

The effects of corticosteroids and nonsteroidal anti-inflammatory drugs, including aspirin, on coagulation

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The immune and coagulation systems have numerous interactions, as evidenced by the increased risk of venous thromboembolism in inflammatory bowel disease. In general, proinflammatory states are prothrombotic, while a reduction in inflammation reduces thrombotic risk. Corticosteroids, such as hydrocortisone and prednisone, tend to reduce inflammation and thus thrombosis, while being prothrombotic in non-inflammatory states, e.g. Cushing's syndrome. The nonsteroidal anti-inflammatory drugs also have a dual effect, through interaction with different cyclo-oxygenase enzyme isoforms, on platelets and the vascular endothelium.

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Introduction

The immune and coagulation systems have numerous interactions, as evidenced by the increased risk of venous thromboembolism (VTE) in inflammatory bowel disease.¹ In general, proinflammatory states are prothrombotic, while a reduction in inflammation reduces thrombotic risk. Corticosteroids, such as hydrocortisone and prednisone, tend to reduce inflammation, and thus thrombosis, while being prothrombotic in non-inflammatory states, e.g. Cushing's syndrome.² The nonsteroidal anti-inflammatory drugs (NSAIDs) also have a dual effect, through interaction with different cyclo-oxygenase (COX) enzyme isoforms, on platelets and the vascular endothelium.³

Corticosteroids and coagulation

The direct effects of corticosteroids on coagulation are difficult to separate from their effects on reducing the inflammatory response, which tends to be prothrombotic.

However, the effect of corticosteroid excess in the absence of inflammation, e.g. Cushing's syndrome (increased pituitary adrenocorticotrophic hormone or cortisol-producing adrenal adenoma), results in a prothrombotic state due to increases in fibrinogen, factor VIII and von Willebrand factor, with reduced fibrinolysis which is not offset by an increase in the anticoagulant proteins, C and S.⁴

The use of exogenous corticosteroids for the management of systemic inflammation results in more complex effects. A reduction in the inflammatory disease being treated reduces the risk of thrombosis.²

Single doses of dexamethasone, up to 0.1 mg/kg, as an anaesthetic adjuvant to reduce postoperative nausea and vomiting and improve analgesia, are not associated with changes in coagulation.⁵

Short courses of steroids for acute flares of inflammatory diseases, such as asthma or rheumatoid arthritis; or infections,

such as meningitis or pericarditis; are also not associated with changes in coagulation which cannot be explained by reduced inflammation.⁶

However, good epidemiological data support the assertion that the long-term (> 1 month) use of corticosteroids is associated with a two- to threefold increase in the incidence of VTE. The association may be owing to the inadequate suppression of inflammation through fear of corticosteroid side-effects from higher doses or an innate effect of the corticosteroids, as seen in Cushing's syndrome.⁷

The effect of steroid deficiency is less clear as the presentation of Addison's disease is usually accompanied by cardiovascular (CV) collapse, which requires rapid steroid supplementation. The adrenal function may be suppressed by adrenal haemorrhage as a complication of excessive anticoagulation.²

Nonsteroidal anti-inflammatory drugs, including aspirin

The NSAIDs produce their effects through a blockade of the conversion of arachidonic acid to prostaglandins by COX. Corticosteroids reduce the availability of arachidonic acid, contributing to the anti-inflammatory activity of these drugs.⁸

COX-1 is the predominant isoform in the platelets, producing thromboxane, which promotes platelet adhesion and vasoconstriction.

COX-2 is the predominant isoform in the vascular endothelium, producing prostacyclin (PGI₂), which reduces platelet adhesion and promotes vasodilation. Activated immune cells are the other major site for COX-2 production, and promote the inflammatory response. Both isoforms are found in the kidney.⁸

Clinically, there are three subdivisions of the NSAIDs according to their effects on the two major isoforms of COX:

- *Non-specific NSAIDs:* Non-specific NSAIDs block both COX-1 and COX-2 to a variable extent. The first refer to aspirin-like NSAIDs, i.e. which predominantly block COX-1, i.e. aspirin and

ketorolac. These have the greatest antiplatelet effects and minimal CV thrombosis. The second refer to cyclo-oxygenase inhibitor (coxib)-like NSAIDs, i.e. which block mixed COX-1 and COX-2, i.e. ibuprofen and diclofenac. These have both antiplatelet and CV thrombotic effects.

