Clinical Investigation

Drug Utilization, Dosing, and Costs After Implementation of Intravenous Acetaminophen Guidelines for Pediatric Patients

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OBJECTIVES: The objectives of this evaluation of medication use were to characterize the use of intravenous acetaminophen at our institution and to determine if acetaminophen was prescribed at age-appropriate dosages per institutional guidelines, as well as to evaluate compliance with restrictions for use. Total acquisition costs associated with intravenous acetaminophen usage is described as well.

METHODS: This retrospective study evaluated the use of acetaminophen in pediatric patients younger than 18 years of age, admitted to a tertiary care hospital, who received at least 1 dose of intravenous acetaminophen between August 1, 2011, and January 31, 2012.

RESULTS: A total of 52 doses of intravenous acetaminophen were administered to 31 patients during the 6-month study period. Most patients were admitted to the otorhinolaryngology service (55%), and the majority of doses were administered either in the operating room (46%) or in the intensive care unit (46%). Nineteen doses (37%) of intravenous acetaminophen were administered to patients who did not meet institutional guidelines' eligibility criteria. Three patients received single doses of intravenous acetaminophen that were greater than the dose recommended for their age. One patient during the study period received more than the recommended 24-hour maximum cumulative dose for acetaminophen. Total acquisition cost of intravenous acetaminophen therapy over the 6-month study period was $530.40.

CONCLUSIONS: Intravenous acetaminophen was used most frequently among pediatric patients admitted to the otorhinolaryngology service during the perioperative period. Nineteen doses (37%) were administered to patients who did not meet the institutional guidelines' eligibility criteria. Our data support reinforcing the availability of institutional guidelines to promote cost-effective use of intravenous acetaminophen while minimizing the prescription of inappropriate doses.

INDEX TERMS: acetaminophen, guideline, intravenous administration, pediatrics

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INTRODUCTION

The United States Food and Drug Administration approved intravenous acetaminophen in November 2010 for management of mild to moderate pain, management of moderate to severe pain with adjunctive opioid analgesics, and reduction of fever. As an antipyretic agent, intravenous acetaminophen has proven effective at reducing fever with a quicker onset of action than oral acetaminophen in endotoxin-induced fever in healthy volunteers.[1] In patients 1 month to 12 years of age, intravenous acetaminophen at a dose of 15 mg/kg was effective in reducing fever produced by acute infection.[2] It is important to consider that these data reflect intravenous acetaminophen's use as an antipyretic medicine and that these effects, such as faster onset of action, may not extend to analgesia. The duration of analgesic effect may be different among routes of administration, as 1 study reported a median difference of approximately 3 hours in time to first rescue medication in a comparison between rectal acetaminophen and intravenous acetaminophen administration in patients undergoing andenotonsillectomy.[3] Patients receiving rectal acetaminophen had a median time to first rescue medication of 10 hours, whereas patients receiving the intravenous formulation required a rescue medication at a median of 7 hours (p=0.01).[3]

Most clinical data regarding the use of intravenous acetaminophen in pediatric patients come from studies in the perioperative setting. Several studies have compared pediatric patients undergoing tonsillectomy or other dental procedures who were treated with intravenous acetaminophen (15 mg/kg/dose) to those receiving other analgesic medications including meperidine and tramadol.[4–6] Compared with meperidine and tramadol, intravenous acetaminophen produced less sedation and resulted in earlier discharge from recovery rooms with no significant differences in pain scores.[4,6] The differences between times to discharge from the recovery room were only approximately 10 minutes in each study.[4,6] One study comparing intravenous acetaminophen with intramuscular meperidine in children undergoing dental restoration procedures reported similar times to recovery room discharge but significantly higher pain scores in the intravenous acetaminophen group.[5] Intravenous acetaminophen demonstrated an opioid-sparing effect in pediatric patients undergoing spinal surgery by significantly reducing the amount of fentanyl administered during the first 2 postoperative days.[7] However, a recent study of pediatric patients undergoing major spinal surgery reported that intravenous acetaminophen improved analgesia only (patients had less elevated pain scores) with no change in total opioid requirements.[8]

Intravenous acetaminophen is approved for use in patients older than 2 years of age but has been used in younger patients at various doses worldwide. A survey of intravenous paracetamol (acetaminophen) use in the United Kingdom revealed a wide range of doses, often in excess of the licensed single and daily doses, particularly in those patients younger than 1 year of age.[9] Iatrogenic dosing errors have been described, the most often being a 10-fold overdose related to the concentration of intravenous acetaminophen (10 mg/mL) and milligram doses being administered as milliliters.[10] Monitoring for age-appropriate doses as well as appropriate indications is warranted given the limited experience with this product in the United States.

