

Practical handling of AIO admixtures – Guidelines on Parenteral Nutrition, Chapter 10

Praktische Handhabung von AIO-Mischungen – Leitlinie Parenterale Ernährung, Kapitel 10

Abstract

All-in-one admixtures (AIO-admixtures) provide safe, effective and low-risk PN (parenteral nutrition) for practically all indications and applications. Water, energy (carbohydrates and lipids), amino acids, vitamins and trace elements are infused together with PN either as industrially-manufactured AIO admixtures provided as two- or three-chamber bags (shelf life usually more than 12 months) completed with electrolytes and micronutrients where appropriate or as individually compounded ready-to-use AIO admixtures (compounding, usually prepared by a pharmacy on either a daily or weekly basis and stored at 2–8 °C). Physico-chemical and microbial stability of an AIO admixture is essential for the safety and effectiveness of patient-specific PN, and its assurance requires specialist pharmaceutical knowledge. The stability should be documented for an application period of 24 (–48) hours. It is advisable to offer a limited selection of different PN regimes in each hospital. For reasons of drug and medication safety, PN admixtures prepared for individual patients must be correctly labelled and specifications for storage conditions must also be followed during transport. Monitoring is required where applicable. Micronutrients are usually administered separately to AIO admixtures. In case compatibility and stability have been well documented trace elements and/or combination preparations including water-soluble or water-soluble/fat soluble vitamin supplements can be added to PN admixtures under strict aseptic conditions. AIO admixtures are usually not used as vehicles for drugs (incompatibilities).

Keywords: infusion systems, compounding, industrial parenteral nutrition systems, stability, quality assurance

Zusammenfassung

Eine sichere, effektive und risikoreduzierte parenterale Ernährung (PE) hat sich in Form der All-In-One-Ernährung (AIO-Ernährung) für praktisch alle Indikationen und Anwendungen etabliert. Bei PE werden Wasser, Energie (Kohlenhydrate und Fett), Aminosäuren, Vitamine und Spurenelementen gemeinsam infundiert, entweder mit industriell gefertigten Standard-AIO-Zwei- oder Dreikammerbeuteln (Haltbarkeit ist in der Regel >12 Monate) komplettiert mit Elektrolyten oder Mikronährstoffen, wo dies geeignet ist, oder mit individuell gemischten anwendungsbereiten AIO-Nährmischungen (Compounding, Herstellung in der Regel täglich oder wöchentlich und Kühlung bei 2–8 °C). Die physikochemische und mikrobiologische Stabilität von AIO-Mischung ist entscheidend für die Sicherheit und Wirksamkeit einer patientenspezifischen PE und erfordert auch für die Qualitätssicherung pharmazeutisches Fachwissen. Die Stabilität muss für eine Applikationsdauer von 24 (–48) Stunden dokumentiert werden. Sinnvoll ist eine begrenzte Zahl an PE-Regimen im einzelnen Krankenhaus. Um die Arzneimittel- und Medikationssicherheit zu gewährleisten ist die korrekte Beschriftung von patientenspezifisch vorbereiteten PE Mischungen notwendig. Die Vorgaben zur Aufbe-

S. Mühlebach^{1,2}

C. Franken³

Z. Stanga⁴

Working group for developing the guidelines for parenteral nutrition of The German Association for Nutritional Medicine

1 CSO Vifor Pharma Ltd, Villars-sur-Glâne, Switzerland

2 University of Basel, Switzerland

3 Central Pharmacy, University of Dusseldorf, Germany

4 Polyclinic for Endocrinology, Diabetology and Clinical Nutrition, Clinic for General Internal Medicine, University of Berne, Switzerland

wahrung müssen auch während des Transportes kontinuierlich garantiert werden. Ein Monitoring ist notwendig. Mikronährstoffe sollen grundsätzlich getrennt von AIO-Mischungen verabreicht werden. Spurenelemente und/oder Kombinationspräparate wasserlöslicher bzw. wasserlöslicher/fettlöslicher Vitaminpräparate Mischungen dürfen bei dokumentierter Kompatibilität und Stabilität zur PE auch zugespritzt werden unter Beachtung strenger Asepsis. AIO-Mischungen sollten in der Regel nicht als Träger für Medikamente verwendet werden (Inkompatibilitäten).

