Conversion from intravenous to oral dosing

□ Introduction:

The ideal route of administration of any medication is one that achieves serum concentrations sufficient to produce the desired effect without producing undesired effects. In the past, patients were switched to oral (PO) therapy to continue treatment after an already adequate course of intravenous (IV) therapy was administered. Today, it is not uncommon to convert a patient to PO therapy as part of the initial treatment course. The available oral formulations on the market are easier to administer, safe and achieve desired therapeutic concentrations, thus making the PO route an ideal choice.

Patients are more comfortable if they do not have an IV catheter in place. Attachment to an IV pole can restrict movement which can hinder early and/or frequent ambulation.

Patients who continue to receive parenteral therapy are at an increased risk for infusion-related adverse events.

In addition, the presence of an IV catheter provides a portal for bacterial and fungal growth. These secondary infections can lead to additional antibiotic therapy, prosthesis failures, sepsis, and in a small number of cases, death. Using PO therapy also reduces hidden expenses such as the cost of IV sets and pumps, laboratory monitoring, and nursing and pharmacy personnel time. Most significantly early use of PO therapy may allow for earlier discharge from the hospital.

□ Types of IV to PO therapy conversions:

-There are three types:

1. Sequential therapy refers to the act of replacing a parenteral version of a medication with its oral counterpart.

-An example is the conversion of famotidine 20mg IV to famotidine 20 mg PO. There are many classes of medications that have oral dosage forms that are therapeutically equivalent to the parenteral form of the same medication.

2. Switch therapy is used to describe a conversion from an IV medication to the PO equivalent that may be within the same class and have the level of potency, but is a different compound.
An example is the conversion of IV pantoprazole to rapidly dissolving lansoprazole. tablets or omeprazole capsules.

3. Step-down therapy refers to converting from an injectable medication to an oral agent in another class or to a different medication within the same class where the frequency, dose and the spectrum of activity (in the case of antibiotics) may not be exactly the same.
Ex: Converting from ampicillin/sulbactam 3g IV q 6hr to amoxicillin/clavulanate 875mg PO q 12hr.

□ Medications Included in an IV to PO conversion Program:

- The ideal medication to include in an IV to PO

therapy conversion program has several characteristics. The oral dosage form should have excellent bioavailability (ideally greater than 80%), be well tolerated upon administration, and its use should be supported by clinical data. Other optimal properties include the availability of multiple oral dosage forms (e.g tablets and liquids) and dosing at a frequency equivalent to or less than the IV formulation.

Ex: Medications That Can Be included in IV to PO Therapy Conversion Programs:

	sequential/switch therapy	Step-down therapy
1. Antibacterials	ciprofloxacin, doxycycline	Amoxicillin, Cefazolin
2. Antifungals	Fluconazole	
3. Antivirals	Acyclovir	
4. Gastrointestinal	Famotidine, Cimetidine Ranitidine	
5. Cardiovascular	Digoxin, diltiazem	

□ General Pharmacokinetic and Pharmacodynamic Issues:

-The ideal oral medication should possess properties that result in minimal disruption to the treatment course. The medication should have recognized activity toward the infection or condition being treated and its use should be supported by clinical trials. To improve patient compliance the medication should be available in dosage forms that do not limit the patient's ability to tolerate the medication. Ingesting large tablets or capsules or having to take multiple doses per days is not desirable. Finally, the medication should be well-absorbed and exhibit good bioavailability.

-Bioavailability is a commonly referenced pharmacokinetic parameter. Simply put, it provides an indication of how much of an oral medication reaches the systemic circulation of a patient. Dosage formulations and bioavailability play an important role in conversion therapy. When medications are administered intravenously, the bioavailability is 100% because they are administered directly into the blood. For oral medications, bioavailability may be less

due to the variability in the rate and extent of dissolution of the oral form and the total amount that is absorbed into the systemic circulation.

Selection of patients for IV to PO Therapy Conversion

-The criteria used to determine whether or not the patient is eligible for PO therapy vary from hospital to hospital, but they generally encompass four key areas:

1. Intact and functioning gastrointestional (GI) tract
2. Improving clinical status
3. Does not meet any exclusion criteria
4. Other

Intact and Functioning Gastrointestinal Tract:

- The ability of the GI tract to absorb the medication is critical for successful conversion to PO therapy.
- Factors that influence absorption include gastrointestinal pH, permeability, Blood flow to

the GI tract is also important because this is how the absorbed medication is carried into the systemic circulation.

- Patients displaying signs and symptoms of shock are not candidates for conversion to oral therapy because blood flow is typically shunted away from the GI track secondary to the shock itself or due to concomitant vasopressor therapy. These types of patients normally reside in the intensive care unit.

