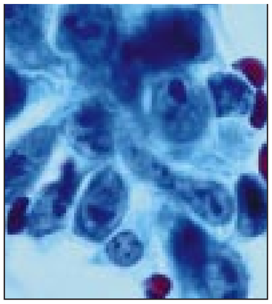

INTRAVENOUS TO ORAL (IV:PO) ANTI-INFECTIVE CONVERSION THERAPY

Gene A. Wetzstein, PharmD

From the Pharmacy Department at the H. Lee Moffitt Cancer Center & Research Institute, Tampa, Fla.

Questions relating to drug use, dosing, and related issues in oncology are presented in this regular feature.

Introduction

The term "anti-infective conversion" describes the practice of converting intravenous anti-infection therapy to an alternative oral formulation. This conversion from intravenous (IV) to oral (PO) therapy has been practiced in an uncontrolled fashion since the earliest years of the anti-infective era. As conversion therapy was based on empirical observations rather than on clinical studies or outcomes, there was concern that oral therapy was less effective. In addition, until recently, no clinical trials were available to support the conversion from the intravenous route to oral administration. Current forces that are accelerating the conversion from intravenous to oral therapy include rising health care costs, limited health care resources, efforts to shorten hospital stays, and demands by patients for cost-effective, safer, and more convenient treatments. This conversion has been referred to as "switch," "sequential," and "step-down" therapy.[1-3] For the purposes of this review, the concept is referred to as IV:PO conversion.

Rationale

Clinical trials have been conducted that demonstrate the efficacy and safety of IV:PO conversion,[4-12] and several studies have addressed the economic impact of conversion.[4,7,9-12] Cost savings may be achieved through lowering direct acquisition costs, eliminating the need for ancillary supplies, reducing pharmacy and nursing time, and shortening the length of hospital stay. Direct benefits to the patient include eliminating adverse events associated with IV therapy, increasing patient comfort and mobility, facilitating a more active role for the patient in his or her treatment, and increasing the possibility of earlier discharge. Improved quality of patient care and the potential for significant and meaningful cost savings make IV:PO conversion a desirable treatment option.

Several factors play a role in the scientific basis of IV:PO conversion. These include (1) newer concepts of antimicrobial pharmacodynamic action and the realization that this can be achieved by oral agents, (2) the advent of newer, more potent, broad-spectrum oral agents that achieve higher and more consistent serum and tissue concentrations, and (3) the availability of randomized clinical trials comparing various IV and oral therapeutic strategies.

Anti-infective action can be divided into two main categories: pharmacokinetics and pharmacodynamics.[13-17] Pharmacokinetics concerns the absorption, distribution, metabolism, and elimination of drugs. These factors, along with dosage regimen, determine the time course of drug concentration in the body. However, these pharmacokinetic parameters become clinically meaningful only when they correlate with the agent's pharmacodynamics — the biological effects resulting from the interaction between the agent and the target's physiology. Because we are currently unable to measure the concentration at the site of infection, surrogate markers such as the minimum inhibitory concentration (MIC) or minimum bacteriocidal concentration (MBC) are typically used to assess the ability of an anti-infective agent to complete these function.

Basing drug selection solely on the pharmacokinetics or pharmacodynamics often leads to inappropriate anti-infective selections. However, pharmacokinetics coupled with pharmacodynamics predict the efficacy of an anti-infective.

Another important factor is the bacteriocidal patterns of the anti-infective. One principle is the "time over MIC," which is the basis of therapy with penicillins, cephalosporins, clindamycin, fluconazole, and macrolides.[15,18,19] A concentration greater than 4 to 8 times the MIC of an organism does not provide more bacterial killing. Clinical trials have shown that better results are achieved when the concentration is greater than the MIC for more than 80% of the dosing interval.[20,21] This concept should be a guiding force when designing dosing regimens. The duration of time that the drug concentration exceeds the MIC is the major determinant of efficacy for these drugs. Nevertheless, the principle of time over MIC can be applied to conversion therapy, which allows the clinician to select oral dosage therapy and administration frequencies that would maintain concentrations above the MIC for most of the dosing interval.

In contrast to time over MIC, the quinolones exhibit concentration-dependent killing.[15,18,19] Forrest and colleagues[22] found that the ratio of the 24-hour area under the curve (AUC) to the MIC (AUIC) was the major parameter in determining efficacy in 64 patients treated with IV ciprofloxacin. A ratio of 125 or greater was associated with a clinical and bacteriologic response rate greater than 80%. Values below 125 resulted in less than 50% efficacy in both clinical and bacteriologic response. A value of 125 simply means that the average concentration over 24 hours should be slightly above 5 times the MIC. These values are virtually equivalent when comparing the 24-hour AUIC ratios for standard IV and oral doses of ciprofloxacin and ofloxacin against major pathogens.[23,24]

Clinical Trials

Craig and Andes[25] reviewed 16 clinical trials of conversion therapy in patients with documented infections. Various sites of infections and medications were evaluated. All studies demonstrated equal clinical and bacteriologic efficacy when treatments were converted to the oral route. However, the mean duration of IV therapy before converting ranged from 2 to 8 days and was solely determined by clinical judgment in most cases. This makes interpretation of the contribution of oral therapy difficult.