Schlüsselwörter: Infusionssysteme, Compounding, industrielle PE-Systeme, Stabilität, Qualitätssicherung

All-in-one (AIO) admixtures

Definition and significance of AIO admixtures

- Water, energy (carbohydrates and lipids), amino acids, vitamins and trace elements are infused together with parenteral nutrition (PN) (B).
- All-in-one admixtures (AIO-admixtures) provide safe, effective and low-risk PN for practically all indications and applications (B).

Commentary

Infusion systems

Infusion systems for the administration of PN comprise of:

- Individual substrates (carbohydrates, lipids and amino acids) administered with separate bottles (multi-bottle system/modular system).
- Combination solutions (carbohydrate/amino acid mixtures) with separate administration of lipids.
- AIO admixtures where the substrates (carbohydrates, lipids, amino acids, electrolytes and micronutrients) are admixed in a single container and simultaneously administered through one intravenous line (“all-in-one”). Ideally, all substrates are administered together, taking compatibility and stability of the components and the admixture into account and limiting particulate matter. This system results in reduced manipulation and savings of material, time and personnel workload. AIO admixtures require only one intravenous line, and the risk of infection is lowered by the closed system. The complete and simultaneous administration of all substrates reduces the risk for metabolic complications. AIO admixtures offer a convenient system for patients, clinicians and nursing staff.

AIO admixtures

AIO admixtures may be obtained by two different ways:

- Industrially-manufactured standard AIO provided as two- or three-chamber bags: In case of a two-chamber bag, a lipid emulsion is admixed with a transfer set

shortly before its administration to the patient, thus creating an AIO admixture. Three-chamber bags contain all the macronutrients and electrolytes in three separate compartments. The substrates are mixed together immediately prior to intravenous application by breaking the separation seals between the bag chambers. Vitamins and trace elements are injected into the bag prior to administration or infused by a separate intravenous line. When not mixed together, these standard multi-chamber bags have usually a shelf life of more than 12 months.

- Individually admixed AIO admixtures (compounding): These allow for the provision of patient-specific ready-to-use admixtures, individually adapted according to energy, volume and substrate needs. These are aseptically manufactured from various components, usually in hospital pharmacies, and are designed for immediate intravenous administration, with no mixing or admixing required prior to administration. These bags are usually manufactured on either a daily or weekly basis due to their limited stability. They require storage at 2–8 °C.

Both approaches require aseptic techniques of handling, because it is not possible to sterilise an AIO admixture after ready-to-use completion [1].

Significance

AIO systems in PN provide microbiological and metabolic advantages as well as benefits in handling and compatibility, as compared to the use of individual components or combination solutions [2], [3], [4], [5], [6], [7], [8]. The use of standardised parenteral admixtures simplifies prescription, compounding and reduces complications. In addition, it improves patient safety and efficiency of treatment [6], [9].

A cost-benefit analysis by Durand-Zaleski et al. [3] compared the costs and financial benefits of multi-bottle systems with an AIO system. The expenditure included the costs for compounding, substrates and equipment. Financial benefits were estimated from reduction in costs due to prevented infections (especially catheter-related infections) and reduction in risks due to the use of an AIO system. Frei et al. [5] took into consideration the costs for material required (bottles, bags, substrates, etc.), tests (laboratory) and staffing. A two-chamber bag together

with a separate bottle for lipid emulsion represented the AIO system. Although the multi-bottle system was more economical, the total daily cost was lower when the two-chamber bag system was used.

Quality assurance is an important aspect of PN therapy. Increased manipulations during PN raise the frequency of nosocomial infections [10], [11], [12]. This risk is higher with multi-bottle systems due to an increased frequency of manipulation and the necessary admixing into bottles. Durand-Zaleski et al. [3] showed a reduction in nosocomial infections with using an AIO system, which resulted in overall savings due to elimination of subsequent expenses.

