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Interaction Between Low-Dose Aspirin and Nonsteroidal Anti-Inflammatory Drugs Can Compromise Aspirin's Efficacy in Preventing Venous Thrombosis Following Total Joint Arthroplasty

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Abstract

Total joint arthroplasty is a rapid recovery procedure with patients optimized quickly in preparation for discharge. Two significant postoperative goals are effective pain management and prevention of postoperative venous thromboembolism (VTE). Low-risk patients receive aspirin 81 mg twice daily for VTE prophylaxis; this dosing regimen has been reduced over the past few years from 325 mg to 162 mg to 81 mg twice daily. Unless contraindications exist, all patients receive multimodal pain management that includes the use of celecoxib or meloxicam. Upon reduction of the aspirin dose to 81 mg twice daily, we rapidly identified 2 patients who developed a pulmonary embolus when celecoxib or meloxicam was administered concurrently with aspirin. The interaction between nonsteroidal anti-inflammatory drugs (NSAIDs) and low-dose aspirin varies among the different NSAIDs. It is also highly dependent on numerous factors, including time of administration, dose of aspirin, and both pharmacodynamics and dose of the NSAID. Real-world outcomes of concomitant administration of NSAIDs with low-dose aspirin led to increased incidence of VTE, possibly due to competitive inhibition of aspirin at platelet receptor sites. This interaction was mitigated by altering the administration times of both agents.

Keywords

celecoxib, nonsteroidal anti-inflammatory drug, drug interaction, low-dose aspirin

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Background

Total joint arthroplasty is a rapid recovery procedure with hospital length of stays shortened to 48 hours or less. Patients must be optimized quickly in preparation for discharge home. Two significant postoperative goals are effective pain management and prevention of postoperative venous thromboembolism (VTE).

The Department of Orthopaedic Surgery at Syosset Hospital/Northwell Health System performs over 1200 joint arthroplasties annually. All surgeons follow one standardized pain management and thromboprophylaxis protocol. Patients are risk-stratified for postoperative VTE using the 2013 version of the Caprini Risk Assessment Model.[1] Patients who score 9 or less are categorized as low-risk and receive aspirin enteric coated (EC) 81 mg twice daily for 6 weeks. Patients who score 10 or greater are considered high-risk.[2] High-risk patients receive apixaban 2.5 mg twice daily for 35 days for total hip arthroplasty (THA) and apixaban 2.5 mg twice daily for 12 days, followed by aspirin EC 81 mg twice daily for 4 weeks for total knee arthroplasty (TKA). All patients are called after postoperative day 60 to assess for any complications.

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Table 1. Postoperative Cases of VTE.

	Patient 1	Patient 2
Procedure	Right TKA	Right TKA
Age/ gender	74/female	64/female
BMI	23	33.6
PMH	Hypothyroidism	HypertensionHyperlipidemia
VTE risk	Low	Low
Post-op meds	Aspirin EC 81 mg q12h × 6 weeksAcetaminophen 1000 mg q8hCelecoxib 200 mg q12hOxycodone 5 mg q3h PRN mild painOxycodone 10 mg q3h PRN moderate painHydromorphone 0.5 mg IV q3h PRN severe painPantoprazole 40 mg QAM	Aspirin EC 81 mg q12h × 6 weeksAcetaminophen 1000 mg q8hCelecoxib 200 mg q12hTramadol 25 mg q3h PRN mild painTramadol 50 mg q3h PRN moderate painHydromorphone 0.5 mg IV q3h PRN severe painPantoprazole 40 mg QAM
VTE	Right distal DVT POD3 Left PE POD4	Right subsegmental PE POD2

Abbreviations: BMI, body mass index; DVT, deep vein thrombosis; EC, enteric coated; IV, intravenous; PE, pulmonary embolus; PMH, past medical history; POD, postoperative day; PRN, pro re nata; q, every; QAM, every morning; TKA, total knee arthroplasty; VTE, venous thromboembolism.

