

Clinical nutrition and drug interactions

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A drug's plasma level, pharmacological effects or side effects, elimination, physicochemical properties or stability could be changed by interactions of drug-drug or drug-nutrition products in patients who receive enteral or parenteral nutritional support. As a result, patients might experience ineffective outcomes or unexpected effects of therapy (such as drug toxicity, embolism). Stability or incompatibility problems between parenteral nutrition admixtures and drugs might lead to alterations in expected therapeutic responses from drug and/or parenteral nutrition, occlusion in venous catheter or symptoms or mortality due to infusion of composed particles. Compatibilities between parenteral nutrition and drugs are not always guaranteed in clinical practice. Although the list of compatibility or incompatibilities of drugs are published for the use of clinicians in their practices, factors such as composition of parenteral nutrition admixture, drug concentration, contact time in catheter, temperature of the environment and exposure to light could change the status of compatibilities between drugs and nutrition admixtures. There could be substantial clinical changes occurring in the patient's nutritional status and pharmacological effects of drugs due to interactions between enteral nutrition and drugs. Drug toxicity and ineffective nutritional support might occur as a result of those predictable interactions. Although administration of drugs via feeding tube is a complex and problematic route for drug usage, it is possible to minimise the risk of tube occlusion, decreased effects of drug and drug toxicity by using an appropriate technique. Therefore, it is important to consider pharmacological dosage forms of drugs while administering drugs via a feeding tube. In conclusion, since the pharmacists are well-experienced and more knowledgeable professionals in drugs and drug usage compared to other healthcare providers, it is suggested that provision of information and drug counselling by pharmacists in terms of detection and prevention of problems (such as interactions, stability, incompatibility) related with enteral/parenteral nutrition and drugs are invaluable in clinical practice.

Key Words: Parenteral nutrition, enteral nutrition, drug interactions, incompatibility

INTRODUCTION

A drug interaction is defined as the alteration of drug's level or its effects by concomitant use of other agents (drug, alcohol, tobacco, nutrient, diagnostic tests). The interaction may result in an inadequate treatment or drug toxicity. The risk of drug interactions increases with polypharmacy (multiple drug use) that is especially observed in elderly patients. The risk of the interaction is not only observed among drugs but also seen between enteral or parenteral nutrition and drugs (1).

In clinical practice, the terms of "drug interaction" and "incompatibility" may be misused for each other during an administration of a drug by parenteral route. Incompatibility is defined as "the formation of a precipitate or acid-base reactions due to changes in physical or chemical properties that results from concurrent administration of particular parenteral drugs or admixtures" (2). Therefore, it is important to use the correct terminology for interaction and incompatibility during the use of parenteral products and drugs.

PARENTERAL NUTRITION-DRUG INTERACTIONS AND INCOMPATIBILITIES

Since parenteral nutrition admixtures include numerous macro and micronutrients, changes in incompatibility and/or stability can be observed when drugs are administered with nutrition (3). Nutritional elements and drug molecules generally react chemically or physically before entering into the body (e.g., at the infusion bag or during mixing), therefore they disrupt each other's activity and effects (4).

There are few studies on incompatibility of parenteral nutrition admixtures with most of the drugs. Parenteral admixtures can vary in terms of content and methods of compounding, therefore differences in the content of an admixture should also be considered when evaluating the results of these studies (3).

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Addition of a Drug to the Parenteral Nutrition Solutions

The administration of parenteral nutrition as intravenous infusion leads to misperception of which can also be suitable for drugs to be delivered concomitantly. Adding the drug into the parenteral nutrition bag is a frequently encountered practice due to its various advantages, including lack of a need for additional fluids in patients with fluid restriction, less venous catheter requirement and reduced time of administration (5, 6). However, the risks of stability and incompatibility problems are very high due to the presence of a several nutrients in parenteral nutrition admixtures (lipid emulsion, amino acids, glucose, trace elements, vitamins, electrolytes), , thus addition of drugs into parenteral nutrition solutions is not recommended (7).

The addition of lipophilic drugs into emulsifier systems, like a parenteral nutrition solution, result in formation of a new drug formulation with different characteristics, and clinically significant differences in the drug's pharmacokinetic properties, bioavailability and stability as compared to its original form. The drug may become inactivated by changes in pH of the admixture, redox reactions, and complex formation. Some incompatibility reactions can be recognized (color change, formation of precipitant or gas), but some of those changes cannot be noticed at the macro level which leads problems in practice (7).

Similarly, emulsion mixture properties of the parenteral nutrition can be changed and an interaction can be seen between drug and bag material due to addition of a drug into parenteral nutrition bags. The effect of a nutrient can be diminished or harmful products occur due to precipitation or radical formation by the drug and the nutrient interactions (6).