An AIO admixture comprises 50 or more components in a ready-to-use bag, and represents an extremely complex pharmaceutical formulation. Good Manufacturing Practice (GMP) is a quality standard (materials, room conditions, equipment, employees (training), processes, documentation, distribution etc.) that must be followed for manufacturing AIO admixtures [13], [14], [15]. PN preparations must be [16]:

- therapeutically and pharmaceutically suitable for the patient
- free of microbiological impurities and pyrogens
- correctly dosed and admixed (proven compatibility)
- correctly labelled, stored and administered.

Total complete admixtures which are true ready-to-use PN are not yet commercially available due to physico-chemical instabilities. Adaptation of AIO admixtures to meet individual requirements must be prepared in accordance to specific pharmaceutical manufacturing regulations and strict aseptic conditions [17], [18] at every step. The evaluation of microbiological (aseptic preparation) and physico-chemical stability (emulsion dispersion, solubility, decomposition, sorption phenomena etc.) requires specialised pharmaceutical knowledge [18], [19]. These parameters influence the quality of PN [20].

Standardisation is a sensible option in PN, when balancing requirements and simplification of treatment, but individual regimens are also needed to meet specific requirements, e.g. in infants and children, long-term (home) PN, etc. [21]. Industrially-prepared multi-chamber bags, with established standard compositions, often are an attractive method of providing PN. They are predominantly used in the short-term PN-treatment of hospitalised adults. Individual compounding is, however, still required [22]. Industrial multi-chamber bags allow the admixing of the stable components in a closed system (asepsis) directly before administration. Multi-layer plastic containers enable long-term storage of the compartmented components (reduction of oxygen permeation in oxidation-sensitive components [23]; cover wrapping with oxygen absorbers further increase this stability). Glucose and amino acids are separated in two-chamber bags so that Maillard reactions (browning) are prevented; the lipid component, which is normally critical for the overall stability (fat droplet distribution), is admixed to the remaining AIO admixture. Addition of electrolytes, trace elements

or vitamins into the AIO admixture must follow GMP standards and the compatibility of the components (controlled conditions, documentation) must be ensured [13], [14], [15], [16].

If further admixing is required (e.g. special amino acids such as glutamine; lipids such as LCT, LCT/MCT, special fatty acid compositions, or electrolytes such as phosphate, magnesium or calcium), these should be individually admixed. Cost-benefit analyses of multi-chamber bags as compared to individual compounding should incorporate the effectiveness and rational for PN use. The presently available studies addressing this topic are either very basic or are outdated [6], [20], [24]. Local specifications and requirements should decide whether individual compounding or commercial multi-chamber bags are used for administration of PN.

Logistics, stability

Role of the pharmacist in the nutrition team in PN

- Close collaboration between a pharmacist and the multidisciplinary nutrition support team is recommended; the extent of such collaboration will depend on the pharmacist's specific skills, standard of knowledge in clinical nutrition and experience in (clinical) pharmacy practice (C).

Commentary

Areas of pharmaceutical care within the nutrition support team are [25], [26], [27]:

- Transfer of pharmaceutical knowledge on products and equipment used for PN.
- Potential interactions or incompatibilities between components and other administered admixtures/medicines, and their prevention.
- Providing instructions regarding the stability of PN regimens and their correct handling (storage, light protection, administration, etc.).
- Checking the patient-specific prescriptions of admixtures, their preparation and concomitant drugs.
- Advisory function regarding the selection, composition and administration of PN as well as further additions in hospital patient and patients discharged on home PN.
- Advising on drug-related problems or observations: admixing, stability, incompatibility, bioavailability, documentation/clarification of adverse reactions to drugs.
- Providing an insight into measures to increase drug safety (evidence-based medicine/pharmacy).
- Support in integration and standardisation of treatment regimens, including suggestions for therapeutic strategies.

- Advisory role on allergies to drugs or nutrition components.
- Support of education and training.
- Co-operation in quality assurance and quality improvement by means of establishing medical and nursing standards as well as monitoring.

