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To Hold (Enteral Feeding) or Not to Hold: That IS the Question; A Commentary and Tutorial

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Enteral nutrition may interfere with drug absorption and lead to therapeutic failure. The best management plan to minimize this interaction remains controversial. One of the solutions to this clinical issue involves withholding enteral feeding for a period of time in order to minimize the potential risk factors that interfere with oral bioavailability of drugs. Although data from the literature suggest that this approach is associated with limited success in some cases, the length of time enteral feeding was held varied among studies. This article serves as a tutorial guide to help clinicians determine when these concerns may be more clinically significant and what actions can be considered to optimize patient outcomes.

INTRODUCTION

Should enteral nutrition (EN) be withheld before this medication is administered? What do we actually accomplish by holding EN? How long should EN be withheld? Should EN be stopped both before and after drug administration? These are some of the questions that many clinicians have been wondering about for a long time. Often times, the responses can be quite different, and even conflicting, depending on who provides the recommendation (1, 2). But in practice, whether or not to withhold EN can have a significant impact on the patient's care plan. From the nutritional perspective, the feeding regimen may require a major adjustment to prevent rendering a significant deficit on caloric intake. This is especially the case if the medication is given multiple times a day with EN temporarily discontinued both before and after each of the doses. From the nursing perspective withholding and then restarting EN affects workflow. If the hourly infusion rate for the EN needs to be increased as a result of withholding feeding, gastrointestinal intolerance of

the new feeding regimen by the patient may become an issue. From the pharmacotherapeutic perspective, there are concerns that the absorption pattern and bioavailability of drug are altered by EN, thus affecting the safety and efficacy profiles of medications. The aim of this article is to discuss when these concerns are clinically significant and what actions could be taken to optimize patient care. The purpose of this paper is to serve as a tutorial to guide clinical decision making rather than a comprehensive review of the existing literature. Clinicians are strongly encouraged to review the literature concerning drug-specific management approaches that have been published and exercise good clinical judgment to individualize the patient care plan.

Rationale Behind Withholding Tube Feeding

The rationale behind withholding EN with drug administration is to either minimize or prevent drug-nutrient interactions. Specifically, it is the interactions that occur either in the delivery device or gastrointestinal lumen that are potentially being avoided (3). These interactions typically involve physicochemical reaction and inactivation between the nutrient(s) and the drug (4, 5). In most cases, the primary concern is the impaired absorption of the drug due to the physical presence of

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specific nutrient(s). This could result in therapeutic failure. The theory is that the physicochemical reactions that decrease the bioavailability of a drug exerted by EN will be minimized by providing the feeding-free period. Based on this theory, the optimal time to withhold EN should be long enough to allow food to pass through, thus creating an environment similar to having an "empty stomach."

The First Clinical Evidence to Support Stopping Enteral Feeding

The first clinical trial to evaluate the impact of continuous EN on drug absorption was conducted by Bauer at the University of Washington (6). In a consecutive series of 53 neurosurgery patients treated at a regional trauma center, Bauer observed that all the patients who received typical doses (300 mg to 400 mg daily) of phenytoin, an anti-seizure medication, experienced subtherapeutic phenytoin serum concentration. Sixty percent of these patients continued to have subtherapeutic therapy even after the dose of phenytoin was increased to 800 to 1200 mg daily. All of these patients received continuous nasogastric feeding. The possibility that hypermetabolism of phenytoin due to traumatic brain injury or adsorption of drug to the plastic tube being the cause of the elevated dose requirement was refuted by the fact that all patients showed signs and symptoms of phenytoin toxicity after the continuous EN regimens were discontinued. A controlled, cohort study was then conducted by the investigator. The study included two study groups: (a) standard doses of phenytoin therapy were added to 10 neurosugery patients who had been stabilized on EN (Isocal at rate of 100-125 mL/hr); (b) EN was added to 10 neurosurgery patients who had been stabilized on phenytoin therapy but with no concurrent EN regimen. In both groups of patients, concurrent nasogastric feeding was associated with subtherapeutic serum phenytoin concentration. Discontinuation of EN was associated with an average of four-fold increase in phenytoin serum concentration without making any changes to the doses.

To further confirm that this observation was not specific to neurosurgery patients, 5 healthy volunteers were recruited to take phenytoin oral suspension with and without continuous consumption of EN formula by mouth at a rate of 100 mL per hour. Phenytoin absorption kinetics was compared between the two phases with multiple blood draws. Consistently, serum phenytoin concentrations were 3 to 4 times lower during concurrent consumption of EN formula compared with the study period without continuous EN intake.

These data strongly suggested that the content inside the EN formulas cause interference with the absorption of phenytoin. Drug malabsorption is not associated with poor solubility, since oral suspension instead of solid dosage forms were used throughout the trial.