Most of the intravenous products used in parenteral nutrition solutions are contaminated with trace elements. The studies showed that most of the electrolyte solutions are contaminated with chromium and aluminum. It is also known that the increase in serum concentration of chromium reduces the glomerular filtration rate in pediatric patients and neurological side effects and bone toxicity have been observed in children by the accumulation of aluminum in the tissues. Therefore, an addition of chromium into the parenteral nutrition solutions should be avoided in children with long-term parenteral nutrition (4).

The addition of drugs into the bag is not recommended due to the complex structure of parenteral nutrition content and the risk of physicochemical incompatibility. Where there is no alternative and an addition of a drug is inevitable; medication-related issues should be considered, which are as follows (2, 5, 6, 8):

- The stability of the drug for 24 hours,
- The stability and compatibility of the drug in the parenteral nutrition solutions
- Eligibility of pharmacokinetic properties of the drug for continuous infusion,
- The stability of the drug at the infusion rate of a parenteral nutrition.

Based on the information available, some of the drugs (insulin, ranitidine, famotidine, etc.) can be incorporated into the parenteral nutrition solutions in the pharmacy in certain circumstances. However, absolutely no additional medication should be added to the parenteral nutrition solutions which is prepared in a such way (2, 3).

One of the problems encountered in clinical practice is the emergence of hyperglycemic state due to administration of parenteral nutrition, where the addition of an insulin into the parenteral nutrition solutions is considered to reduce this risk. Among the types of insulin, only 'regular insulin' is compatible with the parenteral nutrition solutions (2). However, by addition a regular insulin into parenteral nutrition admixtures, 35% of insulin is adsorbed into the bag within 24 hours; the infusion of parenteral nutrition at a constant rate might cause a problem, therefore modifications of the insulin infusion rate may be required according to the patient's blood glucose monitoring (9).

A continuous infusion of H2 antagonists in patients at the intensive care unit is shown to be more effective in adjustment of the pH of the stomach, thus addition of these drugs into parenteral nutrition admixtures has gained broad acceptance in clinical practice. In general, if H2 antagonist drugs are added to parenteral nutrition admixtures, the nutrition solution should be stored no longer than 24 hours in the refrigerator before administration (10). Nevertheless, failure to implement the optimal H2 antagonist therapy may occur due to temporary interruption of parenteral nutrition, and unavailability of intravenous access. Moreover, a second gastroprotective drug can be administered without awareness in addition to the H2 antagonist drug in the parenteral nutrition solutions which result in pharmaceutical duplication in practice (11).

A careless and inaccurate attempts in addition of drugs into parenteral nutrition mixture may result in fatal consequences. In some of the documented cases, an accidental mixture of insulin instead of heparin into parenteral nutrition which caused to severe hypoglycemia was reported (12).

The Effects of Parenteral Nutrition on Drugs's Pharmacodynamics and Pharmacokinetics

By administering parenteral nutrition, a patient indirectly receives multi-vitamin and lipid-mediated vitamin K within the mixture. Lipid emulsions available in the market are usually obtained from vegetable oils that are the natural source of vitamin K1. Soybean, grape seed and olive oils are the rich nutrients for the source of vitamin K1. The amount of vitamin K1 in lipid emulsions varies according to the types of oil. The highest level of vitamin K1 (150-300 µg/100 g) is found in soybean oil, with a lower level (6-12 µg/100 g) in saffron oil. Therefore, in a patient on warfarin requiring parenteral nutrition support, a higher dose of warfarin is needed in order to achieve therapeutic target of INR. In addition, there may be errors in warfarin therapy in a stable patient using warfarin and parenteral nutritional support due to implementation of different oil emulsions and multi-vitamins when the patient is transferred to another hospital (13).

Liver damage due to parenteral nutrition can also affect the hepatic metabolism of drugs. Furthermore, administration of parenteral nutrition enhances pro-inflammatory cytokines and inhibits the activity of cytochrome (CYP) P450 enzymes (8). Although changes in gastrointestinal hormone response, the differentiation in mucosal barrier and possible mechanisms such as sepsis were considered responsible for this effect; the mechanism of parenteral nutrition's effects on enzyme systems in the liver is still not fully understood (14). The products added into the mixture were also shown to have an effect in this situation; by the addition of glutamine into the parenteral nutrition mixture CYP3A and CYP2C activities are suppressed, and by the addition of choline, CYP2E1 activity is increased (8).

One of the main parameters in drug pharmacokinetics is its distribution into tissues and body fluids. Parenteral nutrition fluids are hyperosmolar admixtures; therefore they can effect total volume and extracellular fluid volume in the body. Because of an increased extracellular fluid volume, drugs that are specially distributed into extracellular fluids (aminoglycoside, beta-lactam antibiotics, etc.) may be affected and changes in their pharmacological effects can be observed (8).

