Journal of Surgery
[Jurnalul de Chirurgie]

Review Article Open Access

Intravenous Acetaminophen: Assessment of Medication Utilization Evaluation Data in Peri-operative Pain Management

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Abstract

Intravenous (IV) acetaminophen has become an accepted component of a multimodal analgesic strategy in perioperative patients. It is currently a branded drug (Ofirmev®) in the United States. The purchase price of the drug is greater than oral and rectal acetaminophen, intravenous ketorolac, and parenteral opioids. As a result, a large number of medication utilization evaluations (MUEs) have been conducted to evaluate the appropriateness of IV acetaminophen use. Many of these MUEs have failed to demonstrate the expected benefits observed with the use of IV acetaminophen in randomized, controlled trials. This review summarizes the major methodological flaws seen in many of these MUEs. The most common flaws of the available MUEs were inclusion of inadequate numbers of patients, failure to adequately define the timing and duration of IV acetaminophen use, and failure to adequately match characteristics of patients receiving IV acetaminophen with control patients. An appropriately designed MUE for IV acetaminophen should take into consideration the identified methodological flaws described in this review. A template for a comprehensive MUE of IV acetaminophen is provided in the review. This template can be modified to meet institution specific criteria applied to the use of IV acetaminophen.

Keywords: Acetaminophen; Acute pain management; Medication utilization evaluation

Introduction

The objective of this review is to provide a brief overview of the therapeutic profile of intravenous (IV) acetaminophen, to summarize appropriate use criteria for the parenteral route of the drug, and review methodologies and results of IV acetaminophen medication utilization evaluations (MUEs) that are available in the public domain. Based on methodological problems that have been identified in many IV acetaminophen MUEs, recommendations will be provided concerning the standards of conduct of scientifically optimal MUEs for IV acetaminophen in the peri-operative setting, including a template for data collection as part of an appropriate MUE for IV acetaminophen.

Therapeutic Profile of Intravenous Acetaminophen and Appropriate Use Criteria

Acetaminophen has been used as a FDA approved oral analgesic and antipyretic since the 1950's. The IV formulation of acetaminophen was approved for use in Europe in 2002 and in the United States in November 2010 [1,2]. Acetaminophen is a centrally acting drug although its exact analgesic mechanism of action remains unknown [1]. Acetaminophen crosses the blood-brain barrier via passive diffusion [3]. Cerebrospinal fluid concentrations have been shown to be significantly greater following IV acetaminophen administration compared to the oral or rectal route. The maximum plasma concentration (Cmax) of acetaminophen is a critical factor which dictates the drug's analgesic efficacy [3]. Oral acetaminophen is often poorly absorbed in the post-operative setting [4-7]. The primary differences in absorption characteristics are a lower Cmax and a longer time to peak plasma concentration (Tmax) with oral and rectal acetaminophen compared to IV acetaminophen [3,4-7]. The reduction in the Cmax and increase in Tmax with oral acetaminophen has been shown to result from a delay in gastric emptying often ascribed to the concomitant use of opioids [7]. These pharmacokinetic changes with oral acetaminophen may also result from other physiologic alterations associated with surgery which may be related to the administration of anesthetic agents or other perioperative drugs [8]. As a result, oral or rectal acetaminophen is generally not recommended for pain relief in the first 24 hours following surgery or in settings where the bioavailability of these routes is suspected to be compromised [7]. IV acetaminophen is preferred in the perioperative setting as it achieves peak analgesic activity at approximately 1 hour following administration and has duration of action up to 6 hours [1,2,9]. The duration of IV acetaminophen therapy may exceed 24 to 48 hours in circumstances where delayed or reduced oral absorption of drugs is known to occur (i.e. small or large bowel resection). The most common dosage regimen for adults weighing more than 50 kg is 1000 mg given every 6 hours [1]. A less commonly used dosage regimen is 650 mg administered every 4 hours. Dosing and drug administration recommendations for IV acetaminophen are summarized in Table 1.