The investigator also reported that by stopping EN two hours prior and after the dose of phenytoin and flushing the tube with 60 mL of water, therapeutic phenytoin serum concentrations were achieved with only modest increase in doses. This formally marked the first documented approach to minimize this type of drug-nutrient interaction by withholding EN.

Extrapolation of the Phenytoin Data in Clinical Practice

Since the data from phenytoin investigation suggest that withholding EN for 2 hours before and after drug administration may minimize the negative impact on oral drug bioavailability, this approach for drug administration has since been widely adopted to minimize drug-nutrient interactions that may be associated with drug malabsorption. For example, for drugs that are better absorbed on empty stomach (i.e., the absence of food) based on pre-clinical pharmacokinetic data, such as ciprofloxacin, it becomes common that practitioners would withhold EN before and after each dose. However, subsequent studies provided conflicting data with regard to the clinical outcome of uninterrupted EN on ciprofloxacin oral absorption kinetics and bioavailability, ranging from having no effect to a significant reduction in absorption (7-12). These differences are likely associated with the underlying disease state that affects GI tract function, the EN formulation used, and other uncontrolled confounders (e.g., the location of the tip of the enteral feeding tip [gastric vs. jejunal], how the medication was prepared, etc.).

It is difficult to extrapolate and predict drug absorption pattern among drugs, even within the same drug class. For example, by using the same administration technique in healthy subjects, Ensure has been shown to reduce the absorption of ciprofloxacin more significantly than ofloxacin (-28% vs -10%) (7). This suggests that a slight change in the chemical structure or other physicochemical characteristics of a drug, such as solubility or hydrophilicity, can alter

the magnitude of this drug-nutrient interaction. This point is best illustrated by an *in vitro* study showing that the magnitude of loss of potency of different fluoroquinolones (ciprofloxacin, levofloxacin, ofloxacin) after mixing with Ensure is drug-specific (13). The take home message for clinicians is that when interpreting literature on drug-nutrient interactions, the specific drug studied, and type of patients involved, and the administration technique – including the enteral product used, gastric vs. small bowel delivery, the dosage form of the drug used – must be carefully evaluated and the data may not be accurately extrapolated to any given patient when these variables are changed.

Mechanisms of Interactions Between Drugs and Enteral Feeding Formulas

Unfortunately, scientific studies aimed to systemically determine the mechanism of these interactions are lacking. Therefore, despite having over 30 years of descriptive data from case series or small observation trials, the primary mechanism behind the well reported interacting drugs such as phenytoin, ciprofloxacin, and warfarin remains unclear. Some proposed mechanisms include poor drug solubility, binding with divalent or trivalent cations, or with different protein contents (14-19). Nevertheless, not one mechanism has been consistently shown to be the leading cause of these interactions and the magnitude of interaction was not consistent among different studies. This implies that there is no single approach towards managing these interactions. Clinicians must therefore exercise judgment and take different factors into account to individualize both the medication and EN regimen for each patient.

Does Holding Enteral Feeding Help?

Despite the limitations of study design in the literature, holding EN has been shown to improve drug absorption in most cases (Table 1). This observation, however, is influenced by publication biases in that mini-trials and case reports with positive outcomes are more likely to be shared by clinicians and researchers and ultimately published in the literature. Regardless, the positive impact of certain clinical approaches for specific drugs in selected patient populations cannot be disputed, provided that certain clinical conditions and procedures are followed. Multiple studies with phenytoin suggest that withholding EN for at least one hour can significantly improve phenytoin absorption (14).

Table 1. Drugs that have been shown to have improved GI absorption in at least one case report when enteral feeding is withheld for at least one hour.

Ciprofloxacin
Phenytoin
Warfarin

Similarly, malabsorption of warfarin in critically ill patients receiving continuous EN has been reported in a crossover case series report. Withholding EN 1 hour before and after warfarin administration was associated with a modest yet statistically significant improvement in clinical response based on the patient's internal normalized ratio (INR) (20, 21). On the other hand, in patients with hypothyroidism requiring maintenance levothyroxine therapy when receiving concurrent enteral in, withholding EN 1 hour before and after drug administration is associated with limited success in preventing levothyroxine malabsorption. In the three patients who developed hypothyroidism (as measured by serum thyroxine concentrations) after the inception of continuous EN, only one became euthyrotic while the other two patients remained in a hypothyrotic state. The outcome was not any worse than the patients in the other intervention group who received empirical increase of levothyroxine doses without changing EN infusion regimens (22). Based on these data, one may argue that withholding EN for at least one hour before and after drug administration is a viable option to optimize drug absorption.

