

Pharmacologic and Liability Considerations of Therapeutic Interchange with Low-Molecular-Weight Heparins

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Abstract: Therapeutic interchange (TI), a formulary management process, is used by health care systems to help contain medication costs. A scientifically defensible and pharmacoeconomically beneficial TI program adheres to rigorous criteria enforced by an institution's Pharmacy and Therapeutics Committee. In situations where adherence to essential criteria is not mandated, TI may not produce the intended clinical and economic outcomes, and in practice may have legal implications. Appropriate application of TI has been described within the position statements of certain health care organizations and associations. Due to the high cost and frequent use of low-molecular-weight heparins (LMWHs), health care institutions have identified this pharmacologic class as a potential target for TI. Currently, the application of the TI process to LMWHs is questionable. This paper reviews the TI process and explores its controversial role in the formulary management of LMWHs.

Key Words — low-molecular-weight heparins; therapeutic interchange

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Given rising costs, health care systems are continually seeking innovative methods of providing cost-effective care without compromising patient outcomes. Although drug therapy is one of the more cost-effective ways to treat most patients, between 1990 and 1999, expenditures for pre-

scription medications increased by 141%.¹

Containing drug costs is a difficult task, given that institutions have medication formularies that must reflect optimal, often expensive, therapies, yet at the same time maintain a strong financial profile. One approach to reducing medication costs is to implement drug

product substitutions. These substitutions include generic substitution and therapeutic interchange (TI).

Whereas generic substitution is a well-defined and straightforward practice, TI is more complex. TI is controversial in certain situations and has legal implications for practice. This article discusses the background and appropriate application of TI, and its controversial role in the formulary management of low-molecular-weight heparins (LMWHs).

BACKGROUND: GENERIC SUBSTITUTION AND THERAPEUTIC INTERCHANGE

A health care organization's medical and pharmacy staffs work together through the Pharmacy and Therapeutics (P & T) Committee to create and maintain a medication formulary.² The goal of a formulary system is to provide the institution's practitioners with a comprehensive list of medications that are deemed to be most appropriate for patient care while containing costs. Two formulary medication cost-containment processes that are usually implemented under the guidance of the P & T Committee are generic substitution and therapeutic interchange.

Generic substitution is the dispensing of a drug product that contains the same active ingredient(s) and is chemically identical in

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strength, concentration, dosage form, and route of administration to the drug product prescribed.³ A generic agent can be confidently substituted for a formulary brand product if it is bioequivalent and therapeutically equivalent to that product and is approved by the FDA.

Drugs are considered to be bioequivalent if the rate and extent to which the active ingredient is absorbed and the availability at the site of action for each product are comparable when tested under similar experimental conditions.⁴ Therapeutically equivalent drugs are expected to produce essentially the same therapeutic outcomes and toxicities.³ When the generic formulation is a more cost-effective alternative, generic substitution can be a fairly simple cost-containment process.

Therapeutic interchange differs significantly from generic substitution. According to a recent US survey, the TI process has been adopted as a cost-containment measure in more than 80% of general and children's medical-surgical hospitals.⁵ TI is the interchange of therapeutically equivalent, but chemically unique, drugs in accordance with established policies and procedures within a health care system's evidence-based formulary.^{3,6}

Since TI involves the interchange of two "unique" rather than "identical" medications, it is more complicated than generic substitution and therefore is often controversial. Managed care organizations (MCOs), pharmacy benefit management companies (PBMs), and acute and extended care health care systems frequently use TI, because it is not financially advantageous to include multiple, therapeutically equivalent medications on their formularies.

The goal of TI is to reduce the

total cost of therapy without compromising patient care. Medications that fall into the high cost or high volume of use categories are obvious targets for TI. It is generally accepted that TI should only be implemented when there is sufficient evidence for the safe and efficacious use of the selected formulary interchange agent for each designated clinical indication. Under the guidance of the organization's P & T Committee, a series of criteria must be met and a rigorous review process completed to ensure the appropriate application of the TI process.

TI programs can follow one of two basic formats. Health care systems may implement a blanket agent-specific program in which one agent is dispensed for various indications, regardless of FDA-approved labeling. The other option is an indication-specific program, in which the agent dispensed varies depending on the clinical indication. Indication-specific programs are more difficult to manage administratively. They may also complicate an institution's medication-order process flow and potentially increase the opportunity for errors.