Preparation and manufacturing regulations

Strict requirements and conditions for compounding the all-in-one admixtures are required because it is impossible to sterilise the end product, and because of the large number of components with potential physico-chemical incompatibilities and instabilities (o/w emulsion systems with potential admixture of drugs) [17], [28], [29], [30]. The compatibility of the individual components, and the pH and homogeneity of the emulsion need to be tested, and a weight control inspection of mass (target/actual check) be carried out. The maximum amount of selected components tested as being compatible (or which are known to be compatible according to literature research), must be established. It is essential to work under strict aseptic conditions. This requires the necessary premises (laminar airflow benches, clean rooms, defined air turnover, compounding machines), the validation of the manufacturing process with suitable measures for quality control, and quality assurance according to GMP and supplementary guidelines. The manufacture of AIO admixtures with a defined admixture sequence should be carried out as close to the time of administration as possible because of stability problems. Defined in-process and end-product tests should be carried out, and the maintenance of hygiene standards guaranteed. A standardised and reproducible record of the complete manufacturing process must be documented to enable precise traceability. The expiry dates are established through suitable, validated laboratory tests. Suitable electronic support and use of compounding machines are useful if a large number of PN admixtures are being prepared.

Physico-chemical stability (assessment and documentation)

- Physico-chemical stability of an AIO admixture is essential for the safety and effectiveness of patient-specific PN, and its assurance requires specialist pharmaceutical knowledge (A).
- The stability should be documented for an application period of 24 (-48) hours (C).
- It is suitable to select and restrict the number of different PN regimes offered in each hospital (C).

Commentary

The large amounts of dissolved (reactive) components, and the underlying disperse, meta-stable water-in-oil emulsion system in an AIO PN admixture are reasons for

a high potential of incompatibility and instability. The physico-chemical instabilities include:

- Lipid emulsion destabilisation (lipid droplet aggregation, lipid coalescence, creaming and breaking of the emulsion) [31].
- The formation and precipitation of insoluble salts (i.e. calcium monohydrogen phosphate) or complexation and altered bioavailability of components (trace elements).
- Chemical changes or decomposition of components (oxidation, reduction, hydrolysis) (vitamins, PUFA (lipid peroxidation), amino acids), condensation (Maillard reactions with amino acids and glucose).
- Adsorption, absorption and desorption processes with the container material (insulin, vitamin A, diluents).

These reactions are time-dependant, dependant on the concentration of reactants, pH-value, temperature, light exposure, the presence of catalytically active components and the container material [17], [19], [23]. There are differences in the composition and purity of the starting materials of various providers, which are relevant for the stability and potentially toxicity (e.g. aluminium), thus making extrapolation of data extremely difficult [32]. Manufacturing processes have to be defined, qualified and validated in order to get the necessary final product quality (GMP). A pharmaceutical assessment/documentation of the following factors is required for the ready-to-use manufacture of a PN admixture:

- Defined starting materials
- Manufacturing procedures (admixture sequence)
- Lot-specific documents (process controls, process conditions, involved staff)
- Suitable final product analyses like pH, concentration testing of selected components etc.
- Stability-documented storage and application guidelines (tests).

Problems can occur particularly in the stability (i.e. solubility of phosphate and calcium salts or electrolyte-related destabilisation of lipid emulsion) of paediatric PN admixtures due to the relatively high contents of individual components. Here it is helpful to use only binary, lipid-free PN admixtures and organic phosphates or calcium compounds. Solubility curves [19] or specific data for emulsion destabilisation [32] are useful data for the determination of compatibility, and thus allowed electrolyte dosages.

Simple methods are required for the documentation of stability, considering time, expenses, equipment of a hospital pharmacy, for example, using microscopic instead of other methods in the testing of a lipid emulsion [31], [32], [33].

Defined amino acids (glutamine, cysteine etc.) and oxidisable vitamins and lipids (PUFA) are critical for chemical stability. The presence of oxygen, catalysts (trace elements, light) and anti-oxidants have a significant influence on oxidative decomposition. Toxic and reactive products, like free radicals, can be formed in the process along with

the inactivation of important nutrition components [23], [34], [35] [36], [37].