- Continuous nasogastric (NG) suctioning is a contra-indication because all or part of the medication will be removed immediately after administration unless the process is temporarily suspended.
- Use caution with patients who have difficulty swallowing or have loss of consciousness (without feeding tube access) because they are at risk for aspiration.
- Issues related

TABLE Criteria Indicating Absorption of Oral Medication May Be Compromised

- NPO status (and no medications are being administered orally)
- NG tube with continuous suction
- Severe/persistent nausea or vomiting
- Gastrointestinal transit time too short for absorption (malabsorption syndromes, partial or total removal of the stomach, short bowel syndrome)
- Active gastrointestinal bleeding
- High doses of vasopressor medications (typically in presence of shock)
- Difficulty swallowing or loss of consciousness and no NG access available
- Documented ileus or gastrointestinal obstruction
- Continuous tube feedings that cannot be interrupted and patient requires a medication known to bind to enteral nutrition formulas

to specific medications are discussed in the *specific medication class considerations* section. The nurse, physician, or in some cases, even the patient, can be good sources of information regarding the patient's ability to tolerate oral medications. An additional source of information is the patient's medication administration record (MAR). If a patient is receiving other medications by mouth, this provides confirmation that the patient can tolerate the sequential, switch, or step-down therapy.

It is important to note that the presence of tube feedings should be taken into consideration if the patient is going to be converted to PO therapy. There are certain medications, specifically the fluoroquinolones, warfarin, and phenytoin whose absorption and effectiveness are reduced in the presence of enteral feedings. This is not an absolute contraindication unless the tube feeding cannot be interrupted. The following guidelines are provided to help manage the conversion from IV to PO therapy in the presence of continuous tube feeding[12]:

- Select the most appropriate oral formulation of the medication for NG tube administration. Solutions or suspensions are preferred over tablets. If this is not available, a tablet can be crushed as long as it is not an extended-release or enteric-coated formulation. Dissolve the tablet in a small amount of liquid to make a slurry, and then draw the preparation into an oral syringe for administration. Once the medication has been administered, all equipment used in preparation and administration should be rinsed, and those washings administered.
- Feeding tubes should be flushed with water both before and after medication administration to avoid blockage.
- For medications considered to be compatible with tube feeding, stop the feeding and administer the medication as specified above.
- For oral fluoroquinolones, stop the tube feeding for at least 2 hours before and 2 hours after administration. For phenytoin, which is dosed more than once a day, tube feedings can be stopped approximately 1 hour before and 1 hour after medication administration.
- Medications should never be added directly into the tube feedings.

□ Improving Clinical Status:

Signs and symptoms of the condition for which the medication is prescribed should improving --resolving in patients being converted to PO therapy. The patient should be clinically stable and should not be expected.

• Patients with active infections who are receiving antibiotics should be afebrile or have had maximum temperature of less than 100.4°F in the previous 24 hours. WBC count should be trending downward. The normalizing of WBC count indicates the patient's inflammatory response associated with the infection is declining. It is important to examine the patient's medication therapy for other medications that can cause an increase or sustained high WBC count, such as steroids. For example, some patients may be clinically improving but have maintained a WBC count above the normal reference range (referred to as leukocytosis) due to prednisone therapy. In this case, if the patient meets all other criteria,

a safe conversion to PO therapy can still be made. Conversely patients who are neutropenic are typically excluded from IV to PO therapy conversion but this can vary from institution to institution.

It is also important to review the cultured pathogen (bacteria, fungus etc) and ensure that it is susceptible to the oral medication. If no pathogen is identified, the oral agent should cover commonly suspected pathogens based upon local sensitivities and/or infection type.

For example, community acquired pneumonia in a hospitalized immunocompetent patient on a general medical floor is generally caused by Streptococcus pneumoniae etc. When converting from IV to PO therapy, the selected oral medication should have activity against these organisms in the absence of a positive bacterial culture.

If gastrointestinal bleeding is present, documentation that the bleeding has stopped should be verified before converting to PO therapy.

For cardiovascular medications, the patient should have stable blood pressure and heart rate.
For anticonvulsant medications, the patient should be stable and not be actively seizing. If in doubt, review the chart or discuss with the patient's nurse.

Exclusion Criteria

Antibiotics

Oral therapy can be commonly used to treat a variety of infections. However, there are certain infections that should be treated with parenteral therapy due to the severity or location of infection. These include endocarditis, meningitis, brain abscess, orbital cellulitis, etc. Patients with multiple antibiotic allergies may be restricted to therapy choices that may only be available parenterally.

