Cost Containment for Argatroban Through Reduction in Drug Waste: Experience at a Single Center

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Introduction

Argatroban is a direct thrombin inhibitor mainly used to treat heparin-induced thrombocytopenia (HIT).[1] The drug is administered by continuous infusion and is a source of substantial expense for many hospital pharmacies due to its high cost. Because of the difficulty in diagnosing HIT and the unpredictable duration of therapy with argatroban, waste of argatroban is a concern. This is particularly evident in health care systems where a definitive diagnosis of HIT may be delayed by several days. Another factor contributing to waste is how the medication is dosed. Patient-specific weight-based dosing results in considerable variability in each patient's required dose.

Argatroban is currently supplied by GlaxoSmithKline (GSK) as a concentrated drug (100 mg/mL) in a 2.5-mL vial; reconstitution is required prior to administration.[2] Additional argatroban products of different concentrations have been approved by the FDA: a 125-mL ready-to-use vial (1 mg/mL, Sandoz) and 50-mL ready-to-use vial (1 mg/mL, The Medicines Company).[3,4] Another 50-mL ready-to-use vial product (1 mg/mL) was launched in February 2013 by Sandoz[5]; however, this product was not available at the time of our study. Given the variability in the required doses for individual patients and the duration of therapy, questions have arisen about the optimal quantity of argatroban to prepare in a single bag to reduce waste and maximize efficiency.

In this analysis, we attempted to quantify the waste of argatroban based on actual usage patterns, clarify where this waste happens, and determine if we could reduce cost by switching to a product with less volume.

Methods

Adult patients who received argatroban in the University of Michigan Hospitals (UMHS) between July 2010 and June 2011 with electronic documentation of hang times and dose changes by the nursing staff were included in this analysis. The number of argatroban infusions (250 mg/250 mL, standard concentration) compounded in the pharmacy, the number of infusions hung, and the corresponding administration time and total infusion time by nursing staff were collected.

Total actual dose administered (mg) was calculated using nursing documentation. The time between rate changes (hours) was multiplied by the infusion rate during that time (mg/hr) to determine the amount of argatroban infused (mg) during the specified time frame. All time frames were summed to find the total actual dose administered (mg) for each individual patient. Average dose per 24 hours (mg/day) was calculated by dividing the total drug administered by the total duration of argatroban therapy (days). Total duration of argatroban therapy was determined by finding the exact difference between the start of the argatroban infusion and the end time documented in hours and minutes, then converting to days.

Total drug wasted (mg) was composed of 2 parts: (1) infusions compounded and sent by the pharmacy but not administered to the patient, termed "preparation waste"; and (2) remaining drug not infused into the patient before a new infusion was hung, termed "administration waste." Preparation waste (mg) was calculated by multiplying the number of infusion bags prepared by the pharmacy, but not administered, by 250 mg. Preparation waste for the 50 mg/50 mL and 125 mg/125 mL products was assumed to be zero, as these are ready-to-use products. Ready-to-use products not administered were assumed to be returned to the pharmacy, unopened, and able to be redispensed at a later time. Administration waste (mg) was calculated as the amount of argatroban hung in mg (number of infusions hung × 250 mg) minus the total actual dose administered. Only drug costs were included in the analysis. Personnel costs in the preparation of the products are likely fixed costs in most institutions and would not be impacted substantially by reducing waste. In addition, the cost for additional supplies for reconstitution was not included, as we assumed this cost was minimal compared with the drug cost itself.

Results

Over a 12-month period, 81 patients were identified as receiving an argatroban infusion. However, an electronic documentation system required to derive specific information on infusion rates and start and stop times was not in place for the entire year included in this analysis. As a result, not all patients who received argatroban had the prespecified required data available from their records (time, rate, and duration of infusions) to be included in the analysis. A total of 20 patients met the requirements for inclusion in the study (Table 1). The weighted mean argatroban dose for these 20 patients was 1.91 ± 1 mcg/kg/min, median duration of therapy was 4.57 days (interquartile range, 3.4 to 10.1), and mean dose in 24 hours was 253 ± 131 mg.