Adult dosing for intravenous acetaminophen is similar to dosing for enteral acetaminophen. For pediatric patients, a dose reduction may be needed when transitioning from enteral to intravenous routes of administration. Based on pharmacokinetic data and area under the curve (AUC) modeling, an intravenous acetaminophen dose reduction of 33% in infants 1 month to less than 2 years of age and a reduction of 50% in neonates up to 28 days, with a minimum dosing interval of 6 hours, will produce similar AUC to age-appropriate enteral dosing.[11] These modifications in dosing can be attributed to the significantly reduced clearance and prolonged half-life of acetaminophen in neonates and in children up to 2 years of age.[12] Due to these variations in dosing, guidelines were developed and approved by the Pharmacy and Therapeutics (PT) Committee of our institution, a tertiary care teaching hospital in a major city (Table 1). Our hospital for children is located within a larger academic medical center and contains 32 general inpatient, 14 intermediate care, 10 pediatric intensive care unit, 30 neonatal intensive care unit, and 10 neonatal intensive care unit step-down beds. The pharmaceutical guidelines include recommended single doses and total daily doses for adults and children, as well as restrictions for use. The goals of these institutional guidelines were to restrict the use of intravenous acetaminophen to patients who would benefit most from it and to reduce the risk of dosing errors. The guidelines were prepared and approved by the Pediatrics Subcommittee of the PT Committee. The Pediatrics Subcommittee consists of pharmacists, physicians, and nurses who practice on the pediatric floors in the hospital. Once approved, the guidelines were posted to the hospital's intranet page. When an order for intravenous acetaminophen is entered in the computerized physician order entry (CPOE) system, prescribers are alerted to these guidelines and directed to the guidelines' location on the intranet. The pharmacist verifying the order is responsible for reviewing whether the patient meets criteria and should contact the prescriber if there is a discrepancy.

The objectives of this study were to characterize the use of intravenous acetaminophen at our institution and to determine if acetaminophen was prescribed at the age-appropriate dosing per institutional guidelines as well as to evaluate compliance with restrictions for use. Total acquisition cost associated with intravenous acetaminophen usage is described as well.

MATERIALS AND METHODS

This is a retrospective evaluation of the use of

Table 1. Intravenous Acetaminophen Guidelines

Patient Characteristic	Guideline
Patient eligibility	IV acetaminophen is to be used only in pediatric patients who have a prolonged return of GI function (i.e., use of PO or PR acetaminophen is not feasible) OR Are in the perioperative setting (patients are under general anesthesia in the operating rooms or within 24 hr of postsurgical recovery period)
Dosing recommendations	Dosing recommendations for IV acetaminophen are based on those for healthy individuals who have normal hepatic and/or renal functions, absence of chronic alcoholism, and no signs or symptoms of malnutrition. If the patient has abnormal hepatic and/or renal functions, chronic alcoholism, or signs and symptoms of malnutrition, use IV acetaminophen with caution. Dose adjustments may be warranted.
Adults and adolescents (≥12 yr old and weighing ≥50 kg)	1000 mg IV every 6 hr or 650 mg IV every 4 hr (maximum: 4000 mg in 24 hr)
Adults and adolescents (≥12 yr old and weighing <50 kg)	15 mg/kg IV every 6 hr or 12.5 mg/kg IV every 4 hr (maximum: 75 mg/kg in 24 hr)
Children (≥2 to 12 yr old)	15 mg/kg IV every 6 hr or 12.5 mg/kg IV every 4 hr (maximum: 75 mg/kg in 24 hr)
Children (≥3 mo to 23 mo old)	10 mg/kg IV every 6 hr (maximum: 40 mg/kg in 24 hr)
Children (<3 mo old)	7.5 mg/kg IV every 6 hr (maximum: 30 mg/kg in 24 hr)

IV, intravenous; GI, gastrointestinal; PO, by mouth; PR, by rectum

acetaminophen that was approved by the Institutional Review Board.