Better-defined trials have been recently conducted that facilitate the evaluation of oral conversion. Criteria have been established to identify potential patients for IV:PO conversion (Table 1),[4-8,26] which has made it easier to evaluate the impact of conversion therapy in regards to patient outcomes.

Table 1. — Inclusion Criteria for Conversion Therapy

Completion of 48-72 hours of IV therapy
Functioning gastrointestinal tract
Afebrile <99.6°F for 8-24 hours
White blood cell count <15,000/mm^3 and/or decreasing
Improvement of signs and symptoms of infection from initial presentation

Ahkee and colleagues[6] evaluated conversion therapy in all types of infections including lower respiratory tract, urinary tract, skin and soft tissue, and intra-abdominal. Individuals with neutropenia, meningitis, and endocarditis were excluded. Oral regimens were not limited to a particular class of anti-infectives, and the agent was determined by spectrum of activity. Five inclusion criteria were applied for conversion therapy. Almost 50% of all patients receiving antibiotics were candidates for conversion therapy, and 87% of these were converted to an oral alternative, which resulted in a 98% cure rate. Intravenous antibiotics most frequently converted were cefotaxime, ceftazidime, ciprofloxacin, ticarcillin-clavulanate, and ampicillin-sulbactam. The most commonly used oral alternatives were amoxicillin-clavulanate, ciprofloxacin, cefuroxime, and cefixime.

Przybylski and associates[7] targeted IV antimicrobials that were in high use or at high cost to their institution. Included were ampicillin-sulbactam, ciprofloxacin, imipenem-cilastatin, cefuroxime, cefazolin, ticarcillin-clavulanic acid, and combination of tobramycin with either piperacillin or ceftazidime. Patients were included if they had non–life-threatening infection (community acquired/nosocomial pneumonia, urinary tract, skin and soft tissue, osteomyelitis, and chest tube prophylaxis), were receiving a "targeted" antibiotic, had a white blood cell count of <15,000/mm^3, had been afebrile for at least 24 hours, and were able to tolerate oral antibiotics. Individual life-threatening infections, such as sepsis, bacterial endocarditis, and meningitis, were excluded. A positive response occurred in 99% of patients converted to oral therapy. The average length of stay was shortened by 1.53 days (P<0.003). Other studies have shown similar reductions in length of stay.[4,9-11] Oral alternatives included cefuroxime, amoxicillin-clavulanic acid, and ciprofloxacin in combination with other oral antibiotics that provide anaerobic coverage such as clindamycin or metronidazole.

Another group evaluated critically ill patients with serious infections expected to receive at least 8 days of IV therapy.[12] The two treatment groups were comparable for demographic characteristics, types of infections, bacteria isolated, initial IV antibiotic regimen, and duration of antibiotic treatment. The most common infections involved the skin and skin structure; bacteremia and infections of the lower respiratory tract, urinary tract, and bone and joint were also represented. The most commonly isolated pathogens were *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Escherichia coli*. All patients received 3 days of conventional IV antibiotics and then were randomly assigned to receive either ciprofloxacin 750 mg PO b.i.d. or parenteral antibiotics. Clinical and bacteriologic response was comparable between the oral and IV regimens (88% and 79%, respectively). Oral ciprofloxacin was associated with an average cost savings of $293 per patient with no difference in efficacy.

More recently there has been increasing interest in the management of chemotherapy-induced fever and neutropenia (CIFN) in the ambulatory setting. Recent research now indicates that patients with CIFN may be assessed for complication risk and, with appropriate clinical judgment, treated in outpatient settings with oral anti-infectives. A prediction model for identifying "low-risk" CIFN has been developed by Talcott et al.[27,28] A recent review by Davis and Raebel[29] identified additional risk factors to consider when identifying low-risk CIFN patients (Table 2). Several investigators have utilized this information and have incorporated broad-spectrum oral antibiotics in the management of this population.[30-36]

Table 2. — Suggested Criteria for Selection of Low-Risk Patients With Chemotherapy-Induced Fever and Neutropenia

Anticipated duration of neutropenia <1 week
Solid tumor malignancy
No comorbidities (clinically stable)
Adequate oral intake
Family support/caregiver
Ability to adhere to instructions
Malignancy responding to current therapy
Absolute neutrophil count nadir ≥10 days after chemotherapy

From Davis DD, Raebel MA. Ambulatory management of chemotherapy-induced fever and neutropenia in adult cancer patients. *Ann Pharmacother.* 1998;32:1317-1323. Reprinted with permission (www.theannals.com).