Over the past 3 years, we have reduced the aspirin dose for low-risk patients from 325 mg twice daily to 162 mg twice daily with no change in efficacy (similar VTE incidence) and better gastrointestinal (GI) tolerability. In August 2018, we further reduced the aspirin dose to 81 mg twice daily based on evolving literature showing similar efficacy.[3] Twice-daily dosing was chosen based on accumulating evidence that some patients exhibit a low response to the antiplatelet effects of aspirin, referred to as aspirin resistance, during the early postoperative period. This effect has been observed in both cardiac and orthopaedic surgery and is theorized to be due to increased platelet consumption and production in the postoperative period.[4]

Patients receive acetaminophen 1000 mg every 8 hours and celecoxib 200 mg every 12 hours, or meloxicam 15 mg once daily for patients allergic to sulfa, for multimodal pain management, unless they meet exclusion criteria to any of these agents. Patients are prescribed as needed opiates in doses for mild, moderate, or severe pain. All patients receive pantoprazole 40 mg once daily to protect the gastric mucosa while taking concomitant medications for thromboprophylaxis and multimodal pain management.

Following dose reduction to aspirin 81 mg twice daily, 2 TKA patients developed postoperative pulmonary embolus (PE) within a 1-month time period. A detailed review of each case revealed one concerning commonality based on a known drug interaction between aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs): the celecoxib or meloxicam was administered concurrently with aspirin during hospitalization.

Discussion

Multimodal therapy has become the mainstay for postoperative pain management and includes around-the-clock dosing of acetaminophen plus an NSAID. This improves postsurgical pain control, reduces opiate consumption, and improves early mobilization and rehabilitation.[5-8] This cocktail of medications has gained popularity not only due to its effectiveness in managing postoperative pain[9-11] but also as a means to reduce narcotic consumption in light of the opioid crisis that currently exists in the United States.[12]

Total joint arthroplasty carries a significant risk of postoperative VTE, which includes deep vein thrombosis (DVT) and PE. National guidelines have recommended mechanical and/or chemical prophylaxis to prevent postoperative VTE.[13,14] Over the past decade, new pharmacologic options have been approved for prevention of VTE following arthroplasty.[15-17] In addition, resurgence of the time-honored agent, aspirin, has shown efficacy when used in appropriate, lower risk patients.[2,18-20] The optimal dose of aspirin, however, is still up for debate within the orthopaedic community.

Aspirin is an inexpensive VTE treatment option. Aspirin 81 mg is associated with significantly less GI distress and nausea compared with aspirin 325 mg.[21,22] Additionally, it has been shown to have improved antiplatelet efficacy in lower doses.[23,24] Aspirin 81 mg is rapidly metabolized to an ineffective concentration, with a short half-life of 20 minutes in systemic circulation.[25] Its mechanism of action is complete and irreversible inhibition of the synthesis of platelet thromboxane A_2 by blocking the activity of platelet cyclooxygenase (COX)-1 throughout dosing intervals.[26] This process, however, involves initial reversible binding with weak intrinsic affinity.[27]

Unlike aspirin, NSAIDs are reversible inhibitors of platelet COX-1, causing partial and intermittent inhibition of platelet thromboxane A_2.[26] Celecoxib is a COX-2 inhibitor with some inhibitory activity on COX-1. This agent has become our NSAID of choice due to its safer GI profile with effective pain control.

Platelets lack COX-2 and even supratherapeutic doses of COX-2 inhibitors have been shown not to interfere with platelet function.[28] Multiple studies have concluded that celecoxib does not demonstrate any significant drug interaction with aspirin.[29-31] However, 2 of the 3 studies looked at this interaction with aspirin 300 mg and aspirin 325 mg.[29,30] Although the

Table 2. Literature Review Describing Interaction Between Aspirin and NSAIDs.

