

## Parenteral ketorolac and risk of myocardial infarction

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### SUMMARY

**Purpose** To examine the effects of ketorolac, a non-aspirin non-steroidal anti-inflammatory drug (NANSAID) with anti-platelet properties, on the risk of in-hospital myocardial infarction (MI).

**Methods** A retrospective cohort study was performed among hospitalized patients given 10 219 courses of parenteral ketorolac and patients given 10 145 courses of parenteral opioids, without ketorolac, in 35 hospitals. Patients were matched by hospital, admitting service, and date of study drug initiation. Any MI documented in the chart that occurred during the drug course and up to 3 days after the last dose was recorded by trained abstractors.

**Results** MI occurred in 18 (0.2%) ketorolac and 45 (0.4%) opioid courses (odds ratio (OR) 0.40, 95% confidence interval (CI) 0.23–0.69). This negative association persisted in multivariable analysis adjusting for age, sex, history of diabetes mellitus or cardiovascular disease, and administration of antiplatelet agents (OR 0.42; 95% CI 0.24–0.73). The association also persisted in numerous analyses excluding patients who may have been treated with analgesics for ischemic pain, and when restricting events to those occurring while on the drug (OR 0.34; 95% CI 0.17–0.69).

**Conclusion** These results are consistent with a protective effect of ketorolac against MI. Future research that implements uniform screening for and independent validation of MIs as well as eliminates possible confounding by indication is the next logical step in confirming these findings. Copyright © 2002 John Wiley & Sons, Ltd.

KEY WORDS — anti-inflammatory agents; non-steroidal; myocardial infarction; platelet aggregation inhibitors; cohort studies

### INTRODUCTION

Acute myocardial infarction (MI) results, in about 90% of cases, from acute occlusion of a previously stenotic coronary artery with a platelet-rich intravascular thrombus.<sup>1,2</sup> Platelets can be activated by several pathways, including a thromboxane A<sub>2</sub>-dependent

pathway.<sup>3</sup> Given the important role of platelets in the formation of thrombus in MI, it is not surprising that numerous studies have documented the efficacy of aspirin (ASA), an inhibitor of the platelet cyclooxygenase (COX) enzymes responsible for thromboxane A<sub>2</sub> formation, in preventing MI.<sup>4–6</sup> In fact, the first epidemiologic evidence for the prevention of MI by ASA came from observational studies.<sup>7</sup>

Non-aspirin non-steroidal anti-inflammatory drugs (NANSAIDs) that inhibit both the COX-1 and COX-2 enzyme isoforms ('nonselective' NANSAIDs) also have been shown to inhibit platelet aggregation both *in vitro*<sup>8–10</sup> and *in vivo*.<sup>11–16</sup> A single 0.4 mg/kg dose of ketorolac can inhibit platelet aggregation for at least 24 h.<sup>17,18</sup> Consistent with this action, ketorolac

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has been shown to inhibit thrombosis formation in animal models.<sup>15</sup> Although the platelet effect of non-selective NSAIDs, unlike ASA, is reversible, these drugs might, like ASA, reduce the risk of thrombus formation on ruptured plaques and subsequent MI.

Unlike nonselective NSAIDs, the recently developed COX-2 selective NSAIDs do not have the same inhibitory effect on the COX-1 enzyme responsible for thromboxane production, but they do appear to inhibit production of the arterial wall prostacyclin that reduces thrombus formation on the vessel wall.<sup>19,20</sup> As a result, pharmacodynamic theory predicts that the COX-2 inhibitors may increase the risk of thrombosis.<sup>21</sup> One randomized trial comparing a COX-2 inhibitor with a nonselective NSAID suggested that there may be more cardiovascular events among COX-2 users.<sup>22</sup> However, it is not clear if the differences in cardiovascular event rates was due to an increase in events among COX-2 users, a reduction among nonselective NSAID users, or both.

