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Drug administration via enteral feeding tubes in intensive therapy – terra incognita?

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Abstract

The use of enteral feeding tubes has become more frequent, both in hospital settings and in home care. The feeding tubes serve not only to deliver nutrients, but also as a route for medication provision. Nonetheless, the pharmaceutical, legal and technical implications of medication delivery via enteral feeding tubes are not widely understood by doctors and nurses. Not only is the type of medication relevant, but also the type of feeding tube. Crushing tablets may have detrimental effects for a patient and a staff member too. Administering a drug via enteral feeding tubes usually falls outside the terms of the licence (off-label), so burdening medical staff with the entire responsibility for potential adverse reactions.

Key words: critical care, drugs, enteral tubes

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Apart from being a source of pleasurable experiences associated with the taste, smell, colour and preparation of food, nutrition enables the body to function in terms of health and disease. Food consumed provides nutrients essential for living, i.e. proteins, fats, carbohydrates, vitamins, trace elements and water. At the level of cells and their metabolism, all those substrates are necessary for energy generation, storage (in the form of adenosine triphosphate) and use. Under physiological conditions, ingestion, grinding and absorption of nutrients, as well as excretion of useless residuals or potentially harmful metabolites, are functions of the gastrointestinal (GI) system extensively affected by the neuroendocrine and hormonal system.

Enteral feeding tubes or fistulas are increasingly common among patients treated in hospital and home settings. Such devices are used not only to supply nutrients but also to administer drugs. The technical and formal difficulties resulting from the administration of substances directly to the stomach or small intestine (bypassing several natural levels of the GI system) are often overlooked.

While applying short-term (gastric or intestinal feeding tubes) or long-term (gastrostomy, jejunostomy) access devices to administer nutrients or drugs to the GI tract, it is important to realise that in such cases a mixture of several dozen active components is used, whose physico-chemical compatibility has not been confirmed. Moreover, none of the drugs available on the market has been approved for enteral feeding access directly to the stomach, duodenum or intestine. The drugs are administered off-label, i.e. they are not listed in the summary of product characteristics. The most common examples of violating the safety rules and administering drugs beyond their approved indications are the crushing of solid dosage forms of drugs before administration, pouring out the capsule contents, and using parenteral dosage forms of drugs for oral administration. The problem relates to both the administration of drugs through gastric and intestinal feeding tubes to the GI tract and individuals without such access devices who are incapable of swallowing solid dosage forms of medications whole.

The above practices are associated with the following dangers [1, 2]:

1. Possible interactions between the active drug substance and diet – inactivation of the medicinal substance, formation of toxic compounds and metabolites, formation of precipitates and changes in the pharmacokinetic properties of the medicinal substance.

2. Possible interactions of several drugs when administered simultaneously – the risk of physico-chemical incompatibility during the *in vitro* phase or interactions of various medicinal substances *in vivo*.
3. Inactivation of the medicinal substance or substantial changes in its strength of action due to destruction of its structure during preparation of the drug for administration via the feeding tube/fistula.
4. Clogging of the tube/fistula lumen by fragments of solid dosage forms of drugs/coatings and problems with maintaining patency of tube/fistula lumen, which can be a critical element of therapy.
5. Exposure of patients to complications resulting from the supply of medicinal substances to the wrong GI level.
6. Exposure of medical personnel to directly toxic effects of the active substance released from the pharmaceutical drug form.

When administering drugs off-label, the possible adverse effects and inefficacy of therapy should be considered. Some complications can be fatal [1]. It should be assumed, however, that drugs are used in good faith and for the patient's good, even when their use is beyond the approved indications. Physicians should be fully convinced that the drug is necessary and consider the benefit/risk ratio.

The number of patients receiving nutrition via enteral feeding tubes is increasing, not only in hospital departments including intensive care units (ICUs), but also in the home setting. Patients require not only nutritional support but also drug therapy. The enteral feeding tubes currently used have 6–12 Fr diameters, which makes it virtually impossible to supply mixed diets and substantially hinders the supply of drugs.