Effect of Catheter

The ideal method to prevent incompatibility problems is to use a separate catheter for intravenous administration of drugs where possible. If there is no separate catheter available, the use of a multi-lumen central venous catheter, with one lumen is fully reserved for parenteral nutrition is recommended. If there is a single-lumen central venous catheter available and a separate peripheral catheter insertion for intravenous administration of drugs is not appropriate, an intended to be used drug's compatibility/incompatibility information with parenteral nutrition should be consulted with the pharmacist (3).

Intravenous drugs are generally administered by a rapid infusion in adult patients, therefore the contact time with parenteral nutrition of a drug administered by the same catheter is short, however in pediatric patients, an administration of drugs is by a slow infusion which increases the contact time. Prolongation of the contact time can lead to increased risk of incompatibility with drugs (8).

Effect of the Formulations of Parenteral Nutrition

'All in one' parenteral nutrition admixtures contain intravenous lipid emulsions, that is why some drugs that are compatible with 'two in one' admixtures may be incompatible with 'all in one' admixtures (4).

Incompatibilities with 'two in one' admixtures result in formation of lumpy or yellow precipitate, which causes blurring or discoloration. On the other hand, 'all-in-one' incompatibilities are caused by structural damage of the emulsion and formation of free fat and a produced precipitate is invisible due to the masking effect of lipid content (15).

The manufacturers of drugs can be different where differences in formulation of drugs having the same active agent

may result in differences in drug's pH and other properties that can be associated with a significant impact on compatibility/incompatibility. That is why the compatibility of drugs with parenteral nutrition admixtures can never be guaranteed and the literature analysis can mislead the practices. Table 1 presents the compatibility of some drugs with different parenteral nutrition formulations (4). Although gentamicin is expressed as compatible with 'two-in-one' admixtures in this table, some studies indicate that it is incompatible due to differences in the content of a parenteral nutrition admixture (16).

In a study conducted by Trissel et al. (15) incompatibility was visually inspected in 9 different 'all in one' parenteral nutrition admixtures with 106 commonly used drugs and as a result 23 drugs were found to be incompatible. Considering the difference in the content of parenteral nutrition admixtures, three out of the nine admixtures were used for peripheral administration, three for central administration and the remaining three formulations were prepared to be used for bone marrow transplantation. Among included drugs, a precipitation was observed in 6 (acyclovir, amphotericin B, dopamine, fluorouracil, ganciclovir, cyclosporine) and dissolution and adiposity in the emulsion was observed in 17 (doxorubicin, doxycycline, droperidol, phenobarbital, haloperidol, heparin, hydromorphone, levorphanol, lorazepam, midazolam, minocycline, morphine sulfate, nalbuphine, ondansetron, pentobarbital, potassium phosphate, sodium phosphate). The stability of drugs or nutrients has not been studied.

Ceftriaxone is a drug that has a high tendency to bind calcium. Fatal reactions have been reported due to formation of ceftriaxone-calcium precipitates in infants, when ceftriaxone is administered together with parenteral nutrition admixtures containing calcium. This situation is observed even when the drug and the nutritional admixture are infused through separate lumens. However, this reaction has not been reported in older children or in adults. As a result of those studies, the concomitant use of ceftriaxone with a calcium-containing intravenous admixture in infants less than 28 days old is considered as absolute contraindication. In all other age groups, its administration through the same catheter, even from different lumens, or subsequent administration without rinsing the catheter is not recommended (8).

Effect of Lipid Emulsions

Due to the presence of lipid emulsions in 'all in one' admixtures, light-sensitive nutrients such as retinol in parenteral nutrition admixtures are generally protected against photolysis. However, the lipid emulsions mask the visibility of a precipitate which is formed by the disruption of stability (4).

The emulsion stability is maintained by the prevention of oil droplets approaching each other due to the negative charge build-up on the oil droplets resulting from the presence of emulsifying agents in intravenous lipid emulsions. The decrease in the pH of the environment or decrease in the negative charge on the surface of the oil droplets due to added electrolytes cause oil droplets to cluster to form larger oil droplets. Thus, stability is impaired. Large oil droplets increase

Table 1. Compatibility of some drugs with different parenteral nutrition formulations