Patients

This evaluation of medication use included all pediatric patients (younger than 18 years of age) who received a dose of intravenous acetaminophen from August 1, 2011, to January 31, 2012. The institutional guidelines (Table 1) were implemented on August 1, 2011, when intravenous acetaminophen became eligible for ordering within the medical center.

Data were extracted from patients' electronic medical records, which included electronic medication administration record, operating reports, and anesthesia records. To characterize the use of acetaminophen, data were extracted which included age, sex, weight, history of recent surgery or gastrointestinal (GI) disease, dose of intravenous acetaminophen, liver function test results around the time of acetaminophen administration, medical or surgical service to which the patient was admitted, and the facility in which the patient was located when the dose(s) of intravenous acetaminophen was administered. To assess a patient's GI function and determine whether they met eligibility criteria for prolonged return of GI function, the patient's feeding status was assessed by reviewing the chart for active dietary orders or nothing by mouth (NPO) orders at the time of intravenous acetaminophen administration. At our institution, an order for NPO does not preclude the patient from receiving medications via the enteral route. Therefore, careful inspection of the medication administration record was done to determine if other medications were administered by the enteral/rectal route if an NPO order was active.

Outcomes

To determine whether patients were prescribed an age-appropriate single dose of acetaminophen, the dosage of intravenous acetaminophen that was recorded in the electronic medical record or anesthesia record was extracted and compared to the institutional guidelines. Total daily (24-hour) exposure to acetaminophen was determined by collecting all doses of acetaminophen (intravenous, enteral, and rectal) that were administered during a 24-hour period beginning with the first dose of intravenous acetaminophen. The total 24-hour cumulative dose was calculated and compared to the 24-hour maximum dose recommended by the adopted guidelines.

Table 2. Characteristics of Patients Who Received Intravenous Acetaminophen During Medication Use Evaluation

Characteristic	Value or Detail	
No. of patients	31	
No. of doses	52	
Age (yr) (median IQR)	12 (6-15)	
No. of males (%)	13 (42)	
No. of medical or surgical services caring for the patient (%)	Otorhinolaryngology	17 (55)
	Pediatric intensive care unit	6 (19)
	Pediatric hematology/oncology	2 (7)
	Other	6 (19)
No. of locations of patient care during administration of dose (%)	Operating room	24 (46)
	Intensive care unit	24 (46)
	Other	4 (8)

IQR, interquartile range; No., number

A patient was deemed eligible for intravenous acetaminophen if they met the criteria outlined by the institutional guidelines at the time a dose of intravenous acetaminophen was administered. According to the guidelines, a patient must meet at least 1 of 2 eligibility criteria in order to receive intravenous acetaminophen. A patient must have had an anticipated delay in the return of GI function, due to gastrointestinal surgery or disease; or the patient was in the perioperative setting. The perioperative setting was defined as the patient undergoing general anesthesia in the operating room or within 24 hours of postsurgical recovery period. Patients' electronic medical records were reviewed for operative reports that indicated GI or other surgery, as well as anesthesia records from which dose, date, and time of intravenous acetaminophen were extracted.

Cost Determination

The wholesale acquisition cost (WAC) was determined for intravenous acetaminophen. Each dose of intravenous acetaminophen was multiplied by the WAC to determine the total costs over the 6-month study period. Each dose administered corresponded to 1 vial, as each vial is a single-use vial. Secondary cost-related outcomes were determined by comparing the costs associated with inappropriate doses of intravenous acetaminophen to the potential costs if the patients had been treated with an alternative dosage form, including acetaminophen tablets, unit dose suspension cups, or suppositories.

Statistical Analysis

All data were analyzed using descriptive statistics, which included medians and interquartile ranges. Statistical analyses were performed using Excel 2011 software (Microsoft Corp, Redmond, Washington).

