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FEATURED ARTICLE

A Comparison of a Fentanyl, Morphine, and Hydromorphone Patient-Controlled Intravenous Delivery for Acute Postoperative Analgesia: A Multicenter Study of Opioid-Induced Adverse Reactions

Rob W. Hutchison, PharmD, Eun Hae Chon PharmD,† William F. Tucker, Jr, MD,‡ Richard Gilder, RN, BSN CNOR BCNI,§ Janet Moss, RN, MS, CPAN, APRN,¶ and Phyllis Daniel, RN, MSN, CHPN, CNS≠*

Abstract — Patient-controlled analgesia (PCA) is a widely used delivery system for intravenous (IV) administration of opioids during acute post-operative pain management. Various opioids have been used for IV PCA including morphine, meperidine, hydromorphone, and fentanyl. Morphine is by far the most commonly used opioid in this setting, yet the selection of morphine as the primary opioid is based largely on tradition. Meperidine should not be considered in the PCA armamentarium due to the associated risk of central nervous system toxicity from its metabolite normeperidine. The objective of this study is to compare the rate of opioid-induced adverse reactions among three IV PCA opioids, fentanyl, morphine, and hydromorphone, in acute post-operative pain management. Although morphine is the most frequently used opioid, the results from three US hospitals indicate that fentanyl IV PCA had a significantly lower rate of common opioid induce adverse reactions (nausea/vomiting, pruritus, urinary retention, or sedation), when compared to IV PCA morphine and hydromorphone in acute post-operative pain management. The median pain score on post-operative day-1 and -2 was significantly lower in fentanyl IV PCA group. The quantity of opioid in each group was not significantly different when converted to an analgesic equivalence. Morphine and hydromorphone IV PCA were no different in rates of adverse reactions in any area; although, the hydromorphone group trended toward a lower pruritus and urinary retention rate compared to morphine, but this was not statistically significant. The rate of respiratory depression was not significantly different between the three opioids. Fentanyl IV PCA is an under used opioid for post-operative acute-pain management and should be considered more often due to the lower adverse reaction profile.

Keywords — Patient controlled analgesia; intravenous delivery; adverse reactions, morphine, hydromorphone, fentanyl

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Patient-controlled analgesia (PCA) allows the patient to self-administer incremental doses of opioids on demand for acute post-operative pain. These opioids for IV PCA may include morphine, meperidine, hydromorphone, and fentanyl. By tradition, morphine is the most commonly utilized opioid in this setting, yet studies providing evidence based selection of morphine as the preferred opioid are lacking.[1-2] Meperidine should not be considered in the PCA armamentarium due to the associated risk of central nervous system toxicity from its metabolite normeperidine.[3-5] The objective of this study is to compare the rate of opioid-induced adverse reactions (OIAR) among three IV PCA opioids, fentanyl, morphine, and hydromorphone in acute post-operative pain management.

METHODS

The rate of OIAR among three

*Assistant Professor, Texas Tech University School of Pharmacy, Dallas TX and Clinical Specialist, Pain Management, Presbyterian Hospital of Dallas, Dallas TX; †Staff Pharmacist (at the time of this study—Pharmacy Practice Resident, Presbyterian Hospital of Dallas, Dallas, TX; ‡Orthopedic Surgeon, Presbyterian Hospital of Dallas and Associate Clinical Professor, University of Texas Southwestern Medical School, Dallas, TX; §Board Certified Nurse in OR and Nursing Informatics (at the time of the study—Clinical Information System Administrator Senior Clinical Data Analyst/Programmer Texas Health Resources, Arlington, TX; ¶Principal Investigator, Advocate Christ Medical Center, Oak Lawn, IL; ≠Principal Investigator, Carilion Roanoke Memorial Hospital, Roanoke, VA. Address correspondence to Dr. Hutchison at robhutchison@texashealth.org.