Lipophilic compounds may result in interactions with the container and administration materials. Plastic components can be extracted (e.g. phthalates from PVC), or PN components can be either absorbed or adsorbed [18]. The need to document the stability of PN admixtures shows the necessity of selecting and restricting the number of PN regimes and products available in a hospital. This will enhance safety and effectiveness in relation to physico-chemical stability data over the period of storage and administration. These tasks require specific pharmaceutical knowledge and need to be supported by (own) investigations.

Labelling

- PN admixtures prepared for individual patients must be correctly labelled for reasons of drug safety (A).

Commentary

Complete labelling principally serves to prevent incorrect administration and to provide controls prior to administration. It is part of the documentation process. Labelling, therefore, should contain both the patient (name, date of birth, body weight) and the product data. This comprises the following points:

- Date of manufacture
- Expiry date (storage period, administration period)
- Composition including indication of concentration and daily dosage (in SI units)
- Energy and protein content
- Storage instructions
- Administration instructions
- Lot number
- Manufacturer
- Patient name and date for use

Standardised, printed labels are a useful and practical solution.

Storage and transport

- Specifications for storage conditions must also be followed during transport, and monitoring is required where applicable (A).

Commentary

Admixtures should be protected from light and stored in the fridge (2–8°C) for reasons of hygiene and stability. If the admixture is lipid-free it can also be frozen. Cool boxes are suitable as a means of transport [13], [17], [19], [28].

Addition of micronutrients (trace elements and vitamins)

- Micronutrients can be administered separately to AIO admixtures since there is a lack of specific documentation regarding compatibility and stability (B), even though micronutrients injected to the admixture in home PN prior to administration are without identifiable adverse effects (C).
- Trace elements and/or combination preparations including water-soluble or water-soluble/fat soluble vitamin supplements can be added to PN admixtures for PN compatibility and stability has been documented (B).
- Considering micronutrient stability it can be stated:
 - Trace elements may be added to AIO admixtures in the event of documented compatibility (B).
 - Fat-soluble vitamins formulated as lipid emulsion are added to lipid-containing AIO admixtures or lipid infusions prior to administration (B).
- Micronutrients must be injected to admixtures under strict asepsis, optimally and according to GMP using a laminar airflow. Admixing should be restricted on hospital wards for hygienic reasons (A). If this is not possible due to, structural or organisational reasons, this may be carried out according to pharmaceutical guideline in individual cases, immediately before administration, by specially trained medico-pharmaceutical staff. Medical prescription, pharmaceutically documented stability and authorised ready-to-use preparations (authorised product information) have to be considered. The procedure to be followed should be documented in a written Standard Operating Procedure (C).

Commentary

Simultaneous administration of trace elements and multivitamins in AIO admixtures is problematic due to physico-chemical reasons; it shows increased degradation of oxidation-sensitive vitamins; (lipid) peroxidation is increased. Trace elements and vitamins normally have a high reactivity in the solution: some individual trace elements show catalyst functions for chemical decomposition reactions. Oxidation/reduction reactions can be further intensified by light (especially UV radiation), see peroxide formation [34], [35], [37], [38]. Therefore, the co-administration of multi vitamins and trace elements is not generally recommended, even if administered separately from AIO admixtures.

Micronutrients can inactivate each other (e.g. vitamin C and ionised iron), can be inactivated by light (e.g. vitamin K, A, B₂) or absorbed into plastic (e.g. vitamin A). Degradation products form insoluble salts (e.g. Ca and oxalate as a degradation product of vitamin C) [39], [40].

Trace elements should only be added to AIO admixtures if stability has been documented. Trace element solutions show a strong acidic pH and represent in part polyvalent

Table 1: Approximate increases of osmolarity with electrolyte additions. Adapted from Sobotka et al. [48]

Electrolyte	Standard PN (mmol/day)	Salt form	Daily dosage mosmol (theoretical)
Na ⁺	80–100	NaCl	160–200
K ⁺	60–150	KH ₂ PO 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

cations, which can greatly reduce the emulsion stability [18], [31], [38] depending on their concentration.