Estimated Waste

A total of 36 infusion bags (250 mg/250 mL preparation) were wasted within the

Table 1: Baseline Demographics of Patients on Argatroban with Nursing Documentation (July 2010 to June 2011)

Characteristic	Study Population[a] N = 20
Age (years)	58.2 ± 15.4
Gender (% male)	70
Weight (kg)	93.1 ± 25.4
Indication (%)	
HIT	30
HITT	15
Suspicion of HIT	30
History of HIT or HITT	5
Clotting deficiency	10
Other	10
Average weighted dose (mcg/kg/min)	1.91
Median duration of therapy (days)	4.57

[a]Denotes mean ± standard deviation unless otherwise specified.
HIT = heparin-induced thrombocytopenia; HITT = heparin-induced thrombocytopenia with thrombosis.

pharmacy. At the site of administration, 16,878 mL of waste was calculated, equaling approximately 68 infusion bags (Table 2 and Table 3). Combined, this totaled a waste of 104 infusion bag equivalents. Based on the wholesale acquisition cost (WAC) for argatroban of $1314 as of June 2012,[5] the calculated total cost of the waste was $136,604 for these 20 patients. A total of 237 infusion equivalents were administered to the 20 patients; therefore, 31% of all drug compounded was wasted. If this waste cost were extrapolated to the entire population of patients receiving argatroban during this year, the total cost of waste would be $546,416.

Modeling Costs and Waste With Other Preparations

Argatroban drug costs per vial, based on WAC, are $1314 for 250 mg/2.5 mL vial (GSK), $227 for 50 mg/50 mL vial, and $567 for 125 mg/125 mL vial (Table 3).[5] As noted previously, estimated total drug costs at UMHS using the 250 mg/250 mL reconstituted product were $445,277, of which $136,604, or 31%, was wasted drug. By switching to the 50 mg/50 mL product or 125 mg/125 mL product, the total cost of waste and percentage of cost wasted would be $2270 and 1%, versus $6242 and 2%, respectively (Table 3). With the 50 mg/50 mL product, the total argatroban cost would decrease by $175,828 and the total cost of waste would decrease by $134,334 compared with the 250 mg/250 mL product. Similarly, the total argatroban cost would decrease by $172,343 using the 125 mg/125 mL product compared with the 250 mg/250 mL product, and the total cost of waste would decrease by $130,362. Based on WAC, an approximate $170,000 cost savings could be realized for the 20 patients in this study, largely due to a reduction in waste, by utilizing either the 50 mg/50 mL or 125 mg/125 mL product compared with the innovator product. If these cost savings were extrapolated to the entire patient population that received argatroban at UMHS during the 12-month study period, the 50 mg/50 mL product would save UMHS $712,103 in drug costs. Likewise, the 125 mg/125 mL product would save UMHS $697,989.

Table 2: Comparison of the Actual and Theoretical Argatroban Waste Using the Compounded Infusion of 250 mg/250 mL and the Argatroban 50 mg/50 mL and 125 mg/125 mL Products

Characteristic	Study Population N = 20
Median number of bags sent but not administered (range)	0 (0-14)
Total drug wasted, mL (bags)[a]	
250 mg/250 mL product	25,879 (104)
50 mg/50 mL product	2279 (46)
125 mg/125 mL product	5754 (47)

[a]Total drug wasted = [(number of bags hung × number of mg in product) – (total actual dose administered)] + (number of bags sent but not administered × number of mg in product).

Discussion

Drug cost and total cost for waste of the argatroban 250 mg/250 mL product at our center during a 12-month period was $445,277 and $136,604 (31% of total cost), respectively. Comparatively, model estimates suggest drug costs for the argatroban 50 mg/50 mL and 125 mg/125 mL products to be $269,449 and $272,934, respectively, while total waste was $2270 (1% of total cost) and $6242 (2% of total cost), respectively. The use of ready-to-use products could result in an overall reduction in total cost of waste of approximately $170,000 and an absolute reduction in the percentage of the total drug cost wasted of at least an estimated 29%. If extrapolated to the total number of patients receiving argatroban throughout the year (N = 81), overall total costs would be reduced by approximately $700,000.

Argatroban is a high-cost medication; therefore, finding solutions to decrease waste and costs is important. A few problems arise with the current method of compounding 250 mg/250 mL bags. Because argatroban doses are compounded close to the needed administration time to reduce the potential for waste, they are prepared in a pharmacy satellite location that does not meet <USP 797> standards. Thus, the hang time for these immediate-use doses is only 12 hours. Reconstitution must also occur on an as-needed basis

Table 3: Comparison of Actual and Projected Total Drug Costs, Total Waste Cost, and Percentage of Drug Cost That Is Waste in 20 Patients at University of Michigan Hospitals for the Argatroban 250 mg/250 mL, 50 mg/50 mL, and 125 mg/125 mL Products

	Argatroban 250 mg/250 mL	Argatroban 50 mg/50 mL	Argatroban 125 mg/125 mL
Drug cost[a]	$1314	$227	$567
Total bags hung (bags/day[b])	303 (0.83)	1187[c] (3.25)	481[c] (1.32)
Total bags sent but not administered	36	0	0
Total drug cost[d]	$445,277	$269,449	$272,934
Total bags wasted	104	10	11
Total cost of waste[e]	$136,604	$2270	$6242
% of cost that is waste	31	1	2