Authors	Method	Conclusions
Lawson et al[33]	Coadministration of aspirin 81 mg once daily with acetaminophen (1000 mg), ibuprofen (400 mg), diclofenac (75 mg), or rofecoxib (25 mg). The NSAIDs were administered either 2 hours before or 2 hours after the aspirin.	The concomitant administration of ibuprofen, but not rofecoxib, acetaminophen, or diclofenac antagonized the irreversible platelet inhibition induced by aspirin. The effect of ibuprofen could be bypassed by administering aspirin 2 hours before a single dose of ibuprofen; however, when multiple doses of ibuprofen were given, these competitive effects were seen.
MacDonald and Wei[34]	Review of an anonymous database for 7107 patients who received low-dose aspirin (<325 mg) alone, aspirin plus ibuprofen, aspirin plus diclofenac, aspirin plus other NSAID	Statistically and clinically significant increased risk of mortality in users of aspirin plus ibuprofen compared with users of aspirin alone. No such increased risk was noted in users of aspirin plus diclofenac or other NSAIDS.
Capone et al[26]	Interaction between aspirin 100 mg and naproxen 500 mg twice daily in healthy patients in vitro and ex vivo	Naproxen interfered with the irreversible inhibitory effect of aspirin on platelet COX-1. Naproxen combined with aspirin might undermine the sustained inhibition of platelet COX-1 necessary for cardioprotection by aspirin.
Gladding et al[29]	Interaction between aspirin 300 mg and naproxen, tiaprofenic acid, ibuprofen, indomethacin, sulindac, and celecoxib. NSAIDS were given 2 hours prior to the aspirin.	Ibuprofen, indomethacin, naproxen, or tiaprofenic acid all block the antiplatelet effect of aspirin. Sulindac and celecoxib did not demonstrate any significant antiplatelet effect or reduce the antiplatelet effect of aspirin.
Wilner et al[30]	Healthy volunteers received celecoxib (400 mg/d) or placebo for 4 days. On day 5, they also received a single 325 mg dose of aspirin with either 200 mg celecoxib or placebo.	There was also no significant difference in the effect of aspirin on platelet aggregation due to ADP, collagen, or arachidonic acid between the groups. Therefore, these data indicate that celecoxib does not alter the effects of aspirin on platelet function.
Renda et al[31]	Twenty-four patients who were undergoing long-term treatment with aspirin (100 mg daily) for cardioprotection were coadministered celecoxib 200 mg twice daily, ibuprofen 600 mg 3 times daily, or placebo for 7 days	Unlike ibuprofen, celecoxib did not interfere with the inhibition of platelet COX-1 activity and function by aspirin despite a comparable suppression of COX-2 ex vivo in patients with osteoarthritis and stable ischemic heart disease.
Rimon et al[35]	In vitro and in vivo analysis (in dogs) of the effect of celecoxib administered at 8 AM and 5 PM with aspirin 81 mg administered at 12 PM	In vivo results indicated that celecoxib could interfere with the action of aspirin on COX-1 in vivo, and in the dog model, celecoxib did interfere with the effect of low-dose aspirin.
Saxena et al[32]	In vitro analysis in healthy volunteers. Aspirin either alone or in combination with ibuprofen, naproxen, oxaprozin, diclofenac, ketorolac, flufenamic acid, piroxicam, dipyrone, and celecoxib.	Ibuprofen, naproxen, oxaprozin, flufenamic acid, piroxicam, celecoxib, and dipyrone led to potent interference with the platelet inhibitory action of aspirin. Oxprazosin and celecoxib showed a decline of platelet aggregation at their highest concentrations. Ketorolac, diclofenac, and acetaminophen did not interfere with aspirin at all.
Ruzov et al[36]	Ex vivo interaction between celecoxib and aspirin for COX-1 binding and measured resulting antiplatelet effects. Data were then analyzed using PK/PD modeling to predict in vivo platelet aggregation for different doses and administration schedules for aspirin and celecoxib.	Celecoxib (100 mg twice daily) can attenuate to a limited extent the in vivo antiplatelet effects of low-dose aspirin. This interaction can be substantial during the first few days of aspirin initiation in patients already treated with celecoxib and cannot be prevented by separating administration times. However, at high doses celecoxib will compete efficiently with low-dose aspirin and may be mitigated by changing administration times.

Abbreviations: ADP, adenosine 5'-diphosphate; COX-1, cyclooxygenase 1; NSAIDs, nonsteroidal anti-inflammatory drugs; PK/PD, pharmacokinetics/pharmacodynamics.

third study did evaluate the interaction of celecoxib with low-dose aspirin (100 mg), these patients were receiving long-term treatment of aspirin for stable ischemic heart disease when the NSAID was introduced to the regimen. Of interest as well, all study patients were male.[31] To date, no one has studied this drug interaction in the arthroplasty population who are at high risk of postoperative VTE (Table 1).