In 2011, the manufacturer of branded oral acetaminophen (Tylenol®) voluntarily reduced the maximum daily dose of the 500 mg extra strength tablet to 3000 mg per day [10]. The manufacturer also indicated it would change the recommended maximum daily dose of the 325 mg tablets to 3250 mg per day. Generic manufacturers have not changed the labeling for the maximum dose of oral acetaminophen. Since this unilateral decision by the manufacturer of branded oral acetaminophen, there has been increased confusion regarding the total maximum daily dose when IV/oral acetaminophen is used in the same patient. In the absence of risk factors for the development

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Received October 25, 2014; **Accepted** February 19, 2015; **Published** February 24, 2015

Citation: Malesker MA, Bruckner AL, Loggie B, Hilleman DE. Intravenous Acetaminophen: Assessment of Medication Utilization Evaluation Data in Peri-operative Pain Management. Journal of Surgery [Jurnalul de chirurgie] 2015; 10(4): 257-261 DOI: 10.7438/1584-9341-10-4-3

Table I: FDA approved dosing of IV acetaminophen [1]

Age Group	Dosing given every 4 hours	Dosing given every 6 hours	Maximum single dose	Maximal total daily dose of acetaminophen (by any routes)
Adults and adolescents (13 yrs and older) weighing ≥ 50 kg	650 mg	1000 mg	1000 mg	4000 mg in 24 hours
Adults and adolescents (13 yrs and older) weighing < 50 kg	12.5 mg/kg	15 mg/kg	15 mg/kg (up to 750 mg)	75 mg/kg in 24 hours (up to 3750 mg)
Children ≥ 2 to 12 yrs of age	12.5 mg/kg	15 mg/kg	15 mg/kg (up to 750 mg)	75 mg/kg in 24 hours (up to 3750 mg)

of hepatotoxicity, hospital policies restricting the maximal daily dose of IV acetaminophen to 3000 mg per day solely out of concern for an increased risk of hepatic toxicity is unnecessary [10]. When IV acetaminophen is used, the maximal daily dose of acetaminophen administered via all routes remains at 4000 mg per day [1]. No oral acetaminophen containing products should be administered while patients are receiving IV acetaminophen. Depending on the dosing regimen used for IV acetaminophen, transition to oral acetaminophen or acetaminophen containing products should occur 4 to 6 hours after the last IV acetaminophen dose. Acetaminophen is contraindicated in patients with a known history of hypersensitivity to the drug, severe hepatic impairment, or severe active liver disease. IV acetaminophen should be used with caution in patients with hepatic impairment or active hepatic disease, in cases of alcoholism, chronic malnutrition, severe hypovolemia, or severe renal impairment. In cases of severe renal impairment, longer dosing intervals and a reduced total daily dose of acetaminophen may be warranted [1].

The labeled indication for IV acetaminophen is in the management of mild-to-moderate pain (as monotherapy), in the management of moderate-to-severe pain with adjunctive opioid analgesics, and for the reduction of fever [1]. A substantial number of randomized, controlled trials have demonstrated the clinical efficacy and safety of IV acetaminophen in a variety of settings [2,11]. Unless contraindicated, IV acetaminophen may be considered as a primary analgesic in a multimodal analgesic regimen with opioids reserved only for breakthrough pain or to fill analgesic gaps. IV acetaminophen should always be given via a scheduled dosing regimen and not on an as needed basis. Studies have found IV acetaminophen to be an effective part of a multimodal analgesic strategy in cesarean section, total abdominal hysterectomy, lumbar discectomy, open-heart surgery requiring sternotomy, oral surgery, mastectomy, retinal surgery, laparoscopic cholecystectomy, and orthopedic surgery [2,11]. Although many of the studies evaluating the peri-operative use of IV acetaminophen have used durations of therapy of 24 hours, the FDA approved label for IV acetaminophen does not limit the duration of its use [1].