Table 1. Characteristics and Demographics of Post-operative Orthopedic Patients Receiving PCA (N = 254)

	OPIOID		
Characteristics	*Morphine n = 93*	*Hydromorphone n = 89*	*Fentanyl n = 72*
Female gender (%)	56	62	63
Age[a] (years)	63	63	71
PCA duration[a] (days)	2.3	2.5	2.4
APAP/NSAID[b] (%)	51	54	58
Knee Procedure (%)	69	69	57
Hip Procedure (%)	31	31	43
BMI[c] > 35 (%)	18	27	14
Sleep Apnea (%)	5	7	3

[a]*Mean value*

[b]*Mean APAP (acetaminophen) and NSAID nonsteroidal anti-inflammatory usage on post-operative day-1 and -2*

[c]*BMI –Body Mass Index*

Table 2. Incidence Rate (%) IV PCA Opioid Adverse Reactions Post-operative Orthopedic Patients (N = 254)

Adverse Reaction	*Morphine*	*Hydromorphone*	*Fentanyl*
Nausea/vomiting	31	33	18
Pruritus	16	10	3
Urinary retention	16	10	3
Sedation	8	9	1
Respiratory Depression	8	7	4
Headache	7	2	3
Confusion	5	1	0
Agitation	2	0	1
Hallucination	0	1	0
Nightmare	0	0	0
Monoclonus (muscle rigidity)	0	0	0

IV PCA opioids, fentanyl, morphine, and hydromorphone, in the acute post-operative pain management were retrospectively analyzed from 254 hospital patients' medical records in three US hospitals located in Texas, Illinois, and Virginia. This multicenter study was approved by the Texas Tech University, Presbyterian Hospital of Dallas, Advocate Christ Medical Center, and Carilion Roanoke Memorial Hospital institutional review boards. Each opioid was converted to an equal analgesic equivalent (see Appendix A). The time period of the actual orthopedic surgical procedures occurred between June 2001 and March 2005 and involved either surgical hip or knee repair. The OIAR occurrence rate was collected during IV PCA use time frame of post-operative day (POD) 1 and 2. POD 1 start time is defined as 7 AM the day after surgery. The OIAR analysis included respiratory depression, nausea, vomiting, constipation, sedation, pruritus, urinary retention, confusion, hallucinations, nightmares, agitation, headache, and monoclonus (muscle rigidity). Respiratory depression was defined as a rate less than 12 respirations per minute or oxygen saturation less than 90%. The numeric pain scores (based on the 0 to 10 numeric pain scale – see Appendix B) and amount of other analgesics administered during PCA use were also recorded (acetaminophen and nonsteroidal anti-inflammatory).

The primary analysis consisted of comparing the daily rates of OIAR from the three IV PCA opioids morphine, hydromorphone, and fentanyl. The secondary analysis consisted of specific gender differences in rates of OIAR and pain scores among the three opioids. Analysis of variance analysis (ANOVA) was used for continuous data to compare the three opioids for any significant difference (*P*-value of < 0.05) in OIAR. The Kruskal-Wallis test was used to compare median pain scores.

RESULTS

Of the 254 patients who received IV PCA opioid for acute post-operative pain management, the demographic values (see Table 1) of duration of PCA, gender, and use of non-opioid analgesic were similar among the opioid groups. The average duration of IV PCA in all patients was 2 days. The three opioid groups did not significantly vary in equivalence. The fentanyl group was slightly older and had approximately 2% more surgical

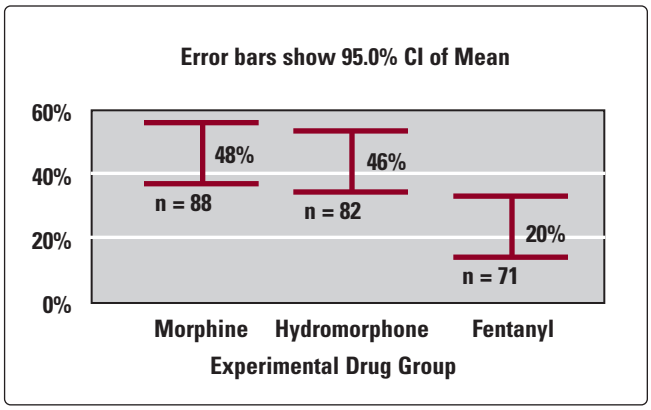

Figure 1. Incidence rate of opioid nausea/vomiting, pruritus, urinary retention, or sedation in post-operative orthopedic patients (N = 241) receiving PCA.

knee repair procedures than the morphine and hydromorphone groups. The hydromorphone group tended to have a higher body mass index and a slightly higher history of sleep apnea. The morphine group had a low percentage of sleep apnea and lowest percentage of opioid allergy.