Drug	Two-in-one admixtures	All-in-one admixtures
Acyclovir 7 mg/mL D5W	-	-
Amikacin 5 mg/mL D5W	+	+
Amphotericin B 0.6 mg/mL D5W	-	-
Ampisilin 20 mg/mL %0.9 NaCL	+	+
Dopamine 3200 mcg/mL D5W	+	-
Dobutamine 4 mg/mL D5W	+	+
Famotidine 2 mg/mL D5W	+	+
Fentanyl 12.5 mcg/mL D5W	+	+
Fentanyl 50 mcg/mL (non-diluted)	+	+
Gancyclovir 20 mg/mL D5W	-	-
Gentamicin 5 mg/mL D5W	+	+
Haloperidol 0.2 mg/mL D5W	+	-
Heparin 100 units/mL (non-diluted)	+	-
İnsulin 1 ünite/mL D5W	+	+
Midazolam 2 mg/mL D5W	-	-
Morphine 1 mg/mL D5W	+	+
Morphine 15 mg/mL (non-diluted)	None	-
Ofloxacin 4 mg/mL D5W	+	+
Ondansetron 1 mg/mL D5W	+	-
Potassium phosphate 3 mmol/mL (non-diluted)	-	-
Ranitidine 2 mg/mL D5W	+	+
Cefazolin 20 mg/mL D5W	-	+
Ceftazidime 40 mg/mL D5W	+	+
Ciprofloxacin 1 mg/mL D5W	-	+
Cyclosporine 5 mg/mL D5W	-	-
Sodium bicarbonate 1 mEq/mL (non-diluted)	-	+
Tacrolimus 1 mg/mL D5W	+	+
Ticarcillin/clavulanate 30/0.1 mg/mL D5W	+	+
Tobramycin 5 mg/mL D5W	+	+
Trimetoprim/Sulfametoxazol 0.8/4 mg/mL D5W	+	+
Vancomycin 10 mg/mL D5W	+	+

+ Compatible, - Incompatible, None: No data

the risk of pulmonary embolism, therefore clinical use of lipid emulsions with impaired stability is not safe. In cases of addition of drug into the parenteral nutrition admixture, the stability can be disrupted in the same manner (4).

Propofol formulation used for sedation contains 10% lipid emulsion, which provides 1.1 kcal energy to the patients by an infusion of 1 mL. When propofol is administered to patients receiving parenteral nutritional support, its contribution to daily calorie intake should be considered and administration of extra calories should be avoided. Furthermore, patients should be monitored in terms of hypertriglyceridemia. It has been proposed that the amount of lipid in the parenteral nutrition

admixture should be reduced according to the calculated amount of propofol administered (4).

Liposomal amphotericin B contains distearoilphosphatidylglycerol, and amphotericin B lipid complex contains dimyristoilphosphatidylcholine and dimyristoilphosphatidylglycerol. These products do not contain essential fatty acids, as they do not contain either linoleic acid or alpha-linolenic acid, therefore provide less calories (<150 kcal/day) (4).

Effect of Infusion Method

There are some other administration methods available for drugs or drugs known to be incompatible or drugs without

any information concerning their compatibility with parenteral nutrition admixtures. One of those methods is allocation of one lumen of a multi-lumen catheter only for parenteral nutrition; and other methods are to give the parenteral nutrition as intermittent infusion and administer drugs during the periods that parenteral nutrition is not given (8).

In patients with continuous infusion of parenteral nutrition where there is no other alternative, an infusion of parenteral nutrition should be discontinued in order to administer the drug and the infusion rate should be rearranged to meet daily nutritional requirements (8).

Effect of Bag Material

For the parenteral nutrition containing lipid admixtures, ethylvinylacetate (EVA) or unplasticized bag materials such as polyolefins are required. By the use of plasticizer bags such as polyvinylchloride (PVC), separation of bag material due to lipids may occur. The efficacy of lipophilic drugs (diazepam, nitroglycerin, dihydropyridines, etc.) is markedly reduced due to a substantial adsorption of the drug to the bag. Protein drugs (albumin, insulin, etc.) may also be adsorbed to the surface of the bag, therefore it is important that such drugs should not be added into parenteral nutrition bags in order to achieve expected effects of the drug (6).

Parenteral Nutrition and Safe Medication Administration

The key points to be considered for a safe administration of drugs in patients who receive parenteral nutrition admixture are listed as follows (2, 5, 6, 8):

- A multi-lumen catheter should be inserted for administration of drugs in patients receiving parenteral nutrition support.
- In the absence of information regarding compatibility, drugs should be administered through a separate catheter from the one used for parenteral nutrition solutions. "If in doubt, don't.." rule applies.
- Available information on compatibility should be evaluated according to the concentration of the drug used and the content of nutritional formulations (two-in-one or all in one).
- In the case of co-administration of parenteral nutrition admixtures and drugs by the same catheter, monitoring of an infusion set is required due to the risk of incompatibility reactions.
- Acquired information on stability and incompatibility should be based on reliable sources or the manufacturer's recommendations.
- 'All in one' admixtures are complex and carry a high risk for interactions; therefore addition of drugs into this admixture should be avoided.
- The drug's with the same active agent may have different pH or other properties due to different manufacturers, thus its effects on incompatibility must be considered.
- The safety of an addition of drug into parenteral nutrition bag or safety of concomitant infusion which may effect on stability/incompatibility, should be assessed and approved by the pharmacist.