Therefore, the purpose of this retrospective cohort study was to examine the effects of the nonselective NSAID, ketorolac, on MI risk and to strengthen the hypothesis that nonselective NSAIDs reduce MI risk.

## METHODS

### *Study population*

Details of the population studied and data collection methods have been described elsewhere.<sup>23</sup> Briefly, we performed a retrospective cohort study in 35 acute-care hospitals in the greater Philadelphia, PA region from November 1991 through August 1993 in order to determine the effects of parenteral ketorolac on various outcomes. The exposed group consisted of all inpatients receiving parenteral ketorolac in one of these hospitals, with or without concomitant opioids. The comparison (unexposed) group consisted of inpatients receiving a parenteral opioid, but not parenteral ketorolac, during the same time period as the ketorolac-exposed group. This comparison group was matched to the exposed group by hospital, admitting service (medical versus surgical), and date of analgesic administration. Physician orders for the index drug (ketorolac or opioids) were identified by examining medication orders, and administration of the drugs was confirmed by examining medication administration records.

### *Data collection*

Data were abstracted from medical records by specially trained nurse-abstractors using a structured,

computerized data collection instrument. The abstractors identified *a priori* outcomes, including in-hospital MIs. Other clinical characteristics were collected for all patients using standardized definitions. The reproducibility of the abstraction process was assessed by re-abstraction by a second nurse for 167 courses. Agreement between abstractors exceeded 90% for the demographic and disease history variables presented in this study.

Data abstraction was based on the course of therapy, which was defined as the time from the first dose through the third day following the final dose. If more than 3 days elapsed between doses, a new course was defined as starting after the lapse. All courses of ketorolac were abstracted in order to identify any outcomes that might occur only after repeated dosing. Because the opioid group was selected to provide a comparison group, rather than to study the effects of opioids, only one course of opioids was abstracted for each control subject. When the index drug was ketorolac, opioids could be used concomitantly.

This study was approved by the University of Pennsylvania's Committee on Studies Involving Human Beings and all participating hospitals' IRBs.

### *Outcome definition*

Myocardial infarction was identified for any patient who had a note in the medical record documenting an MI that occurred any time either during or up to 3 days after discontinuation of the index drug. We relied on the diagnosis of MI recorded by physicians in the medical records. We did not systematically collect electrocardiograms, cardiac enzyme results, or other clinical variables to validate the physician diagnosis.

### *Analysis*

Differences between groups with respect to demographic and disease history variables were evaluated using the chi-square statistic for discrete variables (e.g. disease histories) and the independent sample *t*-test for continuous variables (e.g. age).

The primary comparison was the association between ketorolac use and MI. The odds ratio (OR) was used as the estimate of effect, and 95% confidence intervals (CIs) were calculated for all ORs. Multivariable logistic regression was used to adjust for potential confounders. The *a priori* confounders included in the logistic regression models were age (as a continuous variable), sex, history of diabetes, history of cardiovascular disease (history of MI, congestive heart failure, cardiac arrest, or cerebrovascular

accident) and use of other antiplatelet agents (other NSAIDs or ASA) either at the time, or within 72 h prior to, the index drug. We also tested for confounding by other variables, defined as a change in the crude OR by 10% after adjustment for the potential confounder.<sup>24</sup> These potential confounders were: current smoking, anticoagulant use during the course of the index drug, insurance, and history of hypertension, bleeding disorder, renal disease, malignancy, gastrointestinal bleeding, and anemia. None altered the OR by more than 10%. However, in order to assess the possibility of confounding by these variables when considered simultaneously, we also developed a propensity score that used all of the above-mentioned variables (both *a priori* and potential confounders) to estimate the probability of ketorolac use.<sup>25</sup> We then adjusted for this propensity score in a model that included index drug and deciles of propensity score as independent variables and MI as the dependent variable. Adjustment for hospital, course, and admission date did not alter the results, nor did accounting for clustering by hospital or course.<sup>26</sup> Interactions between all *a priori* variables and the index drug were tested using the relevant product terms in the regression.