A distinct pharmacodynamic (PD) interaction exists whereby traditional NSAIDs that bind to the COX-1 receptor may prevent aspirin's inhibition of platelets via effective competition, most likely at the level of platelet COX-1.[32] Lawson et al[33] were the first to describe this interaction between aspirin and ibuprofen. Subsequent studies have described a comparable PD interaction when traditional NSAIDs were administered concurrently with aspirin (Table 2).[26,29-36] Collectively, the literature has reported an interaction between low-dose aspirin and COX-2 inhibitors in vitro. Rimon et al[35] specifically studied celecoxib's effect on low-dose aspirin (81 mg) and

determined that celecoxib binds tightly to the regulatory subunit of the COX-1 enzyme and does interfere with aspirin's ability to inactivate COX-1.

These conflicting results investigating the interaction between celecoxib and aspirin may be due to several factors. Gurbel et al concluded that the interaction between NSAIDs and aspirin is variable and depends on the dose of aspirin, dose of NSAID, and dose timing. Additionally, in vivo and ex vivo results are not always reflective of the complexity of thrombosis mechanisms.[37] Ruzov et al evaluated celecoxib 200 mg once daily with various aspirin doses and suggested that the interaction can be substantial during the first day of aspirin administration in patients already treated with celecoxib, and it cannot be prevented by separating administration times of the drugs. For a patient treated chronically with low-dose aspirin, the addition of celecoxib 200 mg once daily is not expected to mitigate aspirin's antiplatelet effects. At high doses, however, celecoxib is able to compete efficiently with aspirin for COX-1 binding in vivo and can interfere with the antiplatelet effects of low-dose aspirin.[36] Saxena et al[32] confirmed these findings and showed increasing interference with higher celecoxib concentration. Finally, Hohlfeld et al[38] noted discrepancies between aspirin and NSAIDs with respect to both half-life and binding affinity; they concluded that based on half-life, ASA would be inactivated prior to COX enzyme binding, and the presence of an NSAID with ASA would prevent the access of ASA to platelet receptor sites due to differences in binding affinity.

Our low-risk patients currently receive aspirin EC 81 mg twice daily for VTE prophylaxis. Unless contraindications exist, all patients receive multimodal pain management that includes the use of celecoxib 200mg every 12 hours or meloxicam 15mg once daily. We did not see the same PD interaction when NSAIDs were administered with aspirin 325 mg twice daily or aspirin 162 mg twice daily. However, upon reduction of aspirin dose to 81 mg twice daily, we rapidly identified 2 patients who developed a PE when celecoxib or meloxicam was administered concurrently with aspirin after total joint arthroplasty.

Emerging evidence supports the theory that the timing of NSAID and aspirin administration appears to influence the degree of interaction.[37,38] Gurbel et al[37] recommended administering naproxen at least 2 hours after an aspirin dose to diminish the interaction. Following this recommendation, the dosing schedule was altered for our postoperative arthroplasty patients with EC aspirin scheduled for 0600 and 1800 administration daily. Celecoxib is administered at 0900 and 2100; meloxicam is administered at 0900 daily. Patients are educated prior to discharge on the importance of continuing this practice at home and are specifically instructed to take aspirin at least 2 hours before the NSAID; they are given patient-specific medication calendars with times of administration listed for the duration of therapy. After initiating this dosing schedule, only 2 VTE events were noted postoperatively in the low-risk group over the following year. A detailed review revealed that both were female THA patients and both took the aspirin at the same time each day as the NSAID (1 on celecoxib and 1 on meloxicam).

Conclusion

The interaction between NSAIDs and low-dose aspirin varies among the different NSAIDs. It is highly dependent on numerous factors, including time of administration, dose of aspirin, and both PD and dose of the NSAID. Concurrent administration of aspirin and NSAIDs is common in clinical practice and remains an area for further research. Acetaminophen has never shown any interaction with aspirin and is safe to give concurrently with aspirin.

Real-world outcomes of concomitant administration of NSAIDs with low-dose aspirin led to increased incidence of VTE, possibly due to competitive inhibition of aspirin at platelet receptor sites. This interaction was mitigated by altering administration times of both agents. Patients prescribed low-dose aspirin and NSAIDs, including the COX-2 inhibitor celecoxib, must be educated to modify dosing regimens so that aspirin is administered at least 2 hours prior to the NSAID. This adjustment in timing of administration has shown efficacy to minimize interference of the antiplatelet effects of low-dose aspirin.

This is a case study manuscript. Information collected is part of department annual performance improvement metrics. Informed consent for patient information to be published in this article was not obtained because patient information is de-identified.

Declaration of Conflicting Interests

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