ENTERAL NUTRITION AND DRUG INTERACTION

It is a general rule to check drug incompatibility and stability when adding drugs into parenteral nutrition admixtures or administration through the same catheter. However, similar attention is not paid in the case of drug administration with enteral nutrition (17).

It is reported in studies that 5-43% of practitioners perform rinsing with water before and after drug administration, 32-51% administer drugs separately, 44-64% dilute liquid drugs and 75-85% pay attention to not to be crushed modified release drugs (18). On the other hand, it has been shown that 74% of practitioners make at least two errors when administering the drug through feeding tube (19).

During the administration of medications through feeding tubes, they can interact with other drugs and also with enteral nutrition products in pharmacokinetically (absorption, distribution, metabolization, elimination) and/or in pharmacodynamically (synergistic or antagonistic activity). In order to prevent interactions and minimize the impact of adverse effects to the patient, the basis of interactions and its triggers should be thoroughly evaluated.

In order reduce or prevent the interactions between enteral nutrition and drugs, changing the dosing scheme to avoid co-administration of drugs, reducing the number of medications and/or temporarily suspending drugs that are not urgently needed are some of the measures to be undertaken. Changing the dosage form or the route of administration or using different groups but having the same therapeutic activity should also be considered as an alternative.

The use of same tubes for the administration of drugs and for the enteral nutrition causes problems like bioavailability, incompatibility, complications and interactions. However, the complications arising from co-administered drugs' pharmaceutical dosage forms and formulations are generally interpreted as intolerance of enteral nutrition (20). The most frequent complication is reported as diarrhea (45%) (21).

Effect of Feeding Tube Size

The small-bore (5-12 French) nasoenteric tubes help to maintain lower esophageal sphincter (LES) function, but they may be easily clogged with an administration of drug or a concentrated, dense and fibrous enteral nutrition products due to their narrow diameter. The administration of drugs or viscous enteral nutrition products (≥ 14 French) with a larger gastric tube has a much lower risk of clogging (20, 22). An obstruction in the small-bore feeding tube usually occurs in 15% of the patients and an increased tendency for clogging is observed with the number of medications used (22).

Effect of Feeding Tube Placement Site

The region of the distal end of the tube should be considered along with the administration of a drug from the feeding tube. An immediate release dosage forms usually disperse and dissolve in the stomach, followed by dissolution and absorption in the intestine. Passing through the stomach via a feeding

tube influences the dissolution and absorption of certain drugs (18).

High concentrated and hypertonic drugs can be better tolerated in the stomach compared to small intestine. Moreover, some drugs should have an effect especially in the stomach or needed to be applied into the stomach (17, 18, 20, 23, 24):

- Antacids used to neutralize gastric acid secretion do not show any benefit in the small intestines due to bicarbonate secretion from the pancreas.
- Sucralfate and bismuth show their effects by forming a protective layer in the stomach, but with a minimal benefit in the small intestine, therefore only gastric administration is preferred.
- Drugs such as ketoconazole and itraconazole need an acidic environment for activation, if not given in stomach, the bioavailability is reduced, and expected effects of the drug may not be seen.
- Drugs like opioids, tricyclic antidepressants, beta-blockers, and nitrates undergo a high rate of first pass metabolism in the liver, administration into the intestine increases their absorption, resulting in increased systemic effects.
- Iron preparations are usually absorbed in the duodenum once dissolved in the stomach; their direct administration into the jejunum can lead to low bioavailability.
- Warfarin is highly absorbed in the proximal small intestine, when it is administered via jejunostomy, the bioavailability may be reduced.
- If the distal end of the tube is in the stomach, nutrition should be discontinued 30 minutes before and 30 minutes after administration of drugs like ketoconazole, penicillins, and tetracyclines which should be taken on an empty stomach. However, if the distal end of the tube is in the jejunum, discontinuation is not necessary, rinsing the tube with water before and after drug administration is sufficient.

Effect of the Type of Enteral Nutrition Administration

When an enteral nutrition is administered intermittently (for approximately 8-20 hours), usually during the night, the interrupted period of enteral nutrition constitutes the ideal time for a drug administration through the feeding tube (25).

In patients who receive continuous enteral nutrition, an interruption may be necessary before and after the administration of medications (24). In order to avoid impairment in the patient's nutritional status, the interruption time for nutrition should be reduced to minimum. The drugs that require a single or two dose administration per day should be preferred. When a single dose administration is preferred, the nutritional intake is decreased by 12.5 to 17%, while this reduction is 25-33% when b.i.d administration is preferred (22).