Given the probable benefit of withholding EN on drug absorption, an equally important question is whether this practice is safe. Unfortunately, there are inadequate objective data in the existing literature to answer this question. The study design of the published data is strongly biased towards optimizing drug absorption. None of the existing reports are aimed to evaluate issues such as the adequacy of nutrient delivery, risk of aspiration, EN intolerance, incidence of adverse events, and clinical outcome differences other than attainment of adequate therapeutic drug concentrations where applicable. Conversely, there has been no report of patients experiencing severe adverse events as a result of withholding EN. Therefore, it is misleading to draw any concrete, evidence-based statement or conclusion to determine whether or not withholding EN before and after drug administration

Table 2. Clinical considerations in approaching potential interaction between drug and enteral feeding formula.

- Has GI malabsorption of the drug been previously reported in the literature in patients receiving continuous tube feeding?
- Is there documented evidence that suggests impaired drug absorption in the presence of food?
- Has target therapeutic goal been achieved?
- Is withholding enteral feeding a feasible option for this patient?
- Does the patient have impaired GI motility?
- Does the patient have altered GI anatomy (short gut, gastric pull-up, sub-total or total gastrectomy, ileostomy, gastric by-pass, etc.)?
- Are there clinical signs and symptoms suggesting drug malabsorption?
- Where is the drug being infused into the GI tract (gastric vs. transpyloric vs. jejunal?)
- Can therapeutic drug monitoring such as serum drug concentration be performed to determine the adequacy of drug absorption?
- Is the drug available in other formations, such as intravenous injection?

is good practice; and if so, how it should be done. As always, clinicians will need to balance the risks and benefits and individualize the approach in each circumstance (Table 2).

Identifying the Clinical Endpoint and Some Misconceptions

In order to settle this constant debate regarding the practice of holding EN for drug administration, clinicians must first clearly define the clinical endpoint they are trying to achieve. From the purely absorption kinetic perspective, unless the presence of food can significantly increase bioavailability (this only applies to a small number of drugs, e.g., gresiofulvin, itraconazole oral capsule), withholding EN would not negatively affect drug absorption in a patient receiving EN. Therefore, if the primary clinical concern is efficacy, withholding EN before drug administration per se would not decrease the efficacy of a drug. Any resultant changes to the serum drug concentration would therefore likely be associated with other factors independent of withholding EN, such as preparation of the dosage form, drug adhesion to the plastic, positioning of the tube, or GI tract function. On the other hand, if the primary concern is nutrient provision and delivery, withholding EN for several hours a day will likely have a negative effect on the patient's caloric intake. This is especially a concerning issue in a patient who has already developed significant gastric intolerance of EN.

It is also important to avoid misinterpreting clinical data. For some drugs, EN may delay the rate of absorption, but not necessarily the total amount absorbed (i.e. bioavailability). Withholding EN would therefore have a negligible effect on improving drug absorption. Drug-food interaction does not necessarily apply to the entire class of drugs. Using the fluoroquinolone class of antibiotics as an example, food has been shown to decrease the bioavailability of ciprofloxacin most significantly whereas the effect on ofloxacin and levofloxacin is more limited (13). So, whether the strategy of withholding EN before drug administration should even be considered really depends on the specific drug rather than the class of drugs. Finally, just because the bioavailability of a drug is decreased by the concurrent administration of mineral supplements or antacids does not necessarily mean that EN formulas will have the same negative effect. Adequate enteral absorption of ciprofloxacin can be achieved in critically ill patients receiving continuous EN, as long as the dose provided is optimal (12). This is because the mineral content, pH, and density of the liquid are quite different between antacids and EN formulas.

What Are Some Logistical Issues to Consider When Approaching a Patient?

At this time, there is no compelling reason to routinely withhold EN before and after the administration of all

medications. Such practice should therefore be triggered by one or more clinical concerns. These concerns may include:

1. Documented risk of drug malabsorption/ erratic absorption pattern associated with concurrent continuous EN based on the literature (e.g., phenytoin, warfarin, ciprofloxacin);
2. Clinical signs and symptoms suggesting drug malabsorption; or,
3. Use of drugs with known impaired absorption in the presence of food even in patients not receiving EN
4. Lack of clinical response.

Regardless of whether EN is held, the feeding tube should be flushed with at least 30 mL of water after drug administration to help maintain the patency of the feeding tube and minimize having residual amount in the tubing leading to decreased drug delivery and potential clogging of the tube.