The fentanyl group had a significantly lower mean rate of common OIAR (nausea/vomiting, pruritus, urinary retention, or sedation) compared to morphine and hydromorphone groups (20% vs 48% and 46% respectively, $P < 0.05$) (see Figure 1). (See Table 2 for the individual OIAR).

The rates of respiratory depression, headache, confusion, agitation, and hallucination were not significantly different between the three opioids. The rate of respiratory depression between morphine, hydromorphone, and fentanyl was 8%, 7%, and 4%, respectively. Also the rates of headache (7%, 2%, and 3%), confusion (5%, 1%, and 0%), agitation (2%, 0%, and 1%), and hallucination (0%, 1%, and 0%) occurred among morphine, hydromorphone, and fentanyl respectively. There was no incidence of nightmares or monoclonus among any of the three groups during the 2.3 to 2.5 days of administration. The rate of adverse reactions between morphine and hydromorphone were not significantly different in any area; although, the hydromorphone group trended toward a lower rate of pruritus and urinary retention compared to morphine. Two specific trends in gender difference were seen. The fentanyl male patients trended toward lower rate ($P = 0.1$) of nausea compared to the morphine group. The fentanyl female patients trended toward lower rate ($P = 0.1$) of pruritus compared to the morphine group. The median of numeric pain scores (0 to 10) was significantly lower in the fentanyl group for both POD 1 and 2 ($P = 0.003$ and $P = 0.002$, respectively) (see Figures 2 and 3).

DISCUSSION

Optimal pain management is a dichotomous balance of adequate pain control and minimal OIAR. The selection of opioid for acute post-operative pain management has not always been based on evidence based considerations as indicated by the continued use of meperidine for PCA. Fifty-four percent of hospitals continue to use prefilled cartridges of meperidine despite the pharmacotherapy evidence for risk of central nervous system toxicity.[1-4] Meperidine was not considered in this study, due the inherent risk of accumulation of the central nervous system toxic metabolite, normeperidine.[2-3]

Regarding demographic comparisons, the fentanyl group had slightly less surgical knee repair patients (57%) than the other opioid groups (69% and 69%) (see Table 1). This could potentially skew pain intensity scores toward a higher intensity in the other opioid groups. Experiential results show the knee procedure to be more painful than surgical hip repair. Constipation is a common OIAR in chronic pain management, but it was not reported in this study due to the narrow time frame of opioid IV PCA use (mean 2.4 days — see Table 1). If IV PCA opioid use were to continue longer

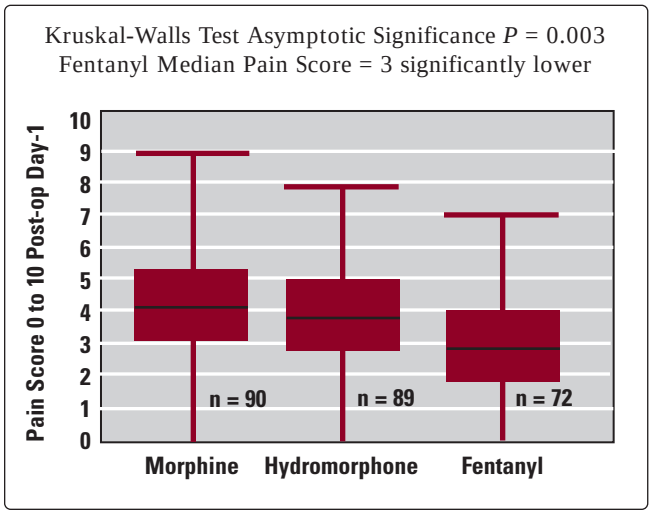

Figure 2. Comparison of the median pain scores for post-operative day-1 orthopedic patients (N = 251) receiving PCA.

