Safety of rapid intravenous infusion of acetaminophen

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Intravenous acetaminophen, Ofirmev®, is approved for management of mild to moderate pain, management of moderate to severe pain with adjunctive opioids, and reduction of fever. The product is supplied as a 100 mL glass vial. As stated in the prescribing information, it is recommended to be infused over 15 minutes. This recommendation is related to the formulation propacetamol, the prodrug to acetaminophen, approved in Europe, which caused pain on infusion, and data from the clinical development of acetaminophen. The objective of this retrospective chart review study was to show the lack of side effects of rapidly infusing intravenous acetaminophen. Charts of American Society of Anesthesiology (ASA) Class I–III ambulatory surgical patients who received only acetaminophen in the preoperative setting were reviewed for any infusion-related side effects. Using standard binomial proportion analyses and employing SAS/JMP software, all vital signs were analyzed for statistically significant changes between pre- and postinfusion values. One hundred charts were reviewed. Only one patient had pain on infusion, which lasted 10 seconds. No reported side effects or erythema was seen at the injection site. No infusions had to be slowed or discontinued. The median infusion time was 3:41 minutes. Of the vital signs monitored, only the systolic ($P < 0.0001$) and diastolic ($P < 0.0099$) blood pressures had statistically significant changes from pre- to postinfusion; however, they were of no clinical relevance. Acetaminophen can be administered as a rapid infusion with no significant infusion-related side effects or complications.

Many drug inserts contain instructions for administration. The basis for these instructions is often unclear. Intravenous acetaminophen was approved for use by the US Food and Drug Administration in November 2010 for treatment of mild to moderate pain, treatment of moderate to severe pain with adjunctive opioid analgesics, and reduction of fever. Based on the full prescribing information for intravenous acetaminophen (available at http://ofirmev.com/include/pdf/OFIRMEVPrescribingInformation.pdf), the contents of the vial should be administered over 15 minutes. This stipulation was based on experience with the prodrug, propacetamol, which caused pain when infused in upwards of 49% of patients (1–3). Propacetamol, supplied as a powder that needed to be reconstituted for delivery, had a pH of 3.5 to 4 and an osmolarity of 410 mOsmol/L. Acetaminophen is more isotonic, with a pH of 5.5 and an osmolarity of 290 mOsmol/L, which was achieved by adding a pH buffer and antioxidant through an oxygen-free manufacturing process. This form is closer to plasma, which has a pH of 7.3 to 7.4 and osmolarity of 275 to 290 mOsmol/L (1). A reduced incidence of infusion-site reaction was demonstrated in the pivotal study for intravenous acetaminophen conducted by Sinatra et al, where the proportion of subjects reporting local infusion site adverse events was significantly lower for acetaminophen (2%) than for propacetamol (38%; $P < 0.001$) and not different from that of placebo (2%) (4). No studies have tested the potential side effects of giving acetaminophen via rapid infusion. This study examined whether the acetaminophen formulation could be given via rapid intravenous infusion without any infusion-related side effects or complications.

METHODS

This retrospective study was completed at Baylor Medical Center at Grapevine and Baylor Surgicare at Grapevine after approval by the Baylor Research Institute institutional review board. Approval for administering acetaminophen as a rapid infusion was obtained as a change in practice at Baylor Medical Center at Grapevine from the Department of Anesthesiology. This approval was granted only if the patient was monitored by an anesthesiologist during and up to 5 minutes after infusion with standard American Society of Anesthesiology (ASA) monitors (electrocardiogram, blood pressure, respiratory rate, pulse oximetry, skin temperature). Patients with any coexisting liver disease or dysfunction were not candidates for rapid infusion.

An institutional retrospective chart review was performed on 100 patients seen from August 2011 to May 2012, all of whom received rapidly infused acetaminophen in the preoperative setting. This number was arrived at by hypothesizing that the usual mean rate of pain on infusion of propacetamol was 29% (1–3). Of interest was to detect whether a rate of 10% or less

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with acetaminophen would be a significant decrease (assuming statistical type I and II error rates of 0.05 and 0.20, respectively). All patients received acetaminophen in the preoperative holding area prior to being transported to the operating room. The study was limited to ambulatory surgical patients in ASA Class I to III who had not received any other medication (anxiolytics, analgesics, antibiotics, etc.) prior to acetaminophen. Patients with any conditions listed in the warnings and precautions section on the FDA label were not eligible for rapid infusion and thus were excluded from this study. The automated dispensing machine data showing patients who had received acetaminophen were the initial basis for the review.