Addition of a Drug to a Solution of Enteral Nutrition

Very few studies have been conducted regarding the compatibility of enteral nutrition products with drugs. Factors related to enteral nutrition (type and concentration of the protein, mineral and fiber content of the formulation), and drug-relat-

ed characteristics (like a pH, viscosity, osmolarity and mineral content of the drug solution) are considered as factors cause to incompatibility. The stability of enteral nutrition is evaluated only in a very few of those studies. Evaluations often include a visual inspection and changes in chemical (such as pH) or physical (such as osmolarity) properties. An obstruction of the feeding tube is reported in 95% of the admixtures with incompatibility (26-28).

The addition of drugs into enteral nutrition bags may result in occlusion of the tube, change in bioavailability of the nutrient or the drug, or alteration of gastrointestinal function by interactions of drug-enteral product. In a study, it was found that 23 out of 24 different incompatible drug-enteral product admixtures were resulted in, tube occlusion (17).

Acidic preparations such as syrups, when incorporated in the formulation of enteral nutrition, can often lead to problems such as clogging or enteral tube obstruction. The compatibility between hydrolyzed proteins or enteral nutrition products containing free amino acids and drugs appear to be much higher compared to the products that contain absolute proteins. Fiber containing products generally are not compatible with drugs (4).

Since there is lack of information on addition of drugs into enteral nutrition bags, as a general rule, an addition a drug into enteral feeding bag is not recommended. Available information on compatibility or stability of a drug with the enteral nutrition product should not be considered as valid for all other enteral nutrition products or for other drugs of the same group. In fact, it should be remembered that compatibility and stability conditions may vary with different formulations of the same drug (18).

The Effects of Enteral Nutrition Products on Drugs

A reduction of plasma proteins in the body due to malnutrition can alter the distribution of drugs that bind to plasma proteins in high ratios. In addition, significant changes in body fluids may also affect the distribution of the drug.

Nutrition with low-protein products has been reported to reduce the effect of the enzyme system which is responsible for the metabolism of drugs. As a result of malnutrition, drugs cannot be effectively metabolized, therefore an increase in side effects can be observed. If otherwise, i.e., nutrition with high protein/low carbohydrate containing products, the enzyme system is induced, the clearance of drugs like theophylline significantly increases, therefore leads to a reduction in the effectiveness of the drug (29).

Enteral products containing unhydrolysed protein and fiber are usually incompatible with drugs, so enteral nutrition should be discontinued before and after the drug administration when using these types of products (4).

The vitamin K within enteral nutrition products may lead to changes in anticoagulation response in patients using warfarin. It should be noted that INR monitoring and dose adjust-

ment according to the patient may be necessary. When patients are switched from enteral nutrition to an oral nutrition, the dose of warfarin might need to be decreased (4).

Weak acidic drugs are often in a non-ionized form in low pH, which require low pH for absorption from the gastrointestinal tract. The exact opposite property is true for weak alkaline drugs. The absorption of drugs can be altered by changing the pH of the gastrointestinal tract with foods or other drugs (29). The American Society for Parenteral and Enteral Nutrition (ASPEN) recommends interruption of enteral nutrition 30 minutes before and 30 minutes after the administration of drugs which absorption properties are affected by enteral nutrition (such as ciprofloxacin, doxycycline, isoniazid, levofloxacin, ofloxacin, penicillin V, rifampicin, phenytoin, carbamazepine, theophylline, strontium, aluminum, magnesium, or calcium-containing preparations). However, in many studies an interruption of 1-2 hours prior to and 1-2 hours after drug administration is suggested (20).

The impact of enteral nutrition on drug absorption can be explained by different mechanisms:

- Diarrhea occurring due to enteral nutrition products or various reasons such as sorbitol can alter the drug absorption (29).
- The absorption of some drugs such as methyl dopa and levodopa can be reduced due to high protein nutrition (29).
- The effectiveness of drug is decreased by withholding on the feeding tube and the therapeutic failure can be observed. An irrigation with water after administration and diluting the drugs in the form of suspension increases the amount of drug taken by the patient (4).
- An absorption is significantly reduced by food in some drugs such as loratadine, ampicillin, and tetracycline, therefore these drugs must be taken on an empty stomach. When administering those drugs through feeding tube enteral nutrition should be suspended (30).
- Divalent cations adhere to fluoroquinolone group antibiotics which constitutes chelation, therefore the bioavailability of ciprofloxacin administered by enteral feeding tube is decreased by 27-67%.
- Due to changes in the bioavailability of narrow therapeutic range drugs, toxicity and insufficient treatment can be seen when administering these drugs via feeding tube, therefore enteral nutrition should be suspended and appropriateness of dosage should be checked with monitoring of blood levels (31).
- The blood level of phenytoin is decreased by 72% when administered through the feeding tube. Phenytoin binds to serum proteins in high ratios. It is thought that blood levels of phenytoin decreases due to binding to proteins within enteral products (31).
- Administration of modified release nifedipine tablets via feeding tube after crushing is shown to result in fatal toxicity due to increased bioavailability (21).
- In critically ill or postoperative patients requiring nasogastric tube application, the bioavailability of drugs admin-

istered through the feeding tube might decrease due to slowing of gastric emptying. It is shown that bioavailability of parasetamol and atenolol is significantly decreased when administered through the feeding tube in postoperative patients (31).