An additional analysis included MIs only if they occurred during the course of therapy with the index drug (i.e. during administration of ketorolac or opioid), excluding the 3-day post-exposure period. Although the antiplatelet properties of ketorolac could last for at least 24 h,<sup>17,18</sup> and although MIs may not have become clinically apparent for several days after drug discontinuation, it is likely that ketorolac would exhibit greater protection against MI during the course of therapy, rather than after discontinuation.

One major concern in any observational study of drug effects is that of confounding by indication.<sup>27,28</sup> In the present study, this could occur if patients with chest pain of cardiac origin were more likely to be given opiates (particularly morphine) than ketorolac. Since these patients also have a higher likelihood of developing an MI, a spurious association of opiates with MI could occur. However, the specific indication for the drug was not recorded in this study (although the general indication—coded as ‘acute pain’, ‘chronic pain’ or ‘perioperative’—was recorded). Therefore, in order to try to determine the likelihood of this confounding, we performed several analyses. In the first set of analyses, we analysed subgroups who were unlikely to be receiving opioids for cardiac chest pain:

- (1) Patients admitted with a diagnosis other than ischemia (angina, chest pain, or rule-out MI).

- (2) The subgroup of patients undergoing surgery (and therefore unlikely to have an acute, evolving MI at the time of analgesic administration).
- (3) The subgroup of patients undergoing non-cardiac surgery.
- (4) Patients who first received their index drug outside of an intensive care unit or emergency room (where most patients with cardiac chest pain were likely to receive opioids for chest pain).
- (5) Patients not receiving the index drug for acute pain.
- (6) MIs that occurred only 2 or more days after first exposure to the drugs, because it would be less likely that analgesics were given for symptoms of an acute MI and the MI was not recorded until the next day or later.

In the second set of analyses, we limited the population to those receiving opioids. We performed two subgroup analyses:

- (1) Limiting the population to those receiving any opioids, i.e. we compared those receiving ketorolac and opioids to those receiving opioids alone.
- (2) Limiting the population to those receiving morphine sulfate (i.e. comparing ketorolac plus morphine use to morphine-only use).

The analyses were performed using SPSS version 10.0.7 (SPSS Incorporated, Chicago, IL) and Stata version 6 (Stata Corporation, College Station, TX), and statistical significance was defined as a two-sided *P*-value of less than 0.05.

## RESULTS

### *Study population*

Compared with patients receiving only opioids, patients receiving ketorolac were more likely to be female, receive other antiplatelet agents, and first receive the index drug in an intensive care unit or emergency department and less likely to undergo a surgical procedure and to have a history of diabetes or cardiovascular disease (Table 1). The mean age ( $\pm$  standard deviation) among ketorolac courses was 51.3 ( $\pm$ 20.4) years compared with 52.0 ( $\pm$ 21.3) years in the opioid group ( $P=0.01$ ). Most of the differences, although statistically significant, were very small.

### *Association between clinical variables and MI*

Factors associated with an increased risk of MI (Table 2) were older age, use of other antiplatelet

Table 1. Distribution of risk factors by medication use

	Medication		OR <sup>†</sup> (95% CI)	P-value
	Ketorolac courses	Opioids courses		
	n (%) <sup>*</sup> (n = 10 272)	n (%) (n = 10 247)		
Age > 65 years	3091 (30.1%)	3448 (33.6%)	0.85 (0.80, 0.90)	< 0.001
Female sex	6199 (60.3%)	5831 (56.9%)	1.15 (1.09, 1.22)	< 0.001
History of diabetes mellitus	997 (9.7%)	1164 (11.4%)	0.84 (0.77, 0.92)	< 0.001
History of cardiovascular disease	1043 (10.2%)	1388 (13.5%)	0.72 (0.66, 0.79)	< 0.001
Use of other antiplatelet agents	2444 (23.8%)	1866 (18.2%)	1.40 (1.31, 1.50)	< 0.001
First use of index drug in intensive care unit or via emergency department	2154 (21.0%)	1890 (18.4%)	1.17 (1.10, 1.26)	< 0.001
Use of index medications for acute pain	7070 (68.8%)	6953 (67.9%)	1.05 (0.99, 1.11)	0.13
Surgical procedure performed	7330 (71.4%)	7467 (72.9%)	0.93 (0.87, 0.99)	0.02

\*n, number; %, percentage of courses; OR, odds ratio; CI, confidence interval.