Depending on established TI policies and procedures, there are two ways in which a physician practicing within a health care system may consent to a TI program: prior authorization and concurrent authorization. According to the "prior authorization" approach, the physician previously consents, potentially at the time of employment, to the interchange programs outlined by the institution. Consultation with the physician is then not required on a patient-to-patient basis. A TI program that stipulates "concurrent consent" requires some form of physician contact prior to initiating the actu-

al therapeutic interchange for each potentially applicable situation. This provides the physician with the opportunity to evaluate the appropriateness of therapy on a case-per-case basis.

POSITION STATEMENTS ON TI

It is generally recognized by health care organizations and associations that TI programs should be founded upon scientifically valid evidence and implemented in conjunction with appropriate policies and procedures. The American Society of Health-System Pharmacists (ASHP) supports TI if there is timely communication between prescriber and pharmacist in the development of the programs; programs are approved by a P & T Committee; programs are routinely reviewed and revised as appropriate; prescribers can override the program; and appropriate follow-up and monitoring processes are established.³ The American College of Clinical Pharmacy (ACCP) supports TI when the policies are developed by a collaboration between pharmacists and physicians to design protocols that provide patients with the best possible care at the lowest possible cost.⁶ Finally, the Academy of Managed Care Pharmacy (AMCP) also endorses TI if it is appropriately implemented and monitored.⁷

The American Medical Association (AMA) is the most conservative group with regard to TI. The AMA only approves TI when rigorous criteria are met regarding P & T Committee review and formulary approval. TI programs based on P & T Committee recommendations must meet the approval of the medical staff. The TI program must also allow the prescriber to override on an individual case basis without experiencing undue administrative obstacles. The

AMA is opposed to TI when an alternate drug is dispensed without the prescriber's concurrent authorization.⁸

TI is usually initiated in an acute or extended care setting where patients can be monitored for adverse effects, drug interactions, and therapeutic effects. In an outpatient or ambulatory care setting, TI programs are more controversial with regard to patient outcomes. The American College of Physicians (ACP) states that TI is unsafe in most ambulatory care settings.⁹

TI CRITERIA

Because TI is a complex process, any such interchange should undergo a thorough and systematic evaluation. A scientifically defensible and pharmacoeconomically beneficial TI program adheres to six basic criteria to ensure that an optimal standard of care is maintained: (1) therapeutic equivalence; (2) clinical evidence supporting interchange; (3) cost or other advantages; (4) a thorough P & T Committee evaluation process; (5) regular monitoring of outcomes, and (6) opportunity for physician override.^{3,10}

Within a comprehensive TI program, the agents considered for therapeutic interchange must be therapeutically equivalent. This requires selected agents to be comparable in terms of their clinical outcomes, including therapeutic benefits and adverse effects. The formulary TI agent chosen must be supported by sound evidence demonstrating its clinical efficacy and safety for each designated indication. Also, the evidence must demonstrate that the agent is as efficacious and safe as other alternative agents used to manage these indications.

The financial analysis for a TI program should employ appropri-

ate scientific pharmacoeconomic models to determine which agent is best for reducing total costs (including indirect expenses associated with administration, monitoring, and adverse events) and to ensure desired patient outcomes. Within the structure of a TI program, the P & T Committee is responsible for providing a thorough and balanced evaluation of the clinical data; finalizing policies and procedures; implementing an educational process for practitioners and other health care team members; and ensuring that the process is maintained and monitored in an ongoing manner. Although costs are a great concern, this committee must ensure that financial incentives do not override optimal patient care. The final TI criterion is that the prescriber must be permitted to override the TI program and tailor patient care without undue administrative hurdles.

These criteria have been established to provide a basic set of standards for developing a TI program. They mandate the comparison of clinical efficacy and safety results between considered agents, the assessment of potential clinical and financial outcomes, and the minimization of risk.

TI STUDIES

TI programs have been initiated with varying degrees of success and compliance to the TI criteria. Clinicians from the Creighton University Cardiac Center published short-term outcomes for a TI initiative involving HMG-CoA reductase inhibitors. Eighty patients with coronary artery disease, who were seen at Creighton University Hospital or its affiliated clinics, received the selected formulary agent, atorvastatin, in place of either pravastatin or simvastatin.