Physicians and nurses are not thoroughly acquainted with the information regarding enteral administration of drugs, bypassing the natural oral route. Patients with enteral feeding tubes/fistulas are typically prescribed the dosage forms of drugs that cannot be crushed. The literature focusing on the above issues is scarce, and literature in Polish has been absent until recently.

The aim of this study was to present the current knowledge on the principles of drug administration via enteral feeding tubes.

GENERAL PRINCIPLES OF ENTERAL DRUG ADMINISTRATION

Drugs can be administered through enteral feeding tubes only in exceptional cases justified by absolute medical indications. The available literature includes little information on enteral administration of drugs, bypassing the oral route; therefore, the majority of recommendations should be considered as theoretical.

Before drug administration, the following should be checked:

— the site of drug absorption
— the location of the enteral feeding tube
— the type and diameter of the feeding tube
— the dosage form of the drug administered
— interactions between the medicinal substance and diet.

The majority of oral drugs are absorbed in the small intestine, some (furosemide, amoxicillin) in its initial segment. However, there are drugs which are mainly absorbed in the stomach (e.g. drugs neutralising gastric juice, ketoconazole requiring acidic pH for optimal action) or those absorbed predominantly in the duodenum (e.g. fluoroquinolones, iron). Their administration to the further part of GI tract (e.g. via jejunostomy or intestinal tube) induces minimal or no therapeutic effect. The weakened action of fenytoin and anticonvulsants is particularly relevant; therefore, their blood concentration has to be monitored if administered to the small intestine. In some cases, it is also important to shorten the time of contact between the medicinal substance and the GI tract. Special attention should be paid to drugs characterised by narrow ranges of therapeutic concentrations, such as warfarin, digoxin, and antiepileptic drugs. Their use requires effect/blood concentration monitoring [3].

Some drugs interact directly with other drugs (zinc/iron and ciprofloxacin, iron and tetracyclines, vitamin C and fluconazole, vitamin D and atorvastatin); thus, appropriate time intervals during their use should be ensured [4].

Fine-bore feeding tubes and fistulas should be managed with great caution. It is recommended to formulate and implement the protocols regarding their flushing and patency maintenance. Special attention should be paid to intestinal feeding tubes. All post-pyloric tubes require flushing exclusively with sterile isotonic solutions. The diets administered through them should also be sterile.

Drugs should not be administered using decompression tubes or decompression lumens of multiple lumen tubes [5]. Feeding syringes (50–100 mL) have to be used for flushing the fine-bore feeding tubes as it reduces the risk of pressure damage [6]. Flushing should be slow to collect the medicinal substance residuals depositing on the tube walls. Clogged enteral feeding tubes should not be cleaned with metal wires (the risk of GI tract perforation). Moreover, it is important to determine the causes of tube clogging [7].

The possible causes include:

— precipitation of the diet with a drug of acidic pH
— retention of the diet in the tube (inaccurate flushing, the transfusion set not disconnected after completion of diet supply)
— biological contaminations of the diet
— improper drug administration

— properties of the material of which the feeding tube is made.

Various substances have been used to unclog feeding tubes: warm/cold water, coca-cola and other CO_2 saturated beverages, bicarbonate solutions, and pancreatic enzymes. The efficacy of most of them is questionable; moreover, the low pH of coca-cola could even favour the formation of protein precipitates in the diet. Marcuard et al. [8] demonstrated that of all the substances mentioned, only pancreatic enzymes are effective.

Furthermore, the location of a feeding tube should be accurately checked using aspiration of contents, determination of their pH, and imaging methods.

All alternative routes of drug administration should be considered (intravenous, intramuscular, inhalation, transdermal, sublingual, rectal); when the patient's condition improves, this can be changed into oral forms straight away.

INTERACTIONS OF DRUGS WITH THE DIET ADMINISTERED ENTERALLY

Many drugs interact with normal diet and chemical diets used for enteral feeding, e.g. warfarin or dietary sources of vitamin K. Interactions can occur at any stage of drug transit through the body — absorption, distribution, metabolism and elimination (pharmacokinetics).