A number of studies using IV acetaminophen as part of a multimodal analgesic strategy were able to demonstrate reductions in the amount of opioids required for pain relief and/or a delay in the use of rescue opioids [2,11]. This favorable effect was often accompanied by a reduction in the frequency and severity of opioid related adverse reactions. A recent meta-analysis found that the use of prophylactic IV acetaminophen was associated with significantly less nausea and vomiting when compared to placebo in surgical patients [12]. Preliminary data from over 23,000 patients undergoing total knee or hip replacement surgery found that the use of IV acetaminophen was associated with significantly fewer side effects, a shorter length of hospital stay, and lower hospital costs compared to matched controls not receiving IV acetaminophen [13].

IV acetaminophen is currently a branded drug (Ofirmev®) in the United States. It is substantially more costly than either oral and rectal acetaminophen or IV ketorolac. It is also more costly than parenteral opioids which are available at generic prices. As a result, there is substantial interest in pharmacoeconomic outcomes data with IV acetaminophen. No formal published studies have directly examined the pharmacoeconomic effect of intravenous acetaminophen. However, randomized controlled trials designed with primary or secondary endpoints to determine total hospital length of stay (LOS), time spent in the post-anesthesia recovery unit (PACU), time to extubation, time to ambulation, and patient satisfaction surveys, suggest that IV acetaminophen may be a cost-effective part of a multimodal peri-operative analgesic strategy [2,11]. As a result, numerous institutions have sought to address this issue by conducting MUEs for IV acetaminophen.

Intravenous Acetaminophen Medication Utilization Evaluations

A literature search was conducted to identify published MUEs evaluating the use of IV acetaminophen. The guidelines defined by the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) were used to develop this systematic review [14]. In addition, the methodology recommended by Cook, et al. and Counsell were followed to identify relevant studies and to evaluate study quality [15,16]. The on-line databases of Pubmed (Medline), EBSCO Host, and the Cochrane Library were searched for the time periods from January 2000 through December 2013 for MUEs including IV acetaminophen. The Medical Subject Headings (MeSH) terms used in the search included acetaminophen, IV acetaminophen, paracetamol, propacetamol, multimodal analgesia, and peri-operative pain control. A manual search of the bibliographies from the identified publications and reviews was also performed. In addition, a search of published pharmacy and nursing conference abstracts and programs was conducted during this same time frame. Only studies available in the public domain were included in the analysis.

A total of 33 IV acetaminophen MUEs were identified in the public domain. None of the MUEs were published in a peer-reviewed journal as a manuscript. All MUEs appeared as abstracts and/or presentations at educational conferences. A variety of utilization criteria and patient populations were included in these MUEs. Although the primary objective of these MUEs was heterogeneous, many MUEs evaluated the efficacy and safety of IV acetaminophen. In the remainder of the MUEs, the primary objective was to assess the appropriateness of IV acetaminophen using institution specific criteria. The objective of some of these MUEs also included an education process to change institutional prescribing behavior and/or to correct inappropriate use of IV acetaminophen if detected.

Of the identified MUEs evaluating IV acetaminophen, 6 reported no results. In the majority of the MUEs, the types of surgery included either an unspecified mix of procedures or grouped different surgical procedures together (n=15) [17-31]. The other most common study populations reported in the MUEs included total knee and/or hip replacement surgery (n=3) and cardiothoracic surgery (n=3) [32-37]. The remaining study populations included unspecified orthopedic surgery in two MUEs and individual MUEs in patients with hip fracture, spine surgery, gynecologic surgery, and bariatric surgery [25,31,38-42]. The most commonly reported outcomes included changes in opioid use in 16 MUEs, length of stay (LOS) in 16 MUEs, pain scores in 12 MUEs, frequency of opioid related adverse reactions in 11 MUEs, and

institution specific criteria in 8 MUEs. None of the MUEs reported follow-up data indicating changes in the use of IV acetaminophen after education or institutional policy changes. The numbers of patients included in the MUEs reporting results were generally small. One study reported only the number of doses of IV acetaminophen administered at its institution, but total number of patients receiving the drug was not reported [19]. Of the remaining MUEs, 9 (35%) included ≤ 100 patients [17,20,23,28,31,33,34,38,43]. Seven (27%) MUEs included ≥ 200 patients with 5 (19%) of these MUEs including a total of ≥ 300 patients [18,24,27,30,35,36,42].