In a review of the cholesterol laboratory results taken at designated time intervals for these 80 patients, the clinical efficacy of atorvastatin was found to be greater than to equal to that of pravastatin and simvastatin. This therapeutic benefit was also accompanied by a cost advantage leading to the overall clinical and financial success of the program.¹¹

Although this pilot program appeared to be successful, in review of the TI criteria, these HMG-CoA reductase inhibitors are not assumed to be therapeutically equivalent. Therefore, as noted by the authors, TI programs focusing on this class of medications must be evaluated carefully due to the potential differences that exist in each agent's ability to decrease low-density lipoproteins (LDLs).

Not all TI initiatives result in positive outcomes, as demonstrated by Unity Health Plans. This Wisconsin MCO implemented a TI program in 1998 that focused on proton pump inhibitors (PPIs). PPIs are prescribed for specific GI disorders such as duodenal and peptic ulcers and esophageal reflux disease. A prospective, observational outcomes study, conducted during the months of April and May 1998, measured the rates of clinical and humanistic outcomes for this TI program. Data from 105 patients suggested that the switch from omeprazole to the selected formulary agent, lansoprazole, was associated with an increased use of nonprescription heartburn medications; a significant rise in the severity of symptoms; and a significant decrease in patient satisfaction. Thus, based on these conclusions, this TI program appeared to actually compromise both therapeutic and economic outcomes.¹²

In applying the TI criteria, it appears that therapeutic equivalence was not demonstrated with these agents in clinical practice even though comparable efficacy and safety were found in controlled trials. In contrast to the clinical trials, the patients enrolled in this program displayed varying degrees of disease severity. Also, it appears that specific regimens were not provided in the protocol, most likely due to the lack of established equivalent doses. This particular TI experience emphasizes the need for ongoing monitoring and detailed protocols, because real-life practice does not always reflect the setting of a controlled clinical trial.

TI WITH LMWHs

First marketed in the early 1990s, LMWHs have become widely prescribed alternatives to standard unfractionated heparin (UFH) for the treatment and prophylaxis of venous thromboembolism and the management of unstable angina and myocardial infarction. The increased use of LMWHs for these indications in place of UFH is based on clinical evidence that suggests that LMWHs are at least as effective as UFH, have superior safety profiles,¹³ and are more convenient to administer. Due to the high cost and high volume of use associated with LMWHs, some health care institutions and organizations have targeted this pharmacologic class for TI programs.

Agents should be therapeutically equivalent to qualify for TI. LMWHs differ in manufacturing processes, molecular weights, pharmacologic profiles, and clinical evidence. Due to these differences, the literature does not provide agreement about therapeutic equivalence within this class. Also, at this time, it has not been deter-

mined which chemical or physical properties of LMWHs are responsible for the efficacy and safety outcomes demonstrated by any one agent for any one indication. Therefore, it is difficult to evaluate the true significance of the differences in these properties between agents.¹⁴ As a result, since therapeutic equivalence cannot be fully established, the application of TI to this pharmacologic class becomes questionable. However, in an attempt to contain costs, some health care systems have chosen to consider the LMWHs as interchangeable.

Clear scientific evidence directly comparing the therapeutic efficacy of the LMWHs is lacking in the medical literature. Only a few studies have been published in which one LMWH is studied, head-to-head, with another. Most studies available for a given indication have compared the efficacy and safety of the LMWH agent with either UFH or placebo. Due to important differences in individual study design and methodology, it is difficult to establish therapeutic equivalence based on a comparison of the final trial results.¹⁴

Furthermore, published randomized, controlled trials have not been equally distributed among the agents within this class. Enoxaparin, dalteparin, and tinzaparin are the three LMWHs currently approved by the FDA for use in the US. Although LMWHs have been evaluated in a variety of patient populations, enoxaparin has demonstrated efficacy in the broadest range of indications. This is clearly apparent when reviewing the current number of FDA-approved indications for each agent. Enoxaparin is approved for eight indications; dalteparin is approved for three; and tinzaparin currently has one indication for use

(see Table 1).¹⁵⁻¹⁷

It is not appropriate to assume that one LMWH agent can be used in a safe and effective manner for a given indication based on the experience of another. Issues that affect therapeutic outcomes, including appropriate dosing, duration of therapy, and safety, may not have been adequately investigated. As a result, if an institution considers a TI for LMWHs, there is little or no supporting data for determining the therapeutic equivalence of the various agents across indications.