<sup>†</sup>Opioids is reference group.

Table 2. Outcome by risk factors examined

	Myocardial infarction risk		OR* (95% CI)	P-value
	With risk factor MI*/number of courses with risk factor (%)	Without risk factor MI/number of courses without risk factor (%)		
Age > 65 years	46/6539 (0.7%)	17/13 980 (0.1%)	5.82 (3.33, 10.16)	< 0.001
Female sex	30/12 030 (0.2%)	33/8489 (0.4%)	0.64 (0.39, 1.05)	0.08
History of diabetes mellitus	18/2161 (0.8%)	45/18358 (0.2%)	3.42 (1.98, 5.92)	< 0.001
History of cardiovascular disease	29/2431 (1.2%)	34/18088 (0.2%)	6.41 (3.90, 10.54)	< 0.001
Use of other antiplatelet agents	34/4310 (0.8%)	29/16209 (0.2%)	4.44 (2.70, 7.29)	< 0.001
First use of index drug in intensive care unit or via emergency department	41/4044 (1.0%)	22/16475 (0.1%)	7.66 (4.56, 12.87)	< 0.001
Use of index medications for acute pain	47/14023 (0.3%)	16/6496 (0.2%)	1.36 (0.77, 2.40)	0.29
Surgical procedure	29/14797 (0.2%)	34/5722 (0.6%)	0.33 (0.20, 0.54)	< 0.001

\*MI, myocardial infarction; OR, odds ratio; CI, confidence interval.

agents, first use of index drug in an intensive care unit or from an emergency department, and a history of diabetes or cardiovascular disease. Patients undergoing surgical procedures and women had a lower risk of MI.

#### Association between ketorolac use and MI

The risk of MI was 0.17% (18 out of 10 272 courses, or 0.18% for the 9900 individual patients) in the ketorolac group and 0.44% (45 out of 10 247 courses) in the opioid group (unadjusted OR 0.40; 95% CI: 0.23, 0.69, Table 3). Multivariable adjustment had essentially no effect on this estimate (multivariable OR 0.42; 95% CI: 0.24, 0.73, Table 2). Adjusting for each

of the separate components of the cardiovascular disease variable (history of MI, congestive heart failure, cardiac arrest, or cerebrovascular accident) did not alter the results. Adjustment for the propensity score as deciles also did not alter the results (adjusted OR 0.38; 95% CI: 0.22, 0.65). There were no statistically significant interactions detected between the index drug and the variables shown in Table 2.

Table 3 also shows the results of the various analyses designed to assess the likelihood of confounding by indication. In the analyses that included only patients who were very unlikely to be presenting with an acute cardiac condition (i.e. patients without a diagnosis of ischemia on admission, patients undergoing surgery, patients first receiving the drugs