- *Coxibs*: Coxibs specifically block COX-2, resulting in no antiplatelet effects and dose-dependent CV thrombosis.

Aspirin is unique as it is an irreversible inhibitor of COX-1. The return of COX-1 function is reliant on replacement by nuclear transcription and translation. Platelets have no nucleus, so when exposed to aspirin, the COX-1 remains inactive for the lifetime of the platelet (five days).⁹

Clinical use of nonsteroidal anti-inflammatory drugs

NSAIDs are an essential component of multimodal pain therapy,¹⁰ which is particularly useful in the management of dynamic pain, thus promoting patient mobilisation. The use of NSAIDs may be limited by the risk of organ dysfunction, particularly bleeding due to the blockade of platelet COX-1. With the advent of the COX-2-specific coxibs in the late 1990s, evidence of prothrombotic effects, particularly in the coronary arteries, became clear, and led to the withdrawal of rofecoxib, e.g. Vioxx[®].

Antiplatelet effects

Aspirin is extensively used for the primary and secondary prevention of coronary thrombosis, acting by irreversibly inhibiting platelet COX-1, thus reducing the synthesis of the procoagulant, vasoconstrictor PG thromboxane, and maintaining vessel patency.¹¹ Aspirin for CV prophylaxis is given at a low dose of 80–120 mg/day to limit gastrointestinal side-effects. With the use of this low dose, unhindered access to platelet COX-1 by the aspirin during the 2–4 hours that the aspirin is present in the plasma is required.

The nonselective NSAIDs, particularly the aspirin-like drugs, e.g. naproxen and ketorolac, are reversible inhibitors of platelet COX-1, and are thought to have similar circulatory effects to aspirin, but only while in circulation.

Aspirin and the nonselective NSAIDs were thought to confer an increased risk of bleeding after trauma or surgery as a result of their antiplatelet activity, but the data supporting this perception are limited and of poor quality.¹²

Prothrombotic effects

Extensive re-assessment of the CV effects of NSAIDs was required after the development and prescription of the COX-2-specific coxibs in the late 1990s. The theory at the time was that these drugs would selectively suppress inflammation by blocking inducible COX-2 from activated white blood cells, without the side-effect of bleeding from trauma, surgery or the gastrointestinal tract, as COX-1 would not be affected.¹³

Rofecoxib was one of the first coxibs proven to be an extremely effective anti-inflammatory drug, but was found to significantly increase the risk of coronary thrombosis, myocardial infarction and death. Adverse CV effects led to the withdrawal of rofecoxib in September 2004. The mechanism was found to be inhibition of COX-2 in the endothelium, which reduced the production

of the anticoagulant, vasodilator PGI₂, while leaving platelet thromboxane synthesis by COX-1 unchanged, resulting in a prothrombotic state.¹⁴

A reduction in nitric oxide (NO) synthesis, through the effects on cyclic guanosine monophosphate, was an additional mechanism that was subsequently found.¹⁵

Subsequent studies have revealed that nonselective NSAIDs, particularly diclofenac, also confer an increased risk of CV thrombosis.¹⁶

Currently, the available coxibs, celecoxib and etoricoxib, do not appear to increase CV risk when used according to the dosage limits specified by the manufacturers.¹⁷

Numerous protective mechanisms associated with a healthy endothelium minimise the risks of reduced NO and PGI₂. By contrast, increased production of proinflammatory (and thus prothrombotic) mediators, such as C-reactive protein, and reactive oxygen species with reduced clearance, are associated with an unhealthy endothelium. Thus, there is a much greater risk of a further reduction in antiplatelet, and in vasodilator mediators, such as NO and PGI₂, with the latter.¹⁸ An at-risk endothelium may be inferred by the presence of risk factors for coronary artery disease (CAD), and especially the presence of angina or a prior myocardial infarction.

A useful matrix for balancing thrombotic and bleeding risk in an individual patient requiring NSAID therapy is indicated in Table 1.

