**Warfarin + NSAIDs**

Non-steroidal anti-inflammatory drugs (NSAIDs) have antiplatelet effects which increase the bleeding risk when combined with oral anticoagulants such as warfarin. The antiplatelet effect of NSAIDs lasts only as long as the NSAID is present in the circulation, unlike aspirin’s antiplatelet effect, which lasts for up to 2 weeks after aspirin is discontinued. NSAIDs also can cause peptic ulcers and most of the evidence for increased bleeding risk with NSAIDs plus warfarin is due to upper gastrointestinal bleeding (UGIB).

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| --- | --- | --- | --- | --- | --- | --- | --- |
| Is NSAID topical or ophthalmic diclofenac? | Yes | No | | | | | |
| Is there a suitable alternative to the NSAID in this patient? |  | Yes | No | | | | |
| Is patient on proton pump inhibitor or misoprostol? |  |  | Yes | No | | | |
| Does the patient have one or more of the following risk factors:  - history of UGIB or peptic ulcer  - > 65 years old |  |  |  | Yes | | No | |
| Is patient also taking:  - systemic corticosteroids  - aldosterone antagonist  - high dose or multiple NSAIDs |  |  |  | Yes | No | Yes | No |
|  |  |  |  |  |  |  |  |
| Not likely to increase risk of UGIB | 1 |  |  |  |  |  |  |
| Use alternative to NSAID |  | 2 |  |  |  |  |  |
| Possible increased risk of UGIB or other bleeding |  |  | 3 |  |  |  |  |
| Substantially increased risk of UGIB or other bleeding |  |  |  | 4,5 |  |  |  |
| Increased risk of UGIB or other bleeding |  |  |  |  | 4 | 5 |  |
|  |  |  |  |  |  |  |  |

 = No special precautions.  = Assess risk and take action if necessary.  = Use only if benefit outweighs risk

**Footnotes**:

1. Topical diclofenac has relatively low systemic absorption; in one study a topical gel (16 g/day) produced about 6% of the absorption seen with systemic administration of 150 mg/day. A higher than recommended dose of topical gel (48 g/day) produced 20% of a systemic dose of diclofenac. The UK Summary of Product Characteristics for Voltarol Ophtha Multidose Eye Drops states, "No measurable levels of diclofenac could be found in humans after ocular application of diclofenac sodium eye drops". The FDA-approved SPL for Diclofenac Sodium Ophthalmic Solution 0.1% states, "Results from a bioavailability study established that plasma levels of diclofenac following ocular instillation of two drops of Diclofenac sodium ophthalmic solution, 0.1% to each eye were below the limit of quantification (10 ng/mL) over a 4-hour period. This study suggests that limited, if any, systemic absorption occurs with Diclofenac sodium ophthalmic solution".

2. If the NSAID is being used as an analgesic or antipyretic, it would be prudent to use an alternative such as acetaminophen. In some people, acetaminophen can increase the anticoagulant effect of warfarin, so monitor the INR if acetaminophen is used in doses over 2 g/day for a few days. For more severe pain consider short-term opioids in place of the NSAID.

3. Proton pump inhibitors and misoprostol may reduce the risk of UGIB in patients receiving NSAIDs and warfarin.

4. Patients with a history of UGIB or peptic ulcer may have an increased risk of UGIB from this interaction. The extent to which older age is an independent risk factor for UGIB due to these interactions is not firmly established, but UGIB in general is known to increase with age.

5. Both corticosteroids and aldosterone antagonists have been shown to substantially increase the risk of UGIB in patients on NSAIDs, with relative risks of 12.8 and 11 respectively compared to a risk of 4.3 with NSAIDs alone (Masclee et al. *Gastroenterology* 2014;147:784-92.)