Table 3. Association of ketorolac and myocardial infarction

Subject subgroups ( <i>n</i> = number of MIs)*	Unadjusted OR* (95% CI)	Adjusted OR (95% CI)†
All courses ( <i>n</i> = 63)	0.40 (0.23, 0.69)	0.42 (0.24, 0.73)
Patients unlikely to be receiving opioids for cardiac chest pain		
Excluding patients with ischemia diagnosis on admission ( <i>n</i> = 50)	0.42 (0.23, 0.77)	0.46 (0.25, 0.84)
Only surgical patients ( <i>n</i> = 29)	0.46 (0.21, 1.01)	0.53 (0.24, 1.17)
Only non-cardiac surgical patients ( <i>n</i> = 21)	0.71 (0.30, 1.68)	0.74 (0.31, 1.78)
Index drugs given outside of intensive care unit ( <i>n</i> = 22)	0.39 (0.15, 0.99)	0.38 (0.15, 0.97)
Index drugs not given for acute pain ( <i>n</i> = 16)	0.24 (0.07, 0.83)	0.39 (0.11, 1.42)
Including MIs only if they occurred $\geq$ 2 days after first exposure to index drugs ( <i>n</i> = 30)	0.36 (0.16, 0.81)	0.35 (0.16, 0.80)
Only patients receiving opioids		
Any opioids (ketorolac + opioids versus opioids only) ( <i>n</i> = 59)	0.37 (0.20, 0.68)	0.44 (0.24, 0.81)
Morphine sulfate (ketorolac + morphine versus morphine) ( <i>n</i> = 44)	0.34 (0.16, 0.74)	0.50 (0.23, 1.08)
MIs by timing relative to index drug exposure		
Only MIs if they occurred while on index drug ( <i>n</i> = 44)	0.33 (0.17, 0.66)	0.34 (0.17, 0.69)
Only MIs if they occurred after index drug stopped ( <i>n</i> = 19)	0.58 (0.23, 1.47)	0.64 (0.25, 1.64)

\*OR, odds ratio; CI, confidence interval; MI, myocardial infarction.

†Adjusted for age, sex, history of diabetes mellitus, history of cardiovascular disease, and administration of antiplatelet agents.

outside of an intensive care or emergency room setting, patients who did not receive the index drugs for acute pain, and patients whose MIs occurred 2 or more days after first exposure to the drugs), the negative association between ketorolac use and MI persisted. There were few outcomes among surgical patients, producing wide confidence intervals. However, the OR remained less than 1. In addition, adjusting simultaneously for ischemia as an admission diagnosis, surgical procedures, reason for index drug use (acute versus other), and location of first use of index drug (intensive care unit/emergency room versus other), the OR was 0.39 (95% CI: 0.22, 0.69).

The negative association also persisted in the analysis that compared opioid-exposed patients with patients receiving both opioids and ketorolac (i.e. comparing groups of patients that both received opioids, Table 3). Similar results were obtained when limiting opioid exposure to morphine sulfate in both groups.

When compared with the results in all subjects, the OR moved further from 1 when including only MIs that occurred while receiving the index drug, and excluding those occurring during the 3-day period after the last dose. The OR moved towards 1 when including only MIs that occurred in the 3-day period after the last use of the index drug.

## DISCUSSION

In this study, parenteral ketorolac, when compared with opioids, was associated with a reduced odds of

MI similar to the effect seen in clinical trials of ASA.<sup>4-6</sup> This association was consistent in several subgroups in which the opioid-exposed patients were unlikely to have different indications for analgesia than the ketorolac-exposed patients.

These findings are consistent with the known antiplatelet properties of ketorolac.<sup>15-18</sup> Like other NSAIDs, ketorolac inhibits the COX-1 enzyme responsible for thromboxane production. Although this inhibition is reversible, it appears to persist for at least 24 h after a single dose.<sup>17,18</sup> Furthermore, ketorolac has been shown to inhibit thrombus formation in animal models of arterial injury.<sup>15</sup>

Several other data support the hypothesis that nonselective NSAIDs reduce MI risk. For example, withdrawal of each of three different nonselective NSAIDs from the British market was associated with an approximately two- to four-fold increase in the number of cases of MI among patients who had these specific NSAIDs discontinued compared with the number of MIs when these patients were using these medications.<sup>29</sup> The observations from these case series, while in no way conclusive, suggest that NSAIDs may be cardioprotective. A recent randomized trial of flurbiprofen versus placebo also supports this hypothesis.<sup>30</sup> Flurbiprofen led to a significant reduction in recurrent MI among patients following successful reperfusion for MI.