The rules to avoid or minimise the risk of incompatibility and formation of precipitates are as follows:

1. Drugs should not be administered directly to the diet. This increases the risk of incompatibility, contamination and a decrease/increase in the drug amount when the rate of diet flow changes [9].
2. The diet supply should be stopped for at least 30 minutes before and after drug administration.
3. Once the drug-diet interaction has been confirmed and is found significant, the interruption in diet supply should be at least 1 hour before and 2 hours after drug administration (fluoroquinolones, hydralazine, warfarin, carbamazepine, hydrochlorothiazide, theophylline, gabapentin). In the case of fenytoin, the interruption should be 2 hours before and after drug administration.
4. The feeding tube should be rinsed with 10–30 mL of water or other recommended agent before and after drug administration. The total volume of rinsing fluids should be added to the daily fluid balance.
5. Simultaneous administration of several drugs should be avoided (due to the risk of physical and chemical incompatibilities and changes in the therapeutic effect of drugs).

When several types of drugs are prescribed to be administered repeatedly during 24 h, the patient is at risk of a substantial loss in enteral diet supply and a poorer protein/energy balance. Therefore, it is essential to limit polypragmasia to a minimum and interruptions in enteral feeding caused by the need to administer medications.

LIQUID DOSAGE FORMS OF DRUGS

Liquid dosage forms of drugs are preferable and recommended for supply via enteral feeding tubes. Not all medicinal substances are available in liquid forms; some however can be prepared in the dispensary. The high osmolality of some drugs presents problems (even > 1,000 mOsm l^{-1} compared to physiological osmolality of GI secretions of 100–400 mOsm L^{-1}). Their administration can lead to secretory diarrhoea, vomiting and abdominal distension. These side effects can be reduced by diluting the drug with 20–30 mL of water or more before administration, unless contraindicated. The administration of liquid dosage forms containing such ingredients as sorbitol, mannitol, saccharose, lactose and magnesium can also lead to abdominal distension and diarrhoea. Drugs containing large amounts of sorbitol should be avoided, if possible, as its cumulative dose > 7.5 g usually results in diarrhoea. At a dose > 15–20 g, diarrhoea can be extremely severe.

Moreover, high viscosity and density of some drugs can be a problem as it favours feeding tube obstruction. In such cases, the manufacturer of a particular drug recommends its dilution before administration (e.g. amoxicillin with clavulanic acid). Sucralfate can lead to the formation of bezoar-like masses when gastric emptying is delayed. Diazepam is not recommended for enteral administration because the active substance is absorbed by the material of which the feeding tube is made. Moreover, diazepam should be accurately dissolved and suspended in 30–60 mL of water due to its tendency to clog the lumens of feeding tubes. A similar problem is observed in the case of fenytoin, clonazepam or carbamazepine [5]. The risk of feeding tube obstruction is also increased by drug pH < 4 due to the possible formation of precipitates caused by interactions with the diet. Therefore, suspensions should be used rather than syrups.

In exceptional cases, parenteral drug forms can be administered enterally. However, such drugs are usually more expensive; some have high osmolality and solvents unfit for oral administration (e.g. polyethylene glycol in amiodarone). High osmolality of some parenteral forms of drugs hinders their administration to the GI tract. Osmolality should always be checked and the drug should be diluted in 30-60 mL of water, if necessary.

SOLID ORAL DOSAGE FORMS OF DRUGS

The crucial practical issue is whether the oral dosage form can be crushed. The knowledge concerning this issue is insufficient among physicians responsible for drug orders and nurses responsible for preparation and administration of drugs via feeding tubes [10, 11].

There are dosage forms of oral drugs whose properties and bioavailability completely alter when their structure is destroyed. They include:

— sublingual tablets
— buccal tablets
— gastric tablets
— enteric-coated tablets
— sustained-release tablets
— oral therapeutic systems.