The majority of the IV acetaminophen MUEs included multiple methodological problems (Table 2). Many of the MUEs are limited by missing data which includes not reporting the numbers of patients in each treatment group, the total daily doses of IV acetaminophen used, and what drugs were used in the usual analgesic protocol. The primary purpose of an IV acetaminophen MUE should be to document that the drug is being used appropriately based on FDA approved prescribing information or protocols published in appropriately designed randomized clinical trials. In MUEs evaluating institution specific use criteria, most of those criteria were either not consistent with the FDA approved prescribing information or not consistent with methods and materials described in the randomized, controlled trial literature. Some examples of institutional restrictions for IV acetaminophen were: exclusion of its use in certain types of surgeries; use limited to ≤ 24 hours; use limited to a single dose; exclusion as a first-line analgesic; use only when other analgesics were contraindicated; limiting total daily IV acetaminophen doses to 3000 mg; and use only by prescription from an attending physician, excluding consultant physicians, fellows, or residents.

MUEs collecting data to evaluate the impact of IV acetaminophen to reduce opiate consumption, opiate related adverse effects, improvement in pain scores, or reductions in length of stay were largely underpowered to reach valid conclusions. Length of stay as a measure of quality of care is impacted by a large number of variables and cannot be easily linked to quality of care unless large numbers of patients are evaluated. LOS in the post-anesthesia care unit (PACU), which is typically the most common LOS parameter reported in surgical studies and in the MUEs, can also be impacted by several variables unrelated to quality of patient care including bed availability and staffing changes. Another methodological flaw observed in many of the MUEs included the failure to adequately evaluate and report on the specifics of the IV acetaminophen dosing regimen [17,19,23,25,27-29,31,33,35-38,40,41,43]. This information should have included the timing of the initiation and discontinuation of IV acetaminophen as well as the dose used. Several MUEs evaluated surgical patients who received only a single preoperative or intraoperative IV acetaminophen dose, yet evaluated pain scores and concomitant opioid use over 24 to 48 hours after surgery. It is inappropriate to evaluate the impact of IV acetaminophen on these outcomes at 24 to 48 hours when the duration of the drug's effect is only six hours. Evaluation of pain control with IV acetaminophen should be based only on the time period during which it is administered. In addition, timing of acetaminophen dosing was not adequately detailed in the majority of MUEs and it is not possible to determine if IV acetaminophen was initiated pre-operatively, just prior to anesthetic induction, intra-operatively, in the PACU, or after transfer to a general post-operative ward. The timing and duration of IV acetaminophen use is critical when pain scores, opiate use, and opiate-related adverse reactions are being assessed. When assessing the ability of IV acetaminophen to reduce the need for opioids, the use of IV and oral opioids other than morphine should preferably be converted to IV morphine equivalents. The conversion used to calculate the morphine equivalent dose should be included in the MUE to allow for comparisons made across different healthcare institutions.