If the decision is to withhold EN, a reasonable starting approach is to withhold EN one hour before and after each dose, according to published experience. Theoretically, holding EN two hours before and after each dose is more likely to provide a true "food-free", "interference-free" environment that favors drug absorption for certain medications. In practice, this is difficult to accomplish, as each dose would be associated with a four-hour loss of nutrient infusion, which needs to be made up for by increasing the hourly infusion rate in the remaining part of the day. This may potentially increase the risk of EN intolerance and aspiration in

some patients. For instance, if a drug were given three times a day, infusion time would be interrupted for 12 hours by this approach. That means that the infusion rate of EN needs to be doubled in the remaining time of the day for adequate caloric provision unless a product with higher caloric density is used instead. But most of all, given the busy workflow for most bedside nurses, especially in the critical care setting where events and patient's conditions are constantly evolving, the labor intensive nature of this management approach is not feasible for drugs that are administered multiple times daily. Arguably, it may even introduce more risks to the patient due to an irregular drug administration schedule or even a skipped dose.

The patient's underlying disease state(s) and other factors that may impair gastric motility/GI transit must be considered. Factors known to negatively affect gastrointestinal motility include sepsis, shock with use of vasopressors, use of neuromuscular blocker agents, continuous infusion of opioid analgesic agents, inadequate glycemic control, history of neuromuscular or motility disorders, including gastroparesis, recent GI tract surgery, and severe fluid and electrolyte disorders (23-28). These conditions may cause a clinically significant delay in gastrointestinal transit and alteration of blood flow to the GI tract such that even withholding EN for one to two hours may not optimize drug absorption. The use of intravenous drug delivery should be seriously considered in these scenarios.

If EN is being held for drug administration, the EN rate should be adjusted accordingly so that the optimal amount of micro- and macronutrients can be delivered for the patient's need. The patient should be closely monitored for any symptoms of feeding intolerance,

Table 3. If Enteral Nutrition is to be Held for Drug Delivery.

- Pad EN rate for time off of pump—follow up to ensure the time off the pump is only the time expected, verify by documenting actual EN delivered into the patient.
- Consider switching to nocturnal EN if drug is dosed during the day as BID-QID doses.
- Can the frequency of drug dosing be decreased for less EN downtime without compromising efficacy and safety of the drug?
- Change to more calorie dense product.
- Consider using an alternate route or an alternate drug if possible.
- Can therapeutic drug monitoring be performed?
- Beware the patient who leaves floor for dialysis, or other procedures, and ALSO has a drug ordered that physician requests EN be held for set period of time—they will miss *even more* feeding.

such as bloating, vomiting, significantly elevated gastric residual volume, abdominal pain, or diarrhea (Table 3). The use of a prokinetic agent may improve some of the symptoms associated with feeding intolerance. However, it may also interfere with drug absorption, including the possibility of introducing a drug-drug interaction. Therefore, a multidisciplinary approach should be commenced to weigh the risk versus benefit of each method. Other options to consider include changing the existing EN formula, supplementing certain nutrients if applicable, electively underfeeding the patient for a short period of time, considering concurrent use of enteral and parenteral nutrition, or switching the patient's medication to a different route of administration if possible.

Another approach that can be considered besides withholding EN is to change the drug regimen by either empirically increasing each of the doses given or give the drug more frequently without interrupting the infusion of the EN formula. The biggest challenge is that when the EN regimen is changed or discontinued, the therapeutic regimens of the affected medications must be readjusted to prevent drug-induced toxicity. To achieve this, a close collaboration and communication among healthcare providers from different disciplines is necessary.

CONCLUDING THOUGHTS

The optimal approach in managing drug-nutrient interaction between EN and drug absorption remains challenging because in most cases, the causes of the interaction is multi-factorial. The mechanism(s) involved specific to a suspected drug-nutrient interaction is often unclear. Thus, it is not possible to provide a standard management approach. A classification recently described and the advanced knowledge in the physiology of the gastrointestinal tract should help advance this area of research (4,5). Ultimately, the management approach must be individualized according to the drug, underlying medication conditions of the patient, the availability of alternative treatment options, and the feasibility of the intervention based on the clinical setting. The plan must be communicated with all healthcare providers involved and may be subject to change, depending on the patient's clinical response. The author's experience is that adverse events are more likely to occur when the patient is being transferred from one facility to another, or to a facility with different levels of care, either because of the change in care plan

or lack of understanding of the existing interventions. Therefore, effective communication is key to ensuring optimal therapy and maximize treatment outcome in managing these interactions. The rationale, plan, goal, and monitoring parameters of the interventions should be clearly documented in the medical record so that other healthcare providers can make an informed decision whenever the management plan is to be changed.

In conclusion, the answer to the question "To hold (EN) or not to hold" is not always definitive and depends on the circumstances and the primary clinical concern specific to the patient. Regardless of the approach, it is imperative to have a clearly defined treatment goal and management plan that is executed with caution and close communication among care providers to optimize treatment outcomes.■

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