The efficacy of the use of oral antibiotics in the management of low-risk CIFN patients has been substantiated by several studies. Rolston et al[35] evaluated 179 "low-risk" neutropenic cancer patients. Patients were randomized to receive ciprofloxacin 500 mg by mouth (PO) 3 times daily (t.i.d.) plus amoxicillin/clavulanic acid 500 mg PO t.i.d. (n=89) vs clindamycin 600 mg IV every 8 hours plus aztreonam 2,000 mg IV every 8 hours (n=90). Treatment groups were similar for age, gender, underlying malignancy, and absolute neutrophil count (ANC) at time of randomization. There was no difference in overall clinical response between the IV group (87%) and the oral treatment group (90%). Both regimens were well tolerated. Another group recently published the results of a prospective, randomized trial that compared ofloxacin 400 mg PO b.i.d. (n=46) vs amikacin/ceftazidime (n=42) in low-risk neutropenic solid-tumor patients.[36] The treatment arms were well balanced for age, gender, underlying malignancy, chemotherapy regimen, and time between last chemotherapy and onset of CIFN. Eighty percent of the oral treatment group and 88% of the inpatient IV treatment group responded to original treatment. Lastly, a multicenter, double-blind, placebo-controlled American study[37] has recently concluded in which 232 episodes of fever and neutropenia in hospitalized pediatric and adult cancer patients were evaluated. The study enrolled only patients whose neutropenia was expected to last 10 days or less and excluded those with underlying medical conditions. Participants received either oral ciprofloxacin plus amoxicillin/clavulanate or IV ceftazidime until their fever and neu-

Table 3. — Four Scenarios of IV:PO Conversions of Anti-Infective Drugs

Drug Characteristic	Examples of Conversions[3,25,38,40,47,48] IV	→	PO	Absorption of the Medication	Comments
1. Same Drug/Same AUC	Levofloxacin	→	Levofloxacin	>95%	Conversion to same drug with virtually equivalent concentrations.
	Ciprofloxacin	→	Ciprofloxacin	70-85%*	
	Fluconazole	→	Fluconazole	>90%	
	Metronidazole	→	Metronidazole	>95%	
	Clindamycin	→	Clindamycin	75-90%	
	SMZ/TMP	→	SMZ/TMP	>95%	
2. Same Drug/Lower AUC	Ampicillin	→	Ampicillin	40%	All of these drugs are characterized by the "time over MIC" principle, so conversion and efficacy are dependent on this.
	Cefuroxime	→	Cefuroxime	40-50%**	
	Erythromycin	→	Erythromycin	50-80%	
	Azithromycin	→	Azithromycin	40%	
3. Different Drug/ Good Bioavailability	Ceftazidime	→	Ciprofloxacin		Conversion may be easily done from another class of anti-infectives; the only requirement is that the agent must cover the same spectrum and have the same characteristics of penetration.
	Cefazolin	→	Cephalexin (>90%) or SMZ/TMP		
	Cefotaxime or ceftriaxone	→	Ciprofloxacin ± clindamycin or cephalexin		
	Ampicillin/ sulbactam	→	Levofloxacin + metronidazole or amoxicillin/clavulanate (60%)		
	Imipenem/ cilastatin	→	Ciprofloxacin + metronidazole[45]		
4. Different Drug/ Bioavailability <50%	Ceftriaxone	→	Cefixime	<50%	Successfully implemented in conversion programs[8]; depends on infection site and MIC of organism.

* Absorption must be taken into consideration when converting from IV:PO (ie, ciprofloxacin 400 mg IV q 12 h should be converted to 500 mg PO q 12 h).

** Absorption increases when administered with food.

SMZ/TMP = sulfamethoxazole/trimethoprim

tropenia resolved. The two groups were similar with respect to age, sex, and type of cancer. Empiric treatment was equally successful in both treatment groups.

Misconceptions

The main obstacle limiting IV:PO conversion is the notion that IV anti-infectives are better than oral.[38] One erroneous concept is that all patients with an infectious disease need IV treatment. Anti-infective therapy should be evaluated regardless of route of administration. If orally administered medications are well absorbed and provide blood and tissue levels that are virtually the same as those attained by IV administration, then there is no difference therapeutically between oral and IV anti-infectives.[39] This is the case in many instances. Another misconception is the same agent must be used both intravenously and orally. The only requirement is the oral anti-infective selected must cover essentially the same spectrum of activity and have the same characteristics of tissue penetration. Lastly, it has been thought that conversion therapy should be used sparingly and only at discharge. Clinicians should use conversion therapy for as many infectious diseases as possible in hospitalized patients, mainly because of the potential advantages to the patient and the institution.

