

THE ANTICOAGULANT EFFECT OF IBUPROFEN AND INTERACTIONS

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November 3, 2022

Abstract

Ibuprofen (IBU) is a non-steroidal anti-inflammatory drug (NSAID). A clinician wishing to avoid opioid pain control may consider a combination of orally administered ibuprofen (IBU) and acetaminophen for pain control. In dentistry, it is commonly recommended to take oral IBU 400-800mg and acetaminophen 325-1000 mg to control postoperative pain following third molar extraction(s). This combination can avoid the use of a narcotic prescription for pain control. However, many patients are taking anticoagulants for a variety of medical conditions and are told not to take IBU fearing an additive effect of IBU with the anticoagulant. This mini-review paper addresses the anticoagulant effects of IBU when administered as a single agent and the interactions with orally administered anticoagulant, antiplatelet, or antithrombotic agents.

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Ibuprofen (IBU) is a non-steroidal anti-inflammatory drug (NSAID). A clinician wishing to avoid opioid pain control may consider a combination of orally administered ibuprofen (IBU) and acetaminophen for pain control. In dentistry, it is commonly recommended to take oral IBU 400-800mg and acetaminophen 325-1000 mg to control postoperative pain following third molar extraction(s). This combination can avoid the use of a narcotic prescription for pain control. However, many patients are taking anticoagulants for a variety of medical conditions and are told not to take IBU fearing an additive effect of IBU with the anticoagulant. This mini-review paper addresses the anticoagulant effects of IBU when administered as a single agent and the interactions with orally administered anticoagulant, antiplatelet, or antithrombotic agents.

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INTRODUCTION

Ibuprofen (IBU) is an over-the-counter (OTC) non-steroidal anti-inflammatory drug (NSAID) (Fig. 1). It is sold as the racemic S enantiomer to produce the desired pharmacologic action. IBU has an elimination half-life of 2 hours (1,2). IBU is used to treat fever, pain, and inflammation (3,4,5). IBU may not be as effective of an anti-inflammatory agent when compared to other NSAIDs (6). Literature on the safety of IBU is plentiful (1). NSAIDs when combined with acetaminophen are highly effective for postoperative pain control (2). Combining ibuprofen 200 mg with acetaminophen 500 mg has significantly more analgesia effect than an opioid medication such as oxycodone 15 mg with acetaminophen (2). Thus, it may be appropriate to use opioids only for severe or refractory pain (2).

There may be a misconception that NSAIDs may have an unacceptable risk of bleeding. Nonetheless, the bleeding risk profile of OTC IBU and the prescription strength (600-800 mg) are not well defined. That is, with the OTC use of IBU there are few controlled studies regarding the anticoagulation effect of OTC use in the general population (1,2).

Gastrointestinal bleeding can occur with OTC IBU use. The GI-bleeding complication hospitalization rate for OTC comparable doses of IBU is less than 0.2%. (1) With increasing age and concomitant medication use, the incidence of bleeding events does increase (1). Nonetheless, there has been no consistent IBU dose-anticoagulation response relationship elucidated. This may mean that patients are poor historians when describing their side effects or there are genetic metabolic differences that produce different outcomes, along with other potential reasons (7). It is agreed that there appears to be a low incidence of bleeding events with OTC IBU.

OTC drugs for pain control are intended for short-term use and should not be taken for analgesia for more than 10 days. Longer use increases possible side effects. To avoid gastric side effects, IBU should be taken with food. Increased age, anemia, smoking, carcinoma, alcohol use, liver disease, frailty, anticoagulants, and selective serotonin reuptake inhibitors (SSRIs) are comorbidities that may increase the risk for gastric side effects. (2,4,5, 8,9,10,11).

METHODOLOGY

A PubMed search was done using the terms, ibuprofen, ibuprofen AND anticoagulant, ibuprofen AND drug interactions, and ibuprofen AND complications. No other search engine was used. The articles retrieved were assessed for relevance and those deemed relevant are included herein. No human or animal subjects were used what so ever in this work.

PHARMACODYNAMICS OF IBUPROFEN

IBU inhibits the cyclooxygenase-1 and -2 (COX-1 and COX-2) enzymes. Inhibition of COX-1 affects the prostaglandin-induced protection of the gastrointestinal tract, and this action is well understood (10). Nonetheless, various isoforms of IBU can cause varying degrees of gastric damage (12). Selective COX-2 inhibitors are known to induce less gastric damage (12). COX-2 leads to the production of prostaglandin E2 (PGE2) which produces redness, pain, and swelling; inhibition of COX-2 produces analgesia (5). Prostaglandins are converted to thromboxane A₂ (TxA₂) by Cox-1 enzymes (5,13). TxA₂ stimulates platelet aggregation for blood clotting. Thus, COX enzymes are inhibited, and then ultimately TxA₂ production is reduced along with platelet aggregation and coagulation (12,14,15).