[a]Based on wholesale acquisition cost (WAC) from reference 6.
[b]Bags per day = total bags hung / 365 days (1-year time frame for study inclusion).
[c]It is assumed that the total bags hung is the minimum number of bags needed to give actual dose administered, the same actual dose administered in the 250 mg/250 mL analysis.
[d]Total drug cost = (total bags hung + total bags sent but not administered) × drug cost.
[e]Total cost of waste = total bags wasted × drug cost

when the infusion is ordered. This affects pharmacy work flow, requires time, and increases labor. Despite this, personnel costs were not included in the cost estimates, as they were considered to be fixed. It is recognized that there is an opportunity cost associated with personnel preparing products that are ultimately wasted. Second, reconstituted but unused bags are often wasted, as there are generally only a few patients receiving argatroban at any given time and the short hang-by time limits their use.

The newer argatroban products may offer benefits to address the problems seen with use of the innovator product. The 50 mg/50 mL product is supplied as a ready-to-use glass bottle, similar to propofol. There is no hang-by time and the product itself has a shelf life of 16 to 18 months in the pharmacy. Similarly, the 125 mg/125 mL product is a ready-to-use vial. In terms of pharmacy time, the already reconstituted products would save both time and pharmacy workload. Both products can be labeled and sent to the hospital floor without compounding and returned to the pharmacy for redistribution if the infusion is not started.

A potential downside to the newer products may be an increase in nursing time due to more frequent hanging of drug doses. Nursing time was considered a fixed cost since it is unlikely that nursing staffing would be impacted by a change in the product used. Therefore, the cost correlated with this increased time was not considered in the analysis. Using the innovator product, the average number of bags to be hung in 24 hours was 0.83. Utilization of the 50 mg/50 mL and 125 mg/125 mL products would have a projected increase to 3.25 and 1.32 bags in 24 hours, respectively (Table 3). The increase of approximately 2 bags daily for the 50 mg/50 mL product and 1 bag every 2 days for the 125 mg/125 mL was considered negligible. If we were to extrapolate these data from our inclusion population of 20 patients to all patients who received an argatroban infusion within the year, the average number of bags to be hung in 24 hours would be 3.3 for the 250 mg/250 mL product, 13.0 for the 50 mg/50 mL product, and 5.27 for the 125 mg/125 mL product. The incremental nursing time for these extra bag changes across the institution is minimal and is overshadowed by the considerable product cost reductions. Finally, the pre-made, newer products may be larger in size than the vials and therefore take up more shelf space. This may be a problem in institutions with limited storage space. Space could be considered an indirect cost in terms of needing to utilize a limited resource.

Limitations

There are a few limitations to our study. First, the accuracy of the data is dependent on nursing documentation for infusion rates and times for starting the infusion, changing rates, and ending the infusion. Likewise, the retrospective nature of our analysis inhibits the ability to verify and clarify documentation. Second, many adult patients who received argatroban infusions during this time period were not directly included in this analysis. During the inclusion period, the electronic nursing flow sheet software was not fully implemented at UMHS. Thus, detailed information regarding infusion times and rate changes was not available for all patients. We attempted to account for this by extrapolating our results to the entire patient population receiving argatroban within the prespecified 12-month time frame. The major obstacle in obtaining administration data on a consistent basis was the lack of an electronic nursing documentation system in some areas of the hospital during the analyzed time frame.

Another limitation was the use of WAC in the calculation of the product costs and waste. It is likely that hospitals will pay a contract price different from WAC; this will impact the results achieved by individual institutions. Hospitals should model their individual costs and potential savings based on their own acquisition costs. The calculated percentage of cost that is waste may also be utilized for estimating potential savings for each institution's specific costs.

Conclusions

Our results confirmed that there is a substantial amount of argatroban waste

in our academic health system resulting in excess costs. This waste occurred at both the product preparation and drug administration stages, with the majority of waste occurring during the drug administration phase. Modeling indicated that utilization of a ready-to-use solution of 50 mg/50 mL or 125 mg/125 mL could reduce overall waste and associated costs, potentially saving the hospital $700,000 in wasted drug costs over the period of 1 year. While personnel costs were assumed to be fixed, use of the smaller volume ready-to-use products would be anticipated to reduce pharmacy preparation time and increase nursing administration time. In either case, these differences in personnel time were considered to be negligible compared with the product cost savings.

This manuscript was written when Jennifer Lose, PharmD, BCPS, was a PGY-2 Cardiology Specialty Pharmacy Resident at the University of Michigan Hospitals and Health Centers.