Due to the uniqueness of each LMWH and lack of demonstrated therapeutic equivalence, the following organizations have issued position statements that LMWHs should not be considered interchangeable: the Food and Drug Administration (FDA); the World Health Organization (WHO); the American College of Cardiology (ACC); the American Heart Association (AHA); the American College of Chest Physicians (ACCP); and the Department of Defense (DOD) Executive Council (see Table 2).¹⁸⁻²¹

LMWH TI Programs

In September 1996, the University of Wisconsin Hospital and clinics, under the recommendation of its P & T Committee, initiated a LMWH TI program. The then-current formulary LMWH agent, enoxaparin, was replaced with dalteparin. A management case study focusing on this initiative was completed.

Results indicated that the use of dalteparin was associated with a \$90,000 decrease in annual drug acquisition costs compared with enoxaparin therapy. However, in a further analysis,²² it was determined that more than 18,000 patient days of therapy would be required to realize this difference in

Table 1. Approved Labeling of LMWHs¹⁵⁻¹⁷

<i>Indication</i>	<i>Enoxaparin</i>	<i>Dalteparin</i>	<i>Tinzaparin</i>
Prevention of DVT in:			
Abdominal surgery	•	•	
Hip replacement surgery during hospitalization	•	•	
Hip replacement surgery following hospitalization	•		
Knee-replacement surgery	•		
Treatment of acute DVT in inpatients with/without PE	•		•
Treatment of acute DVT in outpatients without PE	•		
Unstable angina/non-ST segment myocardial infarction	•	•	
LMWH = low molecular weight heparin DVT = deep vein thrombosis PE = pulmonary embolism			

costs.²³ Also, the original case study was limited to the examination of acquisition costs and not the costs of managing negative outcomes.

A post hoc pharmacoeconomic analysis using a cost model of outcomes was applied to the safety and efficacy data. These results suggested that for every 100 patients who were switched from enoxaparin to dalteparin, an average of \$13,500 in costs of managing negative outcomes was potentially added to the overall cost of dalteparin therapy. This calculation assumed a cost of \$6000 for treating an additional pulmonary embolism (PE) and \$7500 for treating 1.5 additional major bleeding episodes. Extrapolation of the study data suggests that for every 1000 patients switched to dalteparin, 10 additional PEs were possible; based on the known mortality rates for PE, one of these would be potentially fatal.²⁴ This is an example of a program in which

the total costs and safety implications of the interchange were not fully evaluated.²²

South Fulton Medical Center, a 300-bed community hospital in Georgia, conducted a LMWH medication use evaluation (MUE) during 2001 to determine baseline use. Results demonstrated that across indications, enoxaparin accounted for 70% and dalteparin accounted for 30% of LMWH use. Tinzaparin was not used at this institution. Due to this split between agents, the institution was not eligible for any significant share-based discounts.

An LMWH project was initiated to first identify the most cost-effective, evidence-based, sole formulary LMWH and secondly, to appropriately implement a TI program. Due to the supporting clinical evidence and FDA indications, enoxaparin was chosen as the formulary LMWH. Based on a targeted enoxaparin market share of greater than 90%, this institution

predicted an annual cost savings of \$47,000. Dosing regimens were also reviewed in the initial MUE. Results indicated that 92% of the patients receiving enoxaparin 30 mg every 12 hours would have been eligible for 40 mg daily. This would allow for additional cost savings.²⁵

LEGAL IMPLICATIONS

Although cost containment is often the primary incentive for initiating a TI program, clinical effectiveness and patient safety should ultimately be the core of any program if it is to be truly successful. When properly implemented, TI programs have the potential to contain or reduce costs without compromising patient care. However, if optimal patient outcomes are sacrificed for potential financial gain, the health care system may be exposed to legal problems.

At this time, to our knowledge, there are no published legal opinions describing the specific civil liability of a health care system or health care provider for a patient's drug-related injury due to a LMWH TI program. However, the vast majority of medical negligence and malpractice cases are settled out of court and never become public record. Also, the visibility and degree of legal risk(s) may dramatically increase if negative patient outcomes associated with TI programs are published and become known to the legal community.²⁴

In order for the plaintiff to succeed in a negligence action, four components must be established: (1) that the health care facility or practitioner owed the patient a duty to provide an accepted standard of care; (2) that the health care system breached that duty; (3) that the breach of duty resulted in

Table 2. Position Statements¹⁸⁻²¹

FDA	LMWHs cannot be used interchangeably.
WHO	The LMWH drugs are distinct entities.
ACC/AHA	Important to consider each LMWH individually rather than as members of a class of interchangeable compounds.
ACCP	LMWHs may not be clinically interchangeable.
DOD	Enoxaparin and dalteparin are not sufficiently interchangeable for a closed class contract.