Sublingual and buccal tablets contain substances which are not absorbed from the GI tract or undergo the first pass effect in it. Thus, the administration of such a drug via enteral feeding tubes does not induce a therapeutic effect [12]. Gastric tablets/capsules contain medicinal substances absorbed in the stomach. Special polymers present in coatings or substances forming hydrogel upon contact with the gastric juice, which hinders water diffusion to the inside of the swelling mass, prolong the presence of the therapeutic substance in the stomach (floating capsules — hydrodynamically balanced system [HBS]). A similar effect is produced by bicarbonate, a source of CO_2. Thanks to CO_2 bubbles, the therapeutic substance floats longer in the stomach and passes slowly to the further GI parts (floating capsules). Destroyed structures of such dosage forms of drugs significantly reduce their therapeutic effect.

Enteric-coated (EC) tablets enable the delivery of the therapeutic substance in such a way that it reaches the intestinal lumen unchanged. Active substances can decompose in the acidic environment (proton-pump inhibitors), irritate the gastric mucosa (non-steroidal anti-inflammatory drugs), be better absorbed from the intestine than from the stomach (iron, magnesium compounds), or act in inflammatory intestinal diseases (mesalazine). EC tablets are resistant to the effects of gastric juice and dissolve in an alkaline environment. When the coating is crushed, the therapeutic substance is inactivated before the desired place of its action or the gastric mucosa is irritated. The elements of coatings can clog the feeding tube lumen.

Sustained-release tablets after one-time administration guarantee the release of the therapeutic substance for a longer time and the maintenance of a constant therapeutic concentration. The above is possible thanks to the special coating structure and technology of production; the absorption of the therapeutic substance can take place in various GI parts. Sustained-release tablets contain a high dose of the active substance — if crushed, there is a risk of adverse effects, even fatal ones (e.g. after crushing sustained-release opioid drugs). A fatal complication after the simultaneous administration of sustained-release labetalol and nifedipine has been described in the literature [1]. The sustained-release preparations that should not be crushed are denoted by the following abbreviations and terms: XR-, XL-, ER- (extended release), SR (sustained/slow release), SL (slow liberation), TR (time release), R (retard), prolongatum, prolonged release, long, depot, dur, chrono, continus, and MR (modified release). Moreover, the drugs denoted ZOK (zero order kinetic) containing pellets as a carrier or container of the therapeutic substance should not be crushed. The pellet system guarantees constant release and concentration of the therapeutic substance in the blood. Oral controlled-release (CR) therapeutic systems are tablets whose structure ensures a constant speed of drug release, independent of the amount of substance left in the system and pH of the environment or presence of food in the GI lumen. The destruction of CR drug structure can cause quick release of the entire therapeutic substance contained in the system and increase the risk of adverse side effects.

Furthermore, tablets containing caustic, carcinogenic, allergenic, teratogenic and cytotoxic substances should not be crushed due to the risk of toxic effects on the medical personnel.

SOLID DOSAGE FORMS OF DRUGS THAT CAN BE ADMINISTERED ENTERALLY

Solid dosage forms that can be administered enterally include:

a) uncoated tablets;
b) coated tablets with the coating protecting only the oral mucosa against irritation or unpleasant taste;
c) capsules containing the powdered therapeutic substance/pellets;
d) sustained-release capsules containing pellets — the therapeutic substance should be removed from the capsule and suspended in water; these should not be crushed;
e) enteric-coated capsules containing pellets — the therapeutic substance should be removed from the capsule and suspended in water; these should be crushed;
f) liquid-filled gel capsules;
g) effervescent tablets, pellets, powders, tablets to prepare oral solutions/suspensions.

SUMMARY

The administration of drugs via enteral feeding tubes is off-label and physicians must be fully convinced as to its absolute necessity and benefits for the patient. All adverse side effects and complications result in legal liability. Therefore, it is essential that the issues presented in this paper become better understood and the knowledge of physicians and nursing staff be broadened.

Standards of management and procedures regarding drug administration via enteral feeding tubes should be introduced in ICUs and other hospital departments. If this is done, the safety of this increasingly popular form of therapy will increase.

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