To our knowledge, the results of the above-mentioned flurbiprofen trial have not been reproduced. Whether these results are applicable to other NSAIDs, some of which may have less

potent antiplatelet effects,<sup>11,18,31</sup> or other patient populations is unknown. A recent case-control study using the General Practice Research Database found no association between NANSAsIDs and MI, but was limited because only NANSAsIDs prescribed by a physician would have been recorded, actual use of NANSAsIDs was unknown, and control for the use of NANSAsIDs for cardiac chest pain could not be performed.<sup>32</sup>

The newly marketed COX-2 inhibitors (not available during this study) do not inhibit the enzyme (COX-1) responsible for thromboxane synthesis.<sup>19,20</sup> Therefore, unlike nonselective NANSAsIDs (like ketorolac), they may not provide protection against MI.<sup>21</sup> In addition, concerns have been raised that they may increase the risk of MI because they inhibit production of the prostacyclin that reduces thrombosis on arterial vessel walls.<sup>21</sup> One randomized trial comparing the COX-2 inhibitor, rofecoxib, with the nonselective NANSAsID, naproxen, demonstrated fewer MIs in the nonselective NANSAsIDs group.<sup>22</sup> Whether this was due to lower risk of MI in the nonselective NANSAsIDs group, higher risk in the rofecoxib group, or both, could not be discerned from the study. However, another randomized trial of the other COX-2 inhibitor on the US market, celecoxib, did not demonstrate a difference in MI when compared with the nonselective NANSAsIDs ibuprofen and diclofenac.<sup>33</sup> These findings, coupled with the results of our study and the randomized trial of flurbiprofen suggest that the differences between these drug types may be due to the beneficial effects of nonselective NANSAsIDs. Further study, however, is needed to try to determine the relative contributions of these drugs to MI risk.

### Limitations

There are several limitations to this observational study. The most important is the potential for residual confounding, particularly confounding by indication. Because opioids are used to treat cardiac chest pain and because the specific indication for opioid use was not recorded in this study, we cannot exclude the possibility that the findings are due to confounding. Numerous analyses aimed at addressing this possibility suggested that confounding by indication was not the explanation for our findings. However, we cannot completely exclude this as a possible explanation and this study remains hypothesis-strengthening only. Other potential sources of residual confounding include unmeasured differences between ketorolac-exposed and opioid-exposed patients, such as a family

history of coronary disease, prior angina, and hypercholesterolemia.

Another potential limitation is that the MIs were not identified using routine surveillance nor were they independently validated. However, this misclassification of MI was likely to be the same between ketorolac and opioid patients, thus biasing the results towards the null. Nevertheless, we cannot exclude differential misclassification as an explanation for our findings.

The small number of outcomes also limited our ability to analyse subgroups of patients. Nonetheless, the findings among the subgroups examined (although not all statistically significant) are all consistent with the study's hypothesis.

### CONCLUSIONS

This study suggests, but does not prove, that ketorolac may reduce the risk of MI when used as an analgesic in hospitalized patients and strengthens the hypothesis that nonselective NANSAsIDs reduce the risk of MI. Because uniform screening for and independent validation of MIs was not performed, nor were data collected on the specific indication for opioids, these results must be verified with further study. Until further, hypothesis-testing studies are done, the results of this study should not be used to alter clinical practice.

### ACKNOWLEDGEMENTS

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### KEY POINTS

- Platelet aggregation is a key component of acute myocardial infarction
- Non-aspirin non-steroidal anti-inflammatory drugs can inhibit platelet aggregation
- Parenteral ketorolac, a non-aspirin non-steroidal anti-inflammatory drug, inhibits platelet aggregation
- Parenteral ketorolac use, compared with parenteral opioid use, is associated with a reduced risk of myocardial infarction among hospitalized patients
- Further research into the effects of non-aspirin non-steroidal anti-inflammatory drugs on myocardial infarction risk is needed

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