Suitable concentrations of antioxidative vitamin supplements (vitamin C and tocopherols) in an AIO admixture help reduce lipid peroxidation [36], [41]. They have a synergistic effect as chemical stabilisers of unsaturated lipids in vitro.

Fat soluble vitamins (vitamins A, D, E, K) can be injected into lipid-containing PN admixtures; lipid emulsion provides light protection. Micellar-dissolved lipophile vitamins can, according to manufacturer's instructions, also be administered in aqueous admixtures taking into consideration stability and compatibility. If the daily-applied combination preparations of fat and water-soluble vitamins do not contain vitamin K the weekly or even monthly administration of vitamin K added to the lipids in the AIO admixture is often still practice adequate in adults and children [34]. To better control potential osteoporosis a daily administration is recommended.

An example of a hospital guideline for the administration of vitamins and trace element dosage in PN is cited here (cf. chapter "Water, electrolytes, vitamins and trace elements" <http://www.egms.de/en/gms/2009-7/000080.shtml>).

If no specific deficiency is present: in case of PN providing >50% of daily energy requirements:

- **Vitamins:**
 - Cernevit[®] 1 vial (5 ml) per day as a piggy bag infusion over 15–30 minutes or a slow 5-minute bolus at the end or at the beginning of the daily PN administration. Cernevit[®] can also be added to PN during manufacture, if compatible (light protection).
 - Konaktion MM[®] vial 10 mg (diluted to 10 ml): doses of 150 µg (150 µl of the dilution) added daily to the AIO-PN
- **Option:**
 - Vitalipid N Adult[®] (A, D, E, K!) 1 vial (10 ml) per day
 - Soluvit N Adult[®] 1 vial (10 ml) per day
- **Trace elements:** Trace elements 1 vial (Spur-el KSA[®] 10 ml) per day

Effects of adding electrolytes on the osmolarity of the solution are shown in Table 1.

Micronutrients are not included in commercially available multi-chamber bags because of their limited stability in solution and their high risk of incompatibility. They must be prescribed separately, [17] and in a suitable dosage for a PN regime. This mutual incompatibility usually requires separate administration/admixture of trace elements and (multi) vitamins, i.e. two separate intravenous applications, one for vitamins and one for trace elements. The stability of vitamins is extremely limited in the presence of trace elements (vitamin C is decomposed within hours in presence of catalytically active trace elements like iron or copper and oxygen). That is why trace elements and vitamins are not suitable for combined administration in admixtures (accelerated (catalysed) degradation of selected vitamins). Compatibility with the other components in the AIO admixture i.e. physical lipid stability or chemical fatty acid stability (peroxidation) has to be documented with the parenteral admixture even if selected vitamins are compatible with trace elements, especially fat-soluble and water-soluble vitamins with sufficient degradation stability like pantothenic acid or nicotinamide. The increased concentration of polyvalent cations (iron, zinc) is cited as an example for the stability of lipid emulsion or the influence of multi vitamins on lipid peroxidation.

Light protection must be provided when micronutrients in aqueous solutions are applied as a (piggy bag) infusion. Light protection with overwraps must have a documented and proven effectiveness [41], [42], [43]. Fat-soluble vitamins, which are formulated as lipid emulsion, should be added to a lipid emulsion or an AIO admixture containing lipids.

Drugs

AIO admixtures as vehicles for drugs

- AIO admixtures are usually not used as vehicles for drugs due to the possibility of complex interactions. If additions of drugs to the AIO admixture are required as an exception, the stability and effectiveness must be documented (B).

Commentary

Instabilities and physico-chemical incompatibilities often occur due to the many components of AIO admixtures (lipid emulsion, amino acids, glucose, trace elements, vitamins) [44], [45], [46]. New formulations, created in emulsion systems with lipophilic drugs, show clinically relevant differences in pharmacokinetics or changes in bioavailability of the substrates as compared to the original product [47]. Incompatibilities due to pH changes, redox reactions, complex formations, drug association and solvolysis can also contribute to inactivation. Even if some incompatibilities are recognised by precipitation, colourings or gas formation, not all interactions can be analysed in this macroscopic manner. Detailed investigation or analysis and documentation, therefore, are essential before admixing.

Notes

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