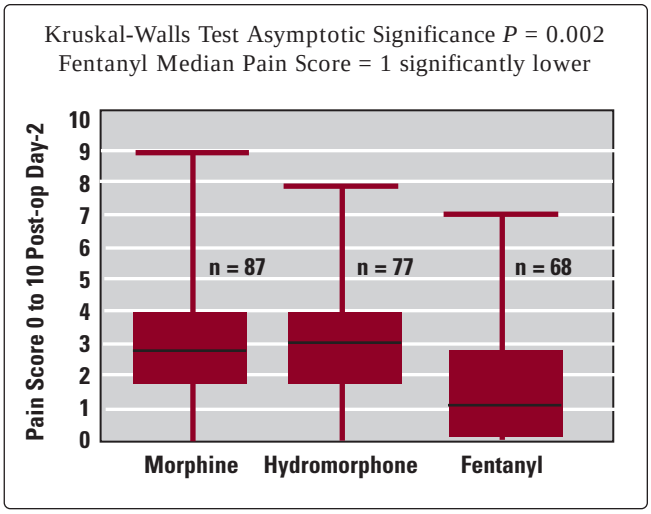

Figure 3. Comparison of the median pain scores for post-operative day-2 orthopedic patients (N = 232) receiving PCA.

than 2 days, the comparison of constipation rates would be warranted. Nausea and/or vomiting events were counted if an antiemetic was administered.

Opioid allergy is an arbitrary clinical descriptor. The hydromorphone and fentanyl groups were approximately twice as likely to be "opioid allergic" compared to morphine. The majority of the hydromorphone and fentanyl opioid allergies were listing morphine as the allergic agent and this was due to the previous high use of morphine. This was not considered to be a confounder due to the arbitrary assignment of allergy reports relating to opioids. None of these allergic listings were anaphylactic type.

In US hospitals, the frequency of IV PCA opioid use in descending order is morphine, meperidine, hydromorphone, and fentanyl.[1] Fentanyl PCA in acute post-operative pain management is under utilized. The under use was in part due to low availability of a premixed fentanyl cartridge. In recent survey of US hospitals, only 8% of the hospitals used prefilled fentanyl PCA, and 39% used staff-prepared fentanyl PCA.[1] A new fentanyl patient controlled transdermal system (PCTS), *IONSYS*, recently approved by the FDA, is another PCA option. The fentanyl PCTS has been studied for use in the management of acute pain.[6–8] Fentanyl PCTS releases medication by iontophoresis after activation of a demand-dose button on the credit card sized patch. The drug is delivered over a 10-minute period, and there is a 1- to 10-minute lock out period. The fentanyl PCTS has been shown to be therapeutically equivalent to IV PCA morphine as measured by pain control, discontinuation rates, and nausea incidence.[6] The fentanyl PCTS should not be confused with the fentanyl sustained-release transdermal patch (*Duragesic* and other generic brands) that is indicated for chronic pain. The July 15th 2005 FDA health advisory warned against using the sustained release fentanyl transdermal patch in opioid-naïve patient and also warned against using it in acute post-operative pain management.[9]

CONCLUSION

Although morphine is the most frequently used opioid, fentanyl IV PCA had a significantly lower rate of common OIAR (nausea/vomiting, pruritus, urinary retention, or sedation) when compared to IV PCA morphine and hydromorphone in acute post-operative pain management. The median pain score on post-operative day-1 and -2 was significantly lower in fentanyl IV PCA group. The quantity of opioid in each group was not significantly different when converted to an analgesic equivalence. Morphine and hydromorphone IV PCA were no different in rates of adverse reactions in any area; although, the hydromorphone group trended toward a nonsignificant lower pruritus and urinary retention rate compared to morphine. The rate of respiratory depression was not significantly different in any of three opioids. Fentanyl IV PCA is an under used opioid for post-operative acute pain management and should be considered more often due to the lower adverse reaction profile.

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Appendix A. Opioid Analgesic Equivalence Values to Morphine 10 mg IV

MORPHINE 10 MG (IV)

Hydromorphone 1.5 mg (IV)

Fentanyl 0.1 mg (IV)

Hydrocodone 30 mg (Oral)

Oxycodone 20 mg (Oral)

Codeine 120 mg (IV)

Codeine 200 mg (Oral)

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Appendix B. 0 to 10 Numeric Pain Score