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References

1. Warkentin TE, Greinacher A, Koster A, et al. Treatment and prevention of heparin-induced thrombocytopenia: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. 8th ed. *Chest*. 2008;133(suppl):340S-380S.
2. Argatroban Injection [package insert]. Research Triangle Park, NC: GlaxoSmithKline; April 2012.
3. Argatroban Injection [package insert]. Princeton, NJ: Sandoz; September 2011.
4. Argatroban Injection [package insert]. Woodcliff Lake, NJ: The Medicines Company; June 2011.
5. Sandoz launches an authorized generic version of argatroban injection (aqueous solution for intravenous infusion) [press release]. Princeton, NJ: Sandoz US Communications; February 19, 2013. http://www.sandoz.com/media_center/news/2013/press_releases/2013_02_19_argatroban_injection.shtml. Accessed February 22, 2013.
6. *Drug Topics Red Book Online.* Montvale, NJ: Thomson Healthcare; 2012. Accessed June 25, 2012.

For further information, please visit www.PharmacyTimes.com.

Brief Summary (For full Prescribing Information, refer to package insert.)

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Argatroban safely and effectively. See full prescribing information for Argatroban.

ARGATROBAN INJECTION, aqueous solution for intravenous infusion only
Initial U.S. Approval: 2000

INDICATIONS AND USAGE

Argatroban is a direct thrombin inhibitor indicated:
- For prophylaxis or treatment of thrombosis in adult patients with heparin-induced thrombocytopenia (HIT)
- As an anticoagulant in adult patients with or at risk of HIT undergoing percutaneous coronary intervention (PCI)

DOSAGE AND ADMINISTRATION

- Argatroban 50 mg in 50 mL aqueous solution (1 mg/mL) is intended for administration to adult patients
- Discontinue all parenteral anticoagulants before administering Argatroban Injection
- Adjust dosing in patients with HIT who have moderate or severe hepatic impairment

Heparin-Induced Thrombocytopenia

The dose for heparin-induced thrombocytopenia without hepatic impairment is 2 mcg/kg/min administered as a continuous infusion
- Discontinue heparin therapy and obtain a baseline aPTT before administering Argatroban
- After the initial dose of Argatroban, the dose can be adjusted as clinically indicated

Percutaneous Coronary Intervention

The dose for patients with or at risk for heparin-induced thrombocytopenia undergoing percutaneous coronary intervention is started at 25 mcg/kg/min and a bolus of 350 mcg/kg administered via a large bore intravenous line over 3 to 5 minutes
- Activated clotting time (ACT) should be checked 5 to 10 minutes after the bolus dose is completed. The procedure may proceed if the ACT is greater than 300 seconds
- Monitoring therapy and dosage adjustments recommendations should be followed
- See special dosing recommendations for hepatic and renal impaired patients

DOSAGE FORMS AND STRENGTHS

Argatroban Injection is supplied in a single use vial, containing 50 mg
Argatroban in 50 mL aqueous solution (1 mg/mL)

CONTRAINDICATIONS

- Major bleeding
- History of hypersensitivity to this product

WARNINGS AND PRECAUTIONS

- Risk of hemorrhage: Hemorrhage at any site can occur (unexplained fall in hematocrit or blood pressure or other unexplained symptom may indicate hemorrhage). Use with caution in patients at risk, including those receiving antiplatelet agents, thrombolytics, or other anticoagulants

- Use in hepatic impairment: Adjust starting dose and titrate carefully in patients with HIT who have moderate or severe hepatic impairment. Avoid use in PCI in patients with clinically significant hepatic impairment

ADVERSE REACTIONS

- HIT patients: The most common (> 5%) adverse reactions were dyspnea, hypotension, fever, diarrhea, sepsis, and cardiac arrest
- PCI patients: The most common (> 5%) adverse reactions were chest pain, hypotension, back pain, nausea, vomiting and headache

To report SUSPECTED ADVERSE REACTIONS, contact Sandoz Inc. at 1-800-525-8747 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Heparin: Allow sufficient time for heparin's effect on aPTT to decrease before initiating Argatroban Injection therapy
- Warfarin: Concomitant use results in increased prolongation of PT and INR
- Thrombolytic agents or glycoprotein IIb/IIIa antagonists: Safety and effectiveness of concomitant use with argatroban have not been established

USE IN SPECIFIC POPULATIONS

- Nursing Mothers: Discontinue nursing or drug, taking into account the importance of the drug to the mother
- Pediatric use: Safety and effectiveness have not been established; if used, initial infusion doses are lower than in adult patients

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