Antiepileptic Medications:

Patients who are at risk for actively seizing or are

unable to tolerate oral medications without risk of aspiration are not appropriate candidates for PO therapy.

oCardiovascular:

Patients with unstable cardiac conditions or for whom frequent dose changes are occuring (e.g through IV drip titration) are not good candidates for PO therapy.

Specific Medication Class Considerations

Fluoroquinolones

Ciprofloxacin, moxifloxacin, and levofloxacin are included in almost all hospital IV to PO therapy conversion programs. These medications are ideal for conversion because of high bioavailability, rapid absorption, and good distribution within the body.) Remember that fluoroquinolone absorption may be affected by concurrent administration of products containing divalent and trivalent cations such as calcium, calcium containing antacids, iron and zinc salts as well as medications like didanosine and sucralfate. For example, ciprofloxacin should be given 2 hours before or 6 hours after these products according to the manufacturer's package insert. Levofloxacin can be administered 2 hours before or 2 hours after these medications and moxifloxacin should be administered 4 hours before or 8 hours after these products. Ciprofloxacin suspension should not be administered via a feeding tube due to its physical characteristics. From a dietary perspective, all quinolones can be taken without regards to meals.[3]

Triazole Antifungals

The oral bioavailability of fluconazole, itraconazole, voriconazole, and posaconazole is relatively good if administered appropriately. Fluconazole is well-absorbed in most patient types and is not affected by food or alteration in gastric pH. One study conducted in surgical patients with compromised gastrointestinal absorption receiving enteral nutrition reported fluconazole bioavailability to be 100%.[4] Itraconazole is unique among the triazoles in that it requires an acidic gastric pH for absorption. Antacids, H2 receptor antagonists, and proton-pump inhibitors can significantly reduce itraconazole's bioavailability. In the product package insert, the manufacturer recommends administering the medication with a cola beverage if the patient is concomitantly receiving an H2 antagonist. Sucralfate may also affect itraconazole's absorption. The solution is better absorbed on an empty stomach while the capsules should be administered with food. On the other hand, voriconazole is best absorbed if administered 1 hour prior to or 1 hour after meals. Both itraconazole and voriconazole intravenous formulations are contraindicated in renal dysfunction because of the potential to accumulate cyclodextran (from the solution), which can lead to toxicity. Finally, posaconazole oral suspension should be administered with high fat foods or tube feedings, if possible, as this significantly increases absorption.

Vancomycin

This antibiotic is unique because it is one of the few medications where the oral and IV formulations have different uses. The IV formulation is used to treat gram positive bacterial infections. However, the oral formulation is poorly absorbed and is typically only used in the treatment of *Clostridium difficile* colitis. This medication should not be included in an IV to PO therapy conversion program.

Other Antibiotics

Some antibiotics are better absorbed on an empty stomach, while others are better absorbed with food or a high fat meal. Dietary restrictions vary for other types of antibiotics. Linezolid is unique because it is a weak, nonselective reversible inhibitor of monoamine oxidase (MAO). Patients receiving this drug should not consume foods or beverages that are high in tyramine because it can place them at risk for a serotonin-syndrome type reaction, which leads to a severe hypertensive reaction.[5] Although these foods are not commonly administered in the hospital setting, it is still a concern and many institutions will place patients on a low tyramine diet as a preventative measure.

Acid Suppression Medications (H_2 receptor antagonists and Proton pump inhibitors)

Because of their mechanism of action, the proton pump inhibitors (PPIs) are most effective when administered on an empty stomach or at least 30 minutes to 1 hour prior to meals. Some of the PPIs are enteric-coated granules that can be sprinkled on fruit or mixed in solution prior to administration through a feeding tube. It is important to not crush or chew these granules and to dissolve them only in acidic substances to keep the enteric coating intact. It is not uncommon for patients to receive these drugs intravenously due to GI bleeding. As previously stated, these patients should not be converted to PO therapy until the active GI bleeding has been resolved.

Pharmacoeconomics of IV to PO Therapy Conversion:

Changing the route of administration from intravenous to oral results in direct cost reductions (medication costs, supply cost) that are easy to document and

calculate. Personnel time spent preparing and administering doses is greatly reduced. There are several studies that document the direct impact of an aggressive and early IV to PO therapy conversion program.

#Myths of IV to PO Therapy Conversion:

1. Infectious diseases need intravenous treatment and conversion to oral therapy should be used sparingly. Oral antimicrobials are not equivalent to intravenous therapy.

Answer: Newer antimicrobials are available with equivalent intravenous and oral bioavailability. The literature has shown that IV to PO therapy conversion is efficacious, convenient, cost-effective, and safe in carefully selected patients.