COAGULATION

Blood coagulation or thrombosis is the biologic action where liquid blood is converted to a gel or a clot (Fig. 2). Coagulation involves platelets and vascular protein factors (16) (Fig. 1). When vascular subendothelial collagen is damaged and exposed to platelets, coagulation begins. Platelets bind directly to the subendothelial collagen to form a plug to occlude the injury. Platelets release stored granules of several clotting factors that then bind fibrinogen. The fibrinogen crosslinks to a glycoprotein and aggregates more platelets completing initial hemostasis (17). Factor VII then induces fibrin formation to strengthen the platelet plug.

The second stage of coagulation has two pathways that are artificially named; (i) extrinsic or tissue factor and (ii) intrinsic or contact activation pathways. Both pathways play a role in fibrin formation to seal off bleeding or leaking blood vessels.

The extrinsic or tissue factor pathway is the more important. This pathway is a cascade of enzymatic reactions by coagulation factors. The main role of the extrinsic pathway is the rapid release of thrombin (18).

The intrinsic pathway is a cascade of reactions that aid clot formation, but its main role appears to be in inflammation and immunity (18,19). A therapeutic blockage of the intrinsic pathway does not increase the risk for significant bleeding but can contribute to the prevention of thrombosis (19).

In the end, the extrinsic and intrinsic pathways both end into a final common interactive pathway of factor X, thrombin, and fibrin.

Coagulation is a complex physiologic series of chemical and enzymatic reactions that are activated and

inhibited by a large variety of enzymes and chemicals. In the end, without interference, a thrombus forms and bleeding ceases (18,19,20).

IBUPROFEN AND COAGULATION

IBU has the lowest risk for gastrointestinal bleeding and platelet inactivation of all NSAIDs (21). A single preoperative dose of 400 mg of IBU does not have a significant intraoperative or postoperative increased occurrence of bleeding. (22,23,24).

To reduce the risk of GI bleeding IBU should not be taken for more than 10 days (25). The lowest dose that produces the appropriate clinical effect is the dose that should be taken (26,27).

Some studies report a low incidence of GI bleeding events with the use of 200-600mg IBU for 10 days (1). The gastrointestinal bleeding incidence among those using OTC-comparable doses ranged from 0 to 3.19 per 1000 patient years. The incidence of a GI bleeding-related events increased with age and polypharmacy (1). However, there was an inconsistent statistically significant ibuprofen dose-dependent-anticoagulant response relationship. The relative risk of any GI bleeding-related events ranges from 1.1 to 2.4% for users of 200-600mg IBU doses for 10 days when compared to non-users (1).

There are few published studies that have specifically investigated OTC IBU use (1). Unfortunately, the large variety of methodologies, exposures and outcomes preclude a direct comparison of many studies by means of a meta-analysis (1). The various outcomes may imply that there are human differences in IBU metabolism (1). Thus, patients with susceptible phenotypes that effect IBU metabolism may react with varying degrees of gastrointestinal bleeding severity (28).

IBUPROFEN INTERACTION WITH ANTICOAGULANT, ANTI-PLATELET, AND DIRECT ANTI-THROMBOTIC AGENTS

Anticoagulants inhibit clot formation. There are many available with various mechanisms of action. Since IBU acts to inhibit platelet aggregation, there may be an increased clinical anticoagulation effect when co-administered with other anti-coagulants, anti-thrombotic, or anti-platelet agents (28).

Ibuprofen and warfarin

In one study, the effect of IBU anticoagulation interaction with warfarin on hemostasis was tested in 20 patients taking warfarin for venous thromboembolism (27). IBU 600 mg taken three times per day orally was tested for 1 week (30). Bleeding time, prothrombin time, platelet count and urinalysis for hemoglobin were observed. These tests were performed just before, 90 minutes after the first dose of IBU and after a one-week duration of treatment. Bleeding time was significantly prolonged after 90 minutes following a single IBU 600mg dose, and after 1 week. Hematuria and hematoma were seen in all cases following week-long co-administration. It was concluded that ibuprofen can cause significant anticoagulation issues in patients being treated with concurrent warfarin after one week (30). Thus, older patients under anticoagulant and polypharmacy therapy may be at increased risk for bleeding complications (30,31,32,33,34).