FDA = US Food and Drug Administration
 WHO = World Health Organization
 ACC = American College of Cardiology
 AHA = American Heart Association
 ACCP = American College of Chest Physicians
 DOD = US Department of Defense

Table 3. Strategies to Minimize Liability Risk with Therapeutic Interchange

1. Formulate, adopt and enforce comprehensive policies for medication use within the institution.
2. Thoroughly educate the medical staff about the content and process of therapeutic interchange.
3. Base decisions concerning appropriate medication use on relevant literature review.
4. Avoid decisions that are driven primarily by financial considerations such as product promotion or preferential prices.
5. Permit prescriber choice of alternatives other than a primary formulary agent based on sound clinical judgment and valid evidence.
6. Conduct drug utilization evaluations for specific critical drugs in order to assess the effect of therapeutic interchange on the quality of care.
7. Update the formulary system on a continuous basis and invite interdisciplinary participation in the update process.

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injury to the patient; and (4) that the patient sustained legally recognized damages as a result.^{2,26}

Establishing a breach of duty is a critical issue in determining liability. A health care system that chooses to ignore or only selectively comply with recognized therapeutic interchange guidelines may be judged to have breached its duty to provide patients with an accepted standard of care. Implementing a TI program without validating

therapeutic equivalence between the included agents may compromise patient safety and clinical outcomes. Since the LMWH agents have not been established as therapeutic equivalents by their respective manufacturers¹⁵⁻¹⁷ or by leading organizations involved with these issues,¹⁸⁻²¹ health care systems and individual health care providers must be aware of the therapeutic and liability risks associated with implementing a

LMWH TI program.

A health care system can be liable for negligence when its policies and procedures play a prominent role in causing patient harm or injury. This is known as corporate negligence.²⁶ Liability may be found due to the decisions made by the P & T Committee and the individual acts of prescribers who follow these decisions. In addition, individual committee members may also be held liable if a decision they endorsed ultimately causes patient harm or injury. In a similar manner, institutional negligence may occur under the doctrine of respondent superior in which an employer is accountable for the actions of its employees.² When a P & T Committee's endorsed LMWH TI program becomes policy within a health care system, subsequent therapeutic options taken by individual practitioners may fall below the accepted standard of care. This situation may increase the risk of adverse patient outcomes and liability for all involved.

Courts have not supported the use of substandard treatment for the sake of cost containment.² If an agent lacks sufficient evidence for use in a specific indication, there is a risk that it may produce less than optimal outcomes. In terms of LMWHs, enoxaparin is the most thoroughly studied LMWH approved in the US, with the most FDA-approved indications. Dalteparin and tinzaparin fall behind in the quantity of published clinical research and approved indications. Thus, the implementation of an LMWH TI program may promote the use of an LMWH agent that lacks a comprehensive FDA indication profile and a broad scope of clinical trials.

All TI programs should give the physician the opportunity to override the endorsed formulary

interchange agent. As a result, the prescribing physician will generally be held accountable for the medications used to manage his or her patients. The physician may claim that institutional cost restraints and formulary decisions influenced or changed prescribing habits; however, when the policies and procedures permit the physician to prescribe off-formulary, this reasoning is usually not successful.²

If the institution denies, restricts, or inhibits the physician's therapeutic decisions, resulting in the delivery of substandard care and patient injury, the institution may be liable. As a result, before complying with any therapeutic interchange program endorsed by a health care system, the physician must be aware of the current, relevant medical literature in order to initiate effective and safe prescribing.

Health care systems must take measures to limit liability associated with formulary decisions, including therapeutic interchange.²⁷ These strategies are summarized in Table 3. Although cost is an overwhelming factor in today's health care environment, the level of patient care provided should not be compromised. Sound decisions, based on scientifically valid clinical evidence, will promote optimal patient care, and in turn, limit liability for the health care system as well as practitioners.

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