Effect of Drugs on Nutrition

In the case of frequent interruption of nutrition in order to administer medications, malnutrition may occur if infusion rate is not increased accordingly in order to provide calorie intake required (24).

In addition, it should be remembered that some drugs might cause electrolyte imbalance in patients. Diuretics generally lower sodium and potassium levels and hydration state of the patient. Steroids may change sodium, potassium and glucose levels. Angiotensin converting enzyme inhibitors increase potassium levels whereas potassium and magnesium levels decrease with amphotericin B. Calcium preparations lower phosphorus levels (20).

A sufficient gastrointestinal blood flow is required for absorption and utilization of nutrition. In hemodynamically instable patients with sepsis, hemorrhage, hypovolemia, polytrauma and cardiogenic shock; vasoactive agents such as norepinephrine, epinephrine, phenylephrine, dopamine and dobutamine are required to maintain blood flow to vital organs like heart and brain. In such cases, gastrointestinal blood flow decreases. If an increased oxygen demand in the intestines due to enteral nutrition is not met, intestinal ischemia, and rarely, intestinal necrosis that has a high risk of mortality, may occur. Since intestinal ischemia and necrosis is a dreaded complication, the application of enteral nutrition in patients requiring vasoactive agents is avoided (32).

The American Society for Parenteral and Enteral Nutrition recommends interruption of enteral nutrition in hemodynamically instable patients receiving high dose catecholamines until patient stability is achieved; and in those receiving low dose catecholamines, a careful administration of enteral nutrition should be sought (32).

Liquid preparations may cause side effects due to adjuvant substances like sorbitol when they are administered through the feeding tube. The studies have shown that 50% of patients develop diarrhea due to constituents of liquid solutions, but clinicians consider that the enteral nutrition product is the cause of diarrhea, therefore they prefer to change the enteral product instead (22).

Drug Administration Through the Tube

The crushing drugs during administration, fluid/water addition or mixing with other drugs/products/solvents might change the drug formulation which affects drug stability (18, 22). A drug formulation includes fillers, binders, buffers, and preservatives besides the active drug component. Thus, therapeutically inactive adjuvant substances and their properties must be considered during the drug administration through the feeding tube (17).

It should be remembered that the smaller the particle size, the lower the risk of clogging when tablets are crushed in order to administer via feeding tube. In addition, irrigation of the tube with water after drug administration reduces the risk of clogging (18, 22).

Most of the tablets or capsules are conventional immediate release products. These products are designed to release the drug content within minutes after reaching the stomach following oral administration. Nevertheless, there are numerous drugs with modified release forms and with different formulations. Modified release drugs should never be crushed to be administered via the feeding tube. Due to crushing of such drugs, its activity can be markedly reduced due to completely changed release properties of a drug or drug-induced toxicity/side effects can occur as a result of a sudden release of 24 hour dose. A different dosage form of the drug or any other drug with the same activity with an appropriate dosage form should be preferred instead of film-coated, enteric-coated and modified release tablets (33).

Tablets are manufactured as scored or the presence of a statement on the drug information sheet which indicates that the drug can be divided does not mean that it is also suitable for crushing and for administration via the feeding tube. Film-coated or enteric-coated tablets cannot be fully crushed. In a case of crushing of enteric coated tablets and capsule contents; property of the formulation may deteriorate, its bioavailability may change and the tube may be clogged (22).

The drugs in the form of capsules are usually administered through the feeding tube by opening the capsule and mixing its content with water; but the contents of enteric-coated capsules or those containing granules/pellets should not be crushed (22). Soft gelatin capsules can be administered via the feeding tube after its liquid contents aspirated into a syringe by a needle puncture. However, there is a risk of failure for administration the entire content of the capsule after this application, therefore dissolving the capsule in warm water in order to administer the whole constituents of mixture into the tube

can be considered as an alternative option. In this method, an undissolved part of the capsule should not be administered into the feeding tube, otherwise this may lead to clogging of the tube.

Commercially available liquid dosage forms are not always suitable for a direct administration via the feeding tube. Although both are in the liquid form, the viscosity of suspensions is much higher than that of solutions. Taking into consideration the viscosity and osmolarity, the medications in liquid dosage forms may need to be diluted with sterile water before administration via feeding tube. The fluidity is improved and the risk of clogging of the tube is reduced by dilution of drugs in liquid dosage forms (34).