Table 1: Nonsteroidal anti-inflammatory drug selection based on risk of bleeding or cardiovascular thrombosis

		Risk of cardiovascular events	
		Low	High
		1	2
Risk of bleeding	Low	Clinician choice	Aspirin NSAID or equivalent
	High	Coxib	Avoid all NSAIDs Short-term coxib

coxib: cyclo-oxygenase inhibitor, NSAID: nonsteroidal anti-inflammatory drugs

Patients with nociceptive pain due to inflammation which is not associated with bleeding, without risk factors for CAD, are represented by quadrant 1. Patients in this quadrant include those with musculoskeletal strains and inflammation, such as acute gout. Postoperative patients include those who have undergone a Caesarean section, or younger patients post an arthroscopy or laparoscopy.

Patients with nociceptive pain due to inflammation with a significant risk of bleeding, but without the risk factors for CAD, are represented by quadrant 2. Patients in this quadrant include those on other anticoagulant therapy, e.g. warfarin, rivaroxaban and dabigatran; adequately resuscitated trauma patients and those post high-risk surgery including neurological, eye and middle ear surgery.

Patients with nociceptive pain due to inflammation which is not associated with bleeding, but with risk factors for CAD, are

represented by quadrant 3. Patients in this quadrant include older patients with chronic inflammatory arthropathies and patients undergoing low-risk surgery, including joint replacement and hernia repair.

Patients with nociceptive pain due to inflammation which is associated with a risk of bleeding and CAD are represented by quadrant 4. The risk to benefit for these patients should be assessed on an individual basis, based on factors including the site and likelihood of bleeding, the extent of the CAD risk, and the likelihood of response to NSAID therapy. Bleeding is most likely to be acutely harmful, so a short trial of a coxib, not exceeding the recommended dose, may be considered as a trial of therapy.

Pharmacological interaction of nonsteroidal anti-inflammatory drugs and aspirin

Nonselective NSAIDs are competitive binders to COX-1, while aspirin is a non-competitive binder.¹⁹ Thus, if aspirin is co-administered with a nonselective NSAID, even an aspirin-like NSAID, the nonselective NSAID will limit access by the aspirin to the platelet COX-1. The plasma half-life of aspirin is only two hours, compared with at least four hours for commonly used nonselective NSAIDs. Inhibition of platelet COX-1 (> 95%) is required to achieve the therapeutic effect of aspirin for the primary and secondary prevention of CV disease. The co-administration of nonselective NSAIDs and aspirin not only reduces the therapeutic effect of aspirin for CV disease, but also amplifies the gastrointestinal side-effects of both drugs.²⁰

Coxibs do not interfere with aspirin binding to platelet COX-1, and do not increase the likelihood of gastrointestinal side-effects with concurrent aspirin use. Short-term coxib therapy may prove to be less harmful than short-term nonselective NSAID therapy in patients on long-term aspirin therapy. However, long-term use is less clear. Rofecoxib increased CV events despite the co-administration of aspirin in one study, while the effect of celecoxib was neutral.²¹

Conclusion

In excess, glucocorticoids are prothrombotic, but reduce the risk of thrombosis when given to reduce inflammation. Patients on long-term exogenous corticosteroids should take extra precaution against thrombosis in high-risk situations, such as the postoperative period.

Nonselective NSAIDs predispose to bleeding through their antiplatelet activity by blocking COX-1 on the platelets.

The coxibs and non-aspirin-like NSAIDs may cause coronary and cerebral thrombosis in patients at risk of CAD through blockade of endothelial COX-2 and the reduction of NO synthesis. Patients with CAD risk factors should use aspirin-like NSAIDs, if possible. The drug should be given at the lowest dose and for the shortest duration possible if a non-aspirin-like NSAID or coxib is required.

Nonselective NSAIDs hinder access and limit the efficacy of aspirin given for prophylaxis against arterial thrombosis if the drugs are co-administered.

Aspirin efficacy can be maintained by delaying the administration of a nonselective NSAID to at least two hours after aspirin

administration, or by using a coxib which does not compete with aspirin at COX-1.

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