Several MUEs failed to adequately control for differences in baseline patient characteristics, types of surgical procedures, or concomitant use of other drugs or procedures (spinal/epidural anesthesia) that may impact outcomes [17-20,22,34]. The groups of patients receiving IV acetaminophen were either substantially different from patients not receiving IV acetaminophen or data was not provided to allow for assessment of baseline characteristics between the treatment groups. Another common limitation observed in several of the MUEs is development of institutional use criteria for IV acetaminophen based on the assumption that if patients can swallow oral medication that those medications are being adequately absorbed. There is substantial evidence that in the 24 hours following many types of surgery that the bioavailability of orally administered medications is compromised [4-7]. The use of a patient's ability to swallow oral medication as an indirect indicator of adequate drug absorption may be an erroneous assumption [4-7]. It appears that concomitant administration of opioids is the most common cause of pharmacokinetic changes with enteral administration of acetaminophen. Petring, et al. found that acetaminophen was poorly absorbed in orthopedic surgery patients following the use of IM morphine with spinal anesthesia compared to patients receiving IM ketorolac with spinal anesthesia [5]. Administration of morphine has also been shown to decrease the absorption of other drugs such as clopidogrel with resultant reductions in antiplatelet activity [44]. Other methodological flaws include the failure to consider pre-operative opiate use as a baseline characteristic. Patients with a tolerance to opiates may inherently require more opiate for pain relief than an opiate-naïve patient. Other medications such psychotropic agents, anti-emetics, and sedative-hypnotics also need to be considered when comparing groups of post-operative patients. The use of post-operative anti-emetic agents or other drugs used to manage opiate-related adverse reactions should not be used as a surrogate for the frequency of opiate-related nausea and vomiting. This would be especially true if the anti-emetics are given on a scheduled basis for prevention of nausea and vomiting rather than on an as needed basis.

Conclusion

This review summarizes appropriate use criteria for IV acetaminophen and describes the methodological flaws seen in many of the IV acetaminophen MUEs conducted to date. Methodological errors noted in these IV acetaminophen MUEs limit the validity of their conclusions. A total of 27 MUEs with results have been presented as posters or abstracts and have been reviewed here. No MUE has been published in a peer-reviewed journal. The most common flaws of the available MUEs were inclusion of inadequate numbers of patients, failure to adequately define the timing and duration of IV acetaminophen, and failure to adequately match characteristics of patients receiving IV acetaminophen with control patients. An appropriately designed MUE for IV acetaminophen should take into consideration the identified methodological flaws described in this review. The MUE is a tool that can allow healthcare institutions to evaluate the appropriateness of medication use [45]. Supplementary file serves as a template for a comprehensive MUE of IV acetaminophen. This template can be modified to meet institution specific criteria applied to the use of IV acetaminophen. Institutional use criteria for IV acetaminophen should be based on approved prescribing information or on methods that have been validated in published, randomized controlled trials.

IV acetaminophen is an effective analgesic that when used as a component of a multimodal analgesic strategy can reduce opiate consumption, reduce opiate related adverse effects, and potentially shorten recovery times. Currently available guidelines recommend a multimodal approach for the management of pain in the peri-operative period [46-48]. These guidelines indicate that all patients, unless contraindicated, receive an around-the-clock regimen of a non-steroidal anti-inflammatory drug (NSAID), a COX-2 selective NSAID,

Table II: Common Methodological Errors Observed in IV Acetaminophen Medication Utilization Reviews