RESULTS

A total of 52 doses of intravenous acetaminophen were administered to 31 patients <18 years of age during the 6-month study period. All patients and doses were included in the data analysis. Baseline characteristics of the population are outlined in Table 2. Patients had a median (IQR) age of 12 (6-15) years, and most were female. Most patients were admitted to the otorhinolaryngology service (55%) and were undergoing tonsillectomy. At the time the doses of intravenous acetaminophen were administered, the most common location of patients was the operating room (46%) or the pediatric intensive care unit (46%).

Therapy-Related Outcomes

The majority of doses (63%) of intravenous acetaminophen were prescribed to patients who fit the eligibility criteria as outlined in the guidelines (Table 3). Nineteen doses (37%) of intravenous acetaminophen were administered to patients who did not meet eligibility criteria. Seventeen doses were administered to patients with adequate GI function as indicated by active orders for enteral

Table 3. Number of Doses of Intravenous Acetaminophen Administered

Factor	Value
Total no. of doses	52
No. of doses that met eligibility criteria (%)	33 (63)
No. of doses that did not meet eligibility criteria (%)	19 (37)
No. with acceptable gastrointestinal functions	17
No. outside the perioperative period	2
Total no. of vials used	52
Total acquisition cost ($10.20 per vial)	$530.40

nutrition and concomitant enteral medications. Two doses were administered to patients outside the perioperative setting. Three patients received single doses of intravenous acetaminophen that were greater than the dose recommended for their age. Two patients were less than 23 months of age and received a dose of 15 mg/kg, which exceeded the guidelines' recommended dose of 10 mg/kg. The third patient was 8 years old and received a dose of 25 mg/kg (650 mg). One patient during the study period received more than the recommended 24-hour maximum for all exposures to acetaminophen. This patient was less than 1 year of age and received a total of 42.5 mg/kg, which exceeded the guidelines' recommended maximum cumulative dosage of 40 mg/kg/day.

Cost Outcomes

Each vial of intravenous acetaminophen was acquired at a cost of $10.20. As these are single-use vials, each dose administered corresponded to 1 vial. Therefore, the total acquisition cost of intravenous acetaminophen therapy over the 6-month study period was $530.40. A list of other common acetaminophen products and their acquisition costs are provided (Table 4). Nineteen doses of intravenous acetaminophen were administered to patients who did not meet the eligibility criteria. These nineteen doses came at a cost of $193.80.

DISCUSSION

Among patients <18 years of age, during the 6 months since it was added to the formulary, intravenous acetaminophen had been prescribed most frequently to patients on the otorhinolaryngology service in the perioperative setting. Despite having institutional guidelines for use, 37% of the doses were administered to patients who did not meet the eligibility criteria. It is difficult to retrospectively assess the patient's clinical status at the time of administration of intravenous acetaminophen, but if a patient was concurrently receiving other enteral/rectal medications, it is a good indication that intravenous acetaminophen may not have been warranted. Although prescribers are alerted to the institutional guidelines at the time of order entry within the CPOE system, they are not forced to view them before an order for intravenous acetaminophen is entered. It is then the verifying pharmacist's responsibility to ensure that the patient meets the eligibility criteria prior to dispensing the medication. If, after reviewing the electronic medical record, the pharmacist believes that the patient may not meet eligibility criteria, they would need to follow up with the prescriber. This delay in order verification and preparation would delay administration, thus reducing potential benefits of the intravenous product, such as a quicker onset of action. Making the guideline restrictions available to prescribers at the point of order entry, as well as providing them with standardized, age-appropriate doses, may reduce the number of doses ordered for patients who do not meet the eligibility criteria. This can be achieved using a similar process that occurs for drug interactions, where when an order is placed, the prescriber would have to attest to reviewing the patient's record and confirm they do meet eligibility criteria.