Warfarin (Coumadin[®]) acts by blocking the enzymatic reduction of vitamin K. Vitamin K is an important cofactor in the synthesis of clotting Factors II (prothrombin), VII, IX, and X. It can take 3-5 days for warfarin to have a full therapeutic effect due to the pre-treatment reservoir of Factors II, VII, IX, and X. (30,34)

IBU causes an increase of the INR in these warfarin patients by an additive effect (35,36). IBU 600 mg taken orally three times a day for 7 days can cause an increase in the INR of patients taking warfarin (35,36); however, there may not be a significant effect on platelet count and prothrombin time. So, the increase in anticoagulation in most patients may remain within normal limits. Nonetheless, microscopic hematuria and hematoma can occur in these patients. These sequelae may be problematic in elderly polypharmacy patients (33,34). Thus, if IBU is to be administered for an extended time-period in these patients, the dental clinician should consult with the patient's physician who should monitor the warfarin INR before and during concurrent IBU-warfarin therapy. If the INR is prolonged beyond the intended clinical range, the IBU treatment should be discontinued (36,37).

Much of the work on IBU-warfarin interaction was done on rats. Rats are much more sensitive to this interaction than humans, nonetheless, extrapolation to human clinical usage may not be appropriate (36,37).

Ibuprofen and Aspirin

The anti-platelet agent aspirin (ASA, acetyl salicylic acid) is a non-selective COX inhibitor NSAID. A single dose of ASA inhibits platelet function for 48 hours and inhibits platelet aggregation for the life of the platelet (32,33). Short-term usage of IBU slightly reduces platelet aggregation as compared to aspirin (25,26,32,35,36). The action of ASA occurs at different loci in the coagulation cascade than IBU. Nonetheless, IBU does interfere with the antiplatelet effect of aspirin (ASA), and this makes the ASA less effective for cardio-protection and stroke prevention (32,33). IBU can inhibit low-dose ASA's ability to reduce the antiplatelet effect (31,32). This problem can be avoided by waiting 30-120 minutes after the ASA dose to administer the IBU or administer the IBU dose 6-8 hours prior to the ASA dose (32,34,35). However, due to the delayed absorption of enteric coated ASA, this time frame may not apply. Another study suggested that IBU may be taken with a 30 to 60-minute hiatus before or after ASA oral administration to prevent an interaction (31,32). However, if IBU is taken only as an occasional single dose or for a short term, then there is minimal disruption of the ASA cardiovascular protective action (32,34).

Recent reports have minimized the therapeutic effect of ASA (38). Since ASA and IBU are NSAIDs this may mean that the effects of these agents are uncertain as well as their interaction. Further investigation needs to be done to elucidate the therapeutics and interactions.

Ibuprofen and Direct Acting Antithrombotics

The direct-acting antithrombotics (DAA) (non-vitamin K antagonists) act by inhibiting elements of the coagulation cascade factor Xa and IIa (39,40). Dabigatran (Pradaxa[®]) is a direct thrombin inhibitor and rivaroxaban (Xarelto[®]) and apixaban (Eliquis[®]) are direct Factor Xa inhibitors (40). These commonly prescribed anticoagulants do not require routine monitoring (41). While this is an advantage, the patient has less contact with the prescriber and may not be mindful of the potential for interactions of OTC medications (41). Nonetheless, the incidence of serious interactions with IBU is low when OTC guidelines are followed, 200mg 4-6 hours for less than 10 days (42). Nonetheless, IBU can increase the incidence of bleeding in patients taking apixaban (Eliquis), rivaroxaban (Xarelto), dabigatran (Pradaxa) by an additive effect (40). Thus, co-administration of IBU with these medications should be avoided.

Ibuprofen and Fish Oil

Many patients routinely take the omega-3 antioxidant fish oil as an OTC medication. Fish oil has been known to have an anti-coagulant effect (43). The additive effects of ibuprofen with fish oil have not been well studied (43). Nonetheless, the clinician should be mindful of the potential for an adverse effect on coagulation.

Ibuprofen and Selective Serotonin Reuptake Inhibitors

Long-term use of selective serotonin reuptake inhibitors (SSRI) has a small anticoagulation side effect (44,45,46). There is frequent self-administration of IBU by patients taking SSRIs (44,45,46). There is no evidence of significant increased GI bleeding with the concomitant use of SSRI and IBU or of the safety of this combination (44,45,46). The SSRI bleeding risk is about the same as IBU as solo agents, but when taken together the risk increases (47). The issue of concern is the long-term concomitant use of these agents which may lead to significant upper gastrointestinal bleeding (47).

Considerations

Table 1 provides a list of considerations before prescribing IBU (Table 1) (48). If IBU must be prescribed, then close monitoring of the patient's compliance and coagulation status should be done (48, 49,50).

CONCLUSIONS

Current information shows that IBU effects coagulation by mildly inhibiting platelet aggregation when taken for less than 10 days. IBU 400 mg every 6 hours taken for less than 48 hours is unlikely to induce an adverse

bleeding event in patients taking anticoagulants. However, after 10 days of daily dosing there may be an increased risk for bleeding.

Most patients have poor compliance, and if IBU is to be administered, the clinician should be certain that the patient understands the implications of IBU dosing and potential drug interactions.

Investigations of these interactions are needed to provide the clinician with appropriate prescribing protocols.

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