All patients were closely monitored by an anesthesiologist from the start of infusion up to 5 minutes postinfusion. Acetaminophen was delivered using new, unopened vials, each containing 100 mL with a concentration of 10 mg/mL. The vial was spiked using the standard intravenous tubing set (secondary set 34-inch non-Di(2-ethylhexyl) phthalate, internal diameter 0.100 in; Hospira, Lake Forest, IL) with the roller clamp set at the fully open position. The vial was vented with a blunt 18-gauge needle.

For each study patient, a study data form was completed, which included the date, infusion time (start, stop, and total), site and size of intravenous cannula gauge, reported side effects, and vital signs every 2 minutes from infusion up to 5 minutes postinfusion. Charts were reviewed to determine if any infusion had to be stopped or slowed due to patient complaints and/or side effects reported that resulted from the rapid delivery method. Vital signs were analyzed to determine if any significant changes occurred from preinfusion values to postinfusion values. Data were analyzed by the Baylor Health Care System Quantitative Sciences Department with SAS/JMP statistical analysis software using standard binomial proportion analyses. Confidence intervals and *P* values were calculated using the standard *t* test with a $P < 0.05$ considered statistically significant.

RESULTS

Of the 100 study patients, 89% had the intravenous cannula placed in the hand, and 98% had a 20-gauge cannula placed *(Table 1).* The mean total time of infusion was 3:45, with a 95% confidence interval of 03:31 to 03:55 *(Table 2).* There were no reports of erythema at the intravenous site, and no patient reported side effects during or after infusion. One patient reported mild pain on infusion, which lasted approximately 10 seconds, but the pain was self-limited despite the infusion still running at a full uninhibited flow rate. Of the vital signs monitored, only the systolic ($P < 0.0001$) and diastolic ($P < 0.0099$) blood pressures and mean arterial pressure (MAP; <0.0001) had statistically significant reductions from pre- to postinfusion *(Table 3).* The MAP was calculated using the formula of 2 times diastolic plus systolic divided by 3. There were no clinically relevant deviations (greater than 20%) in MAP *(Figure),* and no patients had a MAP < 50 mm Hg postinfusion. There were no reported symptoms of hypotension, such as dizziness or lightheadedness, or required intervention for hypotension.

Table 1. Intravenous site and size for intravenous acetaminophen in 100 patients

Category	Variable	Patients
Intravenous site	Right hand	67
	Left hand	22
	Right wrist	3
	Left wrist	3
	Right forearm	1
	Left forearm	0
	Right antecubital	3
	Left antecubital	1
	Total	100
Intravenous size (gauge)	18	1
	20	98
	22	1
	Total	100

Table 2. Infusion time for intravenous acetaminophen in 100 patients

Percentage	Minutes: seconds
100% (maximum)	07:19
99.5%	07:19
97.5%	06:13
90%	04:57
75% (quartile)	04:22
50% (median)	03:41
25% (quartile)	02:57
10%	02:29
2.5%	02:12
0.5%	01:31
0% (minimum)	01:31

Table 3. Differences in pre- and postinfusion vital signs in 100 patients who received rapid intravenous infusion of acetaminophen

Vital sign	Mean difference	Upper 95% mean	Lower 95% mean	*P* value
Systolic blood pressure	–4.31	–2.7804	–5.8396	<0.0001
Diastolic blood pressure	–1.92	–0.471	–3.369	0.0099
Mean arterial pressure	–2.72	–1.562	–3.873	<0.0001
Respiratory rate	0.00	0.0564	–0.0564	1.0000
Heart rate	0.13	0.36004	0.84439	0.7188
Oxygen saturation	0.118	0.33449	–0.0985	0.2821
Skin temperature	–0.003	0.00784	–0.0186	0.7029

DISCUSSION

This study demonstrated that no clinically relevant adverse events resulted from administration of intravenous acetaminophen to patients without an infusion time requirement. Only one patient had a complaint of pain at the infusion site, which lasted only 10 seconds. The infusion was not slowed and was completed without further complaints. Most likely, this pain was due to physical reasons such as an intravenous line that was not entirely patent at the start of infusion rather than the medication itself. No other problems were reported by any patients or observed by the anesthesiologist in attendance during the infusion. The infusion time using fully open secondary intravenous tubing was decreased from 15 minutes to a median time of 3 minutes and 41 seconds. Two potential confounding variables in the infusion time that were not controlled for in this study were cannula gauge and site (5, 6). However, our preoperative nursing staff protocol indicates that a 20-gauge cannula and a hand site are preferred. Approximately 90% of the patients in this study received a 20-gauge intravenous line in the hand.