Liquid dosage forms also contain excipients besides the active drug. Its components of sweeteners and stabilizers increases the osmolarity and may cause diarrhea. Liquid dosage forms with electrolytes also have a high osmolarity. With the administration of hyperosmolar products via the feeding tube, diarrhea, stomach cramps, bloating, and vomiting can be observed (22).

There is a risk of physical and chemical reaction formation when two or more drugs are crushed to administer via the feeding tube (18). Because of crushing tetracycline and iron preparations together, the resulting tetracycline-iron chelates are shown to have very low solubility (31). Furthermore, since there is no information available on the release characteristics and efficacy of drugs which are administered after mixing in this way, it is not recommended to crush and mix drugs together (18).

In a case of mixing drugs in liquid form together, the physico-chemical properties of the solvent of each drug should be considered thoroughly to prevent decomposition of their solubility and stability. A prediction of the stability and incompatibility of the final mixture is not always possible. Therefore, administration of drugs in liquid form via feeding tube by mixing with each other leads to a much more complicated situation (18).

Table 2. ASPEN recommendations on drug administration through the feeding tube and the level of evidence.

- Do not add medication directly to an enteral feeding formula. (B)
- Avoid mixing together medications intended for administration through an enteral feeding tube given the risks for physical and chemical incompatibilities, tube obstruction, and altered therapeutic drug responses. (B)
- Each medication should be administered separately through an appropriate access. Liquid dosage forms should be used when available and if appropriate. Only immediate-release solid dosage forms may be substituted. Grind simple compressed and the level of evidence. until it becomes a fine powder, then mix with sterile water. Hard gelatin capsules can be administered after opening the capsules and mixing its contents with sterile water. (B)
- Before administration of medication, stop the feeding and flush the tube with at least 15 mL water. Dilute the solid or liquid medication as appropriate and administer using a clean oral syringe (≥ 30 mL in size). Flush the tube again with at least 15 mL water considering the status of patient's fluid volume. Repeat the process for the following medication. Finally, flush the tube again with at least 15 mL water. Amount of dilution or flushing should be reduced for pediatric doses or status of fluid restriction.(A)
- Restart the feeding in a timely manner to avoid compromising nutrition status. Only hold the feeding by 30 minutes or more when separation is indicated to avoid altered drug bioavailability. (A)
- Use only oral/enteral syringes labeled with 'for oral use only' to measure and administer medication through an enteral feeding tube. (B)
- Consult with an adult or pediatric pharmacist for patients who receive medications co-administered with enteral nutrition. (C)

Opening capsules or crushing drugs with irritant, teratogenic, carcinogenic or cytotoxic properties like antineoplastics, hormones and prostaglandin analogs is not recommended. During its preparation, a direct contact or an exposure by respiratory tract to such drugs (e.g dutasteride, mycophenolate) may cause harmful effects to the personnel involved. In addition, those who are allergic to antibiotics may suffer due to contact or inhalation exposure while preparing antibiotics to be administered by enteral tube. The resulting particles after crushing drugs with irritant properties (isotretinoin, temozolamide and valproic acid) can cause peptic ulcers when administered via feeding tube, therefore crushing of such drugs is not recommended (22).

Table 2 summarizes ASPEN recommendations and the level of evidence on drug administration through the feeding tube.

CONCLUSION

Concurrent use of nutritional support and administration of medications are common clinical practice. Incompatibility and stability problems may occur both for the drug and for the enteral nutrition product when drugs are administered through the same tube that is used for enteral nutrition. It should be considered that the tube may be clogged, the bioavailability of the drug or enteral product may vary, and the function of the gastrointestinal tract may change as a result of such administration. Paying a less attention on pharmaceutical dosage forms of the drugs during drug administration via enteral feeding tubes may cause alteration in drug efficacy and failure to achieve desired outcomes.

Parenteral nutrition admixtures contain 40 different ingredients (macro and micro nutrients), thus its stability may be disrupted with an administration along with medications due to either interaction or physical/chemical incompatibility. There are few studies on incompatibility of parenteral nutrition solutions with most drugs. Parenteral nutrition solutions can differ in terms of content and mixing methods, therefore differences in the content of the mixture used in particular study should be kept in mind when evaluating the results.

The risk of interactions increases with polypharmacy (multiple drug use), thereby all drugs other than primarily required urgent ones (such as hormone replacement therapy) should be suspended. Then, in accordance with the patient's clinical status and needs, alternative routes of administration of drugs should be considered. For medications that do not have different dosage forms, the use of an alternative drug with same efficacy should be considered. Drug incorporation into either the parenteral or enteral nutrition bags should be avoided.

Pharmacists who must be a part of the health care team in nutritional support units should assist the team on issues like drug stability, incompatibility, appropriateness of formulations and dosage forms, dose adjustment, evaluation of interactions, and convenience of tube administration. The pharmacist should be asked to provide required information on physicochemical properties of the drug after evaluation of stability and compatibility data in the literature.

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