Three dosing errors were identified during the study period. Two errors involved patients younger than 23 months of age who received more than the maximum single dosage of intravenous acetaminophen. This might be in part to deviations of our institutional guidelines, which recommend 7.5 to 10 mg/kg/dose, whereas other references have cited an acceptable dosing range

Table 4. Cost Comparison of Acetaminophen Products

Acetaminophen Product	Wholesale Acquisition Cost
Intravenous, 1000 mg/100 mL vial	$10.20*
325 mg tablet	$0.02
500 mg tablet	$0.02
650 mg suppository	$0.48
160 mg unit dose cup	$0.35

**; Cost does not include the additional costs associated with intravenous drug administration*

of 7.5 to 15 mg/kg/dose for this age group.[9] As our guidelines were based on pharmacokinetic data provided by the manufacturer, we felt confident that they were appropriate to provide the desired level of analgesia while minimizing the risk of toxicity.[11] Because we did not collect pain scores during this study, however, we are unable to assess whether the desired level of analgesia was achieved at the doses recommended in the adopted guidelines. The third dosing error came in the case of an 8-year-old patient who received a dose of 25 mg/kg. This dose was well above the recommended 15 mg/kg/dose. It is unclear why this error occurred. The patient's actual weight was just below the 50th percentile for age, and her stature was at the 25th percentile for age. When the dosage was prescribed, the patient's actual weight might have been overestimated, resulting in the error. This dose was ordered, removed from an automated dispensing cabinet, and administered in the operating room, and therefore was not reviewed by a pharmacist prior to administration. One patient received 42.5 mg/kg of acetaminophen in a 24-hour period, which is greater than the 24-hour maximum dose recommended by the adopted guidelines. The extra 2.5 mg/kg that patient received is not clinically significant and might have been the result of rounding. Reinforcing the availability of institutional guidelines to providers and emphasizing the importance of obtaining accurate weights for pediatric patients will help in reducing the occurrence of error such as these.

The wholesale acquisition cost of intravenous acetaminophen is substantially higher than that of other dose forms. The acquisition cost (Table 4) does not include the associated costs of administering the medication by the intravenous versus enteral route, and therefore, the cost discrepancy between intravenous and enteral administration of acetaminophen may be even greater. As more practitioners become familiar with intravenous acetaminophen, its use may increase and associated costs will rise. Screening patients for eligibility will be an important step in ensuring that the product is used in the appropriate populations. Our present guidelines reserve the use of intravenous acetaminophen for those patients who will likely experience the most benefit from it and are unable to tolerate other routes of administration. The cost savings can be substantial if unnecessary doses of the intravenous product can be avoided.

This study had several limitations. As a retrospective review, it is challenging to fully understand the patient's ability to tolerate enteral medications at the time intravenous acetaminophen was ordered and administered. Most doses that were deemed inappropriate were based on a review of the patient's electronic medication administration record. We are unable to fully assess the prescriber's rationale for selecting the intravenous over alternative products, and therefore, each of those doses might have been appropriate. This study did not assess efficacy or whether the pain or fever that was being treated with acetaminophen was relieved. This information would be useful to determine whether the benefits of intravenous acetaminophen outweigh the risks or costs associated with therapy. For certain populations, particularly those patients undergoing tonsillectomy, intravenous acetaminophen has become frequently used in the perioperative period. Whether this product achieves the desired level of analgesia or reduces the demand for other products such as opioids remains to be determined.

At our institution, intravenous acetaminophen has been prescribed most frequently for pediatric patients on the otorhinolaryngology service undergoing tonsillectomy. The eligibility criteria were adhered to in a majority of cases; however, 37% of doses were administered to patients who did not meet the eligibility criteria. Reinforcing the availability of institutional guidelines will promote cost-effective use of intravenous acetaminophen while minimizing prescription of inappropriate doses. This study revealed that there is an opportunity to promote and enforce institutional guidelines that were designed to ensure the safe and appropriate use of intravenous acetaminophen. Further investigations should

focus on the cost effectiveness of intravenous acetaminophen, especially in reducing the analgesic requirements among surgical patients in the perioperative setting.

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Abbreviations AUC, area under the curve; CPOE, computerized physician order entry; GI, gastrointestinal; IV, intravenous; NPO, nothing by mouth; PT, Pharmacy and Therapeutics committee; PO, by mouth; PR, by rectum; WAC, wholesale acquisition cost

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