

Combining NSAIDs and Bisphosphonates

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Many patients taking bisphosphonates, such as alendronate, etidronate, ibandronate, and risedronate, for osteoporosis may also be taking various nonsteroidal anti-inflammatory drugs (NSAIDs) for arthritis or other disorders. Whereas both of these drug classes can separately cause gastrointestinal (GI) toxicity, it is important to determine if the combination can have additive negative effects on the GI tract.

In a recent report of rheumatoid arthritis patients receiving NSAIDs for at least 3 months with or without concurrent therapy with bisphosphonates, GI ulcers occurred in 17% of patients on NSAIDs without concurrent bisphosphonates, and in 31% of patients receiving bisphosphonates with NSAIDs.¹

The results of previous studies have been conflicting, so we will address possible reasons for the disparate results and make suggestions on how these interactions might be handled.

THE PUBLISHED STUDIES

In a randomized crossover study, 26 healthy volunteers were given alendronate 10 mg/day, naproxen 500 mg twice a day, or the combination, with each treatment lasting 10 days.² Gastric ulcers (based on endoscopy) occurred in 8% of subjects after alendronate alone,

12% after naproxen alone, and 38% after the combination. This study is consistent with the study cited above and suggests a substantial increase in the risk of GI ulcers when combining NSAIDs with bisphosphonates.

Conversely, some other studies looking at upper GI bleeding or other GI adverse effects did not find an increase in GI toxicity when bisphosphonates were combined with NSAIDs, compared with NSAIDs alone.³⁻⁵ One of these studies involved the use of once-weekly alendronate, and it is possible that this reduced the likelihood of additive effects with NSAIDs.⁴

At first glance, it might appear that the positive and negative studies cannot be reconciled, but because the studies differed so widely in design, the results may not be as inconsistent as they initially appear. The most obvious difference is that the studies used different end points. The 2 studies finding additive GI toxicity both used endoscopy to look for ulceration, while the negative studies looked instead at many other factors, including GI bleeding and a wide variety of GI symptoms.

Nonetheless, while it is possible that only GI ulcers are increased, and not most other GI adverse effects, one would expect that more ulcers would lead to more bleeding and perforation. More information is needed to sort out this issue.

Not all studies controlled for concomitant use of proton pump inhibitors (PPIs) or other drugs that may reduce the likelihood of GI adverse effects. The effect of

factors that *increase* the risk of GI ulcers (such as smoking and old age) was also not consistently considered in the studies. There were also wide differences in study design: prospective, retrospective, case-control, post hoc analysis, and large clinical trial.

Overall, the evidence suggests that taking NSAIDs and bisphosphonates concurrently probably increases the risk of GI ulcers, at least in the short term. The effect of the combination on other types of GI toxicity requires additional study.

RECOMMENDATIONS

As with many drug interactions, we do not have enough high-quality data to make a definitive assessment of the risk of giving bisphosphonates with NSAIDs. Nonetheless, we should still take action based on the information we do have.

- Patients taking bisphosphonates should be advised not to take OTC NSAIDs for minor problems such as colds and minor aches and pains. Acetaminophen might be preferable in such cases.
- It is not known if using less than daily administration of bisphosphonates reduces the risk of additive GI toxicity when combined with NSAIDs, but theoretically it might.
- In patients taking bisphosphonates who require long-term therapy with NSAIDs, preliminary evidence suggests that PPIs may reduce the risk of ulcers. Nonetheless, there is not enough evidence to recommend that these patients be routinely given prophylactic PPIs. **PT**

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