1. Failure to specify the timing and number of IV acetaminophen doses. Failure to identify specifics regarding timing of doses makes it impossible to accurately assess the impact of IV acetaminophen on pain scores, opioid consumption, and other important clinical outcomes. Many MUEs determine total opioid consumption and total hospital length of stay in settings where a single preoperative or intraoperative dose of IV acetaminophen is administered.
2. Failure to balance the characteristics of surgeries between patients receiving IV acetaminophen compared to other analgesic regimens. The type, duration, and intensity of surgical procedures should be similar in the different treatment groups. Combining patients undergoing a variety of surgeries into a single group also makes it more difficult to reach valid conclusions about the utility of a specific analgesic regimen, which may be different based on the type of procedure.
3. Failure to balance patient characteristics such as opioid-tolerance, gender, age, weight, and the concomitant use of preoperative and postoperative medications used to treat or prevent nausea, itching, constipation, or other surgery or drug-related adverse events.
4. Use of total hospital length of stay or post-anesthesia care unit length of stay as an efficacy measure of analgesia with IV acetaminophen without evaluating the time of readiness for discharge or transfer. Lengths of stay in any setting in the hospital may be influenced by a large number of variables, many of which may be not related to quality of patient care.
5. Evaluating the change in opioid use based on the number of doses of opioid administered rather than evaluating the total amount of opioid administered in patients receiving IV acetaminophen. Total opioid consumption in mg is probably more relevant than the actual number of doses. Failure to capture the use of bolus opioids given on an as needed basis and the use of patient controlled opioid analgesia may lead to differences in analgesic utility of different treatment regimens. Failure to document opioids administered during surgery may also lead to incorrect assessments of clinical outcomes. Failure to define conversion from different opioids to a morphine equivalent dose can lead to confusion about relevance of outcomes. Different types of opioid conversion formulas are available. MUEs should provide the opioid conversion used.
6. The exclusive reliance on the use of electronic health records (ICD-9 codes) to determine rates of opioid-related adverse events or to determine analgesic response (pain scores) should be reviewed; opioid-related adverse events and pain scores may not be properly coded.
7. Reliance exclusively on the use of electronic health records using billing records for naloxone, antipyretics, laxatives, or anti-emetics as a surrogate marker of adverse reactions may not be an accurate measure of such reactions.
8. Reliance on increases in serum transaminase levels as a marker of hepatotoxicity secondary to IV acetaminophen may not accurately represent actual drug-induced hepatotoxicity. A number of factors such surgical trauma, antibiotic use, and inhalational anesthetics may be associated with changes in serum transaminase levels.
9. Failure to document the use of other non-opioid multimodal interventions including oral celecoxib, pregabalin, or regional anesthesia.
10. Institution-specific appropriate use criteria may be considered in an MUE with IV acetaminophen, but should not be inconsistent with either the FDA approved prescribing information or must at least be consistent with data collection methods from published and properly designed clinical trials. As just one example, administering IV acetaminophen at a dose of 1000 mg every 8 hours to limit the total daily acetaminophen dose to 3000 mg is not consistent with either the prescribing information or the published literature. The duration of action of IV acetaminophen is no longer than 6 hours. Giving the drug at longer intervals would inherently limit the drug's clinical efficacy. In addition, there is no published data to show that using IV acetaminophen at a daily dose of 4,000 mg increases the risk of adverse effects vs placebo.

or acetaminophen. Gabapentin or carbamazepine may also be considered part of a multimodal management strategy in patients with neuropathic pain. Regional spinal or epidural administration of local anesthetics or opioids may also be considered as part of a multimodal pain management strategy. Opioid use would be individualized based on the type of surgical procedure and the severity of pain [46]. In some instances where only mild-to-moderate pain occurs, the use of IV acetaminophen may obviate the need to administer any opioid [1,49]. For more invasive procedures with a greater severity of pain, IV acetaminophen in combination with other non-opioid analgesics often reduces the amount of opioid needed to achieve adequate pain control [11,50,51]. This reduction in opioid dose has been demonstrated to reduce the frequency and severity of adverse effects of opioids [51,52]. Since IV acetaminophen is a branded analgesic (Ofirmev®) with cost of $14-$15 per 1000 mg dose, it has become a focus of many MUEs intended to allow healthcare institutions to evaluate the appropriateness of its use [53]. We propose the use of a template to identify appropriate data elements as a basis for conducting future MUEs with IV acetaminophen. Improvements in standardizing future MUEs will ensure the optimal use of this non-opioid intravenous analgesic.

Conflict of interests

Dr. Hilleman is on the speaker's bureau for Bristol Myers-Squibb, Cadence, and Pfizer.

Drs. Malesker, Bruckner, and Loggie report no conflict of interests.

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