situations specific stability and compatibility testing are mandatory. Extrapolation from published data has to be done with extreme caution (and is frequently not advised) because even identical active pharmaceutical ingredients in drugs from different manufacturers may differ in pH or other product characteristics, and extrapolation of data requires a particular understanding of all of the issues involved. This is important for compatibility and incompatibility assessment and review. Access to a specific analytical laboratory may help assure quality of the admixture and the overall effectiveness and safety of the nutrition and drug treatment.

For drugs with small therapeutic indices (critical dose drugs) the bioavailability/disposition of the drug admixed to PN may be critical and variable; it should always be determined (6, 11).

Some general pharmaceutical considerations are helpful for understanding and assessing the risks. Lipophilic drugs normally distribute into the lipid moiety of the AiO admixture which may affect their bioavailability (disposition). Interactions with solubilizers may occur. Interactions (e.g. with lecithin) may modify drug release and induce different drug kinetics, thereby influencing pharmacological dose-response reactions.

Not only drug action but also the metabolism of nutrients, such as triglyceride clearance, may be affected. For example, an investigation of Cremophor-solubilized ciclosporin showed reduced hydrolysis of LCT in a lipase *in vitro* model (**Fig. 17**). Although physicochemical analyses of both the ciclosporin and the AiO fat emulsion, showed no pharmaceutical instability, there were interactions with free fatty acid release and potentially important effects *in vivo* (6, 43).

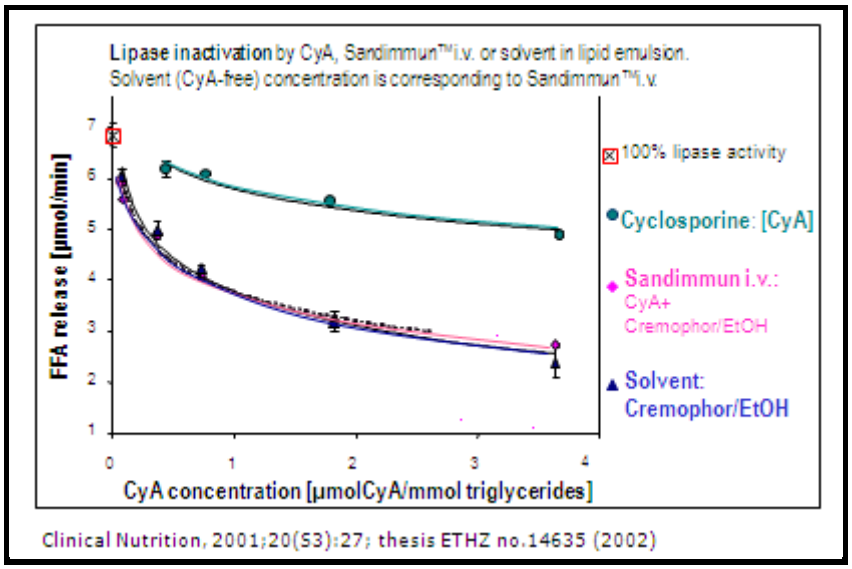

Fig. 17 Drug nutrient interaction.
Cyclosporine (Sandimmun®) admixed to i.v. Intralipid®

A practical approach to the risk evaluation of mixing drugs with AiO PN feeds is given in **Table 4** (4).

3. Summary

All-in-one admixtures are safe, efficient, and convenient. The compounding of tailor-made feeds or the final preparation of ready-to-use commercially available multi-chamber AiO bags need expert pharmaceutical input and supervision; GMP rules apply. Good storage/handling practices prevent instabilities/incompatibilities and help to guarantee the safety and effectiveness of PN. Admixing drugs always carries an element of risk and should be avoided and only carried out when absolutely necessary and with reliance on an expert pharmacist's opinion (which is beyond the expertise of the majority of NST pharmacists).

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