Reducing the infusion time offers potential advantages for both the patient and the hospital staff. Faster achievement of peak plasma levels can lead to better pain control. Previous studies have shown that the intravenous route of administration leads to earlier and higher plasma peaks than the oral and rectal routes (7). Even earlier plasma peaks could potentially be reached with a faster infusion time, although this was not determined in this study. No existing data indicate that speed of infusion has any relation to liver toxicity. Full, uninhibited flow for acetaminophen may obviate the need for expensive infusion pumps. It also decreases medical errors related to the set up of infusion pumps (8). The extra equipment and time needed for the pumps may deter health care providers from using acetaminophen in the preoperative setting, leading to an increase in narcotic use and reduction in patient safety.

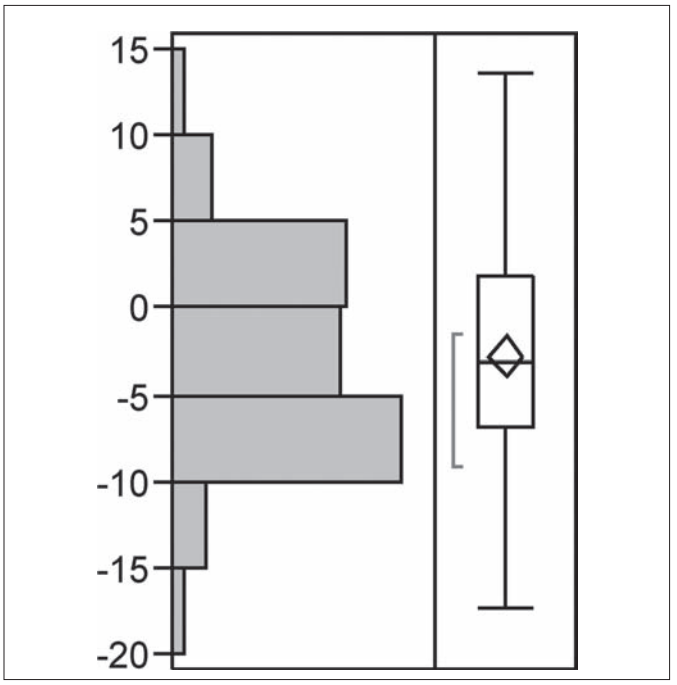

Figure. Distribution of percentage change in mean arterial pressure (MAP). The minimum change in MAP percentage was –17.31; maximum change, 13.59; median change, –3.07; and 95% confidence interval, –3.87, –1.56.

Acetaminophen has been shown to be an effective drug in pain control in outpatient surgical patients (9–11) as well as in major orthopedic surgery (4, 11, 12). The ASA guidelines on acute pain management in the perioperative setting endorse the use of acetaminophen as a component of multimodal analgesia (13). Though the primary reason for a 15-minute infusion time was pain at the infusion site with propacetamol, the prodrug of acetaminophen, and clinical data from the development of intravenous acetaminophen, all vital signs were monitored during the infusion for any possible changes. No patients had their infusion stopped or slowed due to a change in vital signs. Upon statistical analyses, the only significant changes were seen in the patients' lower systolic, diastolic, and calculated MAP after infusion. However, the mean difference for all three was low. No MAP changes were considered clinically relevant (20%).

Importantly, no patient had any reported symptoms of hypotension, such as dizziness or lightheadedness, or required medical treatment for a drop in blood pressure. A factor that may have contributed to the drop in blood pressure could be an abnormally elevated starting blood pressure. Patient stress or "white coat syndrome" can lead to an initial high blood pressure reading. All other vital signs showed no significant changes from pre- to postinfusion.

This study was limited to ASA Class I to III ambulatory surgical patients. It was not determined if more complicated surgical patients, or patients with complex medical problems, would react in the same manner. The possibility of hepatotoxicity from rapid infusion was not examined. All patients received only intravenous acetaminophen, and it was not determined if infusion-related side effects would have been avoided if the study drug were combined with opioids and/or anxiolytics.

This study can benefit hospitals in efforts toward cost-effective pain control. By showing that the FDA-mandated infusion time is not supported by scientific evidence, hospitals can reduce the personnel time and expense of infusion pumps. Further, the infusion time requirement may have led some healthcare providers to avoid intravenous acetaminophen, resulting in increased narcotic use. The results of this study can be an incremental contribution to patient safety, as reduction in narcotic use improves patient safety.

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