2. The oral antimicrobial must be the same medication or from the same medication class as the intravenous agent.

Answer: The selected oral agent should cover the

same or similar spectrum of activity, similar tissue penetration, and should be effective against the isolated or suspected organism(s).

Summary:

Intravenous to oral therapy conversion represents a cost-effective strategy that also minimizes intravenous therapy complications and facilitates earlier hospital discharge. Appropriate oral medication use produces equivalent clinical outcomes, causes fewer complications, less patient inconvenience, and is generally less costly. There are many medications that can be included in this program. Patients eligible for IV to PO therapy conversion should

- tolerate oral medications.
- be converted to an oral agent that acts similarly or equivalent to the IV counterpart.
- Meet inclusion criteria
- Not have any contraindications to PO therapy

- be improving clinically

-Through an IV to PO therapy conversion program, pharmacists have the opportunity to reduce unnecessary medication costs while maintaining the efficacy of therapy and improving patient safety and comfort.

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1. Discuss the following - conversion of IV dose to oral dose. [5M, June 14]

2. Give reasons for conversion from IV infusion to oral dosing of drugs. [2M, Ag10]

3. Explain the principle and significance in converting IV dose to oral dose. [5M, 11] [12] +Ex

4. Explain with suitable examples the principle behind conversion of drug dosing from IV infusion to oral dose [10M, Ag13]

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Conversion from intravenous infusion to oral dosing

After the patient's dosing is controlled by intravenous infusion,it is often desirable to continue to medicate the patient with the same drug using the oral route of administration .
When IV infusion is stopped,the serum drug concertation decreases according to first-order elimination kinetics

For most risk drug product ,the time to reach steady state depends on the first order elimination rate constant for the drug.
Therefore,if the patient starts the dosage regimen with the oral drug product at the same time as IV infusion is stopped ,then the exponential decline of serum levels from the IV infusion stopped,the exponential decline of serum levels from the IV infusion should be matched by the exponential increase in serum drug levels from the oral drug product
The conversion from IV infusion to a controlled-release oral medication given once or twice daily has become more common with the availability of more controlled-release drug products,such as theophylline and quinidine.

Computer simulation for the conversion of IV theophylline therapy to oral controlled- release theophylline demonstrated that oral therapy should be started at the same time as IV infusion is stopped.

- With this method,minimal fluctuation are observed between the peak and through serum theophylline levels.

- Moreover,giving the first oral dose when iv infusion is stopped may make it easier for the nursing staff or patient to comply with the dosage regimen.

- Either of these methods may be used to calculate an appropriate oral dosage regimen for a patient whose condition has been stabilises by an Iv drug infusion .

Both methods assume that the patient's plasma drug concertation is at steady state.

METHOD 1:

Method 1 assumes that the steady state plasma drug concentration ,Css,after IV infusion is identical to the desired Cav after multiple oral doses of the drug.therefor,the following equation maybe used :

Cav=SFD0/kV DT

D0/T=CavKvD/SF

Where S is the salt form of the drug and D0/T is the dosing rate.

EXAMPLE:

An adult male asthmatic patient(age 55,78kg) has been maintained on an iv infusion of aminophylline at a rate of 34mg/hr.the steady-state theophylline drug concentration was 12 µg/mL and total body clearance was calculated as 3.0L/hr.calculate an appropriate oral dosage regimen of theophylline for this patient.

SOLUTION:

- Aminophylline is a soluble salt of theophylline and contains 85% theophylline (S=0.85).theophylline is 100% bioavailable (F=1)after an oral dose.because total body clearance ,CL t=kVD

Theophylline dose rate= SFD0/T=(0.85)(1)(34)/(1)=28.9 mg/hr

The theophylline dose rate of 28.9 mg/hr must be converted to a reasonable schedule for the patient with a consideration of the various commercially available theophylline drug products.

Therefore,the total daily dose is 28.9 mg/hr×24 hr or 693.6 mg/day .

Possible theophylline dosage schedules might be 700 mg/day ,350 mg every 12 hours,or 175 mg every 6 hours .

Each of these dosage regimens would achieve the Same Cav but different CMax and CMin ,which shouid be caiculated .

The dose of 350 mg every 12 hours could be given in sustaine-release form to avoid any excessive high drug concentration in the body.

Method 2: assumes that the rate of IV infusion(mg/hr) is the same desired rate of oral dosage.

Example:use previous example

Solution

The aminophylline is given by iv infusion at a rate of 34 mg/ hr.the total daily dose of aminophylline is 34 mg/hr×24 hr=816mg.the equivalent daily dose in terms of theophylline is 816×0.85=693.6 mg.

Thus ,the patient should receive approximately 700 mg of theophylline per day or 350 mg controlled – release theophylline every 12 hours.