Table 4. - Anti-Infective Drugs - Average Wholesale Price[49]

Anti-infective	Dosage Regimen	Rx Cost per 10-day Course ($)* IV	PO
Levofloxacin	500 mg IV q d 500 mg PO q d	396.00	81.07
Ciprofloxacin	400 mg IV q 12 h 500 mg PO q 12 h	576.24	79.89
Clindamycin	600 mg IV q 8 h 300 mg PO q 6 h	415.87	84.23
Metronidazole	500 mg IV q 8 h 500 mg PO q 8 h	460.20	9.54
Sulfamethoxazole/ trimethoprim	160 mg (10 mL) IV q 12 h 1 DS tablet (800/160 mg) q 12 h	124.00	3.30
Fluconazole	200 mg IV q d 200 mg PO q d	856.13	118.54
Ceftazidime	2 g IV q 8 h	868.02	n/a
Ampicillin/sulbactam	3 g IV q 6 h	578.52	n/a
Imipenem/cilastatin	500 mg IV q 6 h	1,151.84	n/a
Amoxicillin/ clavulanic acid	875 mg PO q 12 h	n/a	92.94
Cephalexin	500 mg PO q 6 h	n/a	38.31

*Costs associated with preparation, administration, pump rental fees, and laboratory monitoring are not included.

Parenteral to Oral Conversion

Jewesson[14,40] has previously described conversion from parenteral to oral anti-infective as occurring in one of four scenarios (Table 3). Scenario 1 involves the use of the same drug in an oral dosage form, if it has excellent bioavailability and assures concentrations consistent with the IV formulation. Scenario 2 involves the same drug with a reduction in achievable systemic drug concentration. For IV anti-infectives that lack an oral counterpart, an oral agent from a different class with similar spectrum of activity and good absorption is indicated (scenario 3). Scenario 4 involves conversion to a different drug with relatively limited absorption. This is the least desirable option for the clinician.

Advantages

Conversion therapy has several advantages. First, studies have demonstrated that oral therapy can be as effective as parenterally administered anti-infectives in the treatment of infections ranging from mild to moderate to severe. Secondly, the potential exists for decreasing adverse effects associated with IV therapy. Patients who

Table 5. — Exclusion Criteria for Conversion Therapy

• Patients who cannot use oral route (risk of aspiration, need for complete bowel rest, gastrointestinal obstruction, preoperative/postoperative fast)
• Patients with an unreliable response to oral medication (severe nausea/vomiting, continuous nasogastric suction, malabsorption syndrome, motility disorder of the gastrointestinal tract, unresponsive to previous oral therapy, short bowel syndrome)
• Patients whose disease state or infection does not permit conversion (eg, high-risk neutropenia, meningitis, endocarditis)

continue to receive parenteral therapy are at increased risk for infusion-related adverse effects such as line infections and phlebitis.[41,42] Phlebitis, the most common complication of IV therapy, affects up to 70% of all infusions and may lead to increased hospital stays and, more importantly, a negative impact on clinical outcomes. Third, oral anti-infectives are easier to administer than IV preparations, require less time to prepare, and often improve patient comfort, mobility, and independence, which can result in a shorter hospital stay. Lastly, oral anti-infectives are often less expensive than parenteral agents (Table 4).[43,44]

Although oral anti-infectives are generally preferred for the reasons stated previously, certain patients are not candidates for IV:PO conversion (Table 5).[4-8,25,26,45,46] These include individuals with gastrointestinal abnormalities, which will alter drug absorption. In addition, specific disease states, such as high-risk neutropenia, have not been studied in a controlled clinical setting. Also, in the case of meningitis and infective endocarditis, antibiotic penetration is poor, and concentrations to eradicate the microorganism may be better achieved with the IV route.

Conclusions

Conversion from intravenous to oral anti-infective therapy is indicated as soon as the patient's clinical condition allows. With careful selection and monitoring, outpatient use of oral antibiotics therapy in chemotherapy-induced fever and neutropenia appears safe and efficacious. This can result in substantial reduction of hospital expenditures by decreasing both the resources being utilized and the patient's length of hospital stay. These considerations are important in the current climate of economic restraint in the health care system. Implementation of IV:PO conversion can have a substantial impact of reducing hospital expenditures without compromising clinical outcomes.

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