

Risk Stratification in Decisions about Nonsteroidal Anti-Inflammatory Drug Cotherapy

Summary

Successful application of risk stratification in decisions about nonsteroidal anti-inflammatory drug (NSAID) therapy could enable patients with a lower baseline risk of gastrointestinal (GI) complications to take a nonspecific generic NSAID and those with greater risk of GI complications to take the cotherapies.

Complications of nonsteroidal anti-inflammatory drug (NSAID) therapy can result in significant rates of morbidity, and even mortality, as well as increase the cost of care. The frequent occurrence of major gastrointestinal (GI) tract complications has led physicians to prescribe a cyclooxygenase-2 (COX-2)-selective NSAID, or misoprostol plus a traditional NSAID, which incurs a much greater cost than a nonspecific, generic NSAID. If risk stratification could be successfully applied to the widely prescribed NSAIDs, then patients with a lower baseline risk for GI complications could receive a nonspecific, generic NSAID and only those with a higher risk for GI complications could receive the more costly cotherapies. © Medical World Communication

Categories of Risk Reduction

Relative risk reduction, absolute risk reduction, and number needed to treat (NNT) are 3 key concepts that researchers use to determine the level of risk reduction that could be expected from a particular therapy. *Relative risk reduction* is

the decreased risk of an adverse outcome in the treatment group compared with the risk in the control group. This reduction is calculated by subtracting the percentage of adverse outcomes experienced in the treatment group from the percentage in the control group and dividing the result by the percentage in the control group. Bombardier et al¹ (Vioxx Gastrointestinal Outcomes Research [VIGOR] Study Group) compared the incidence of upper GI complications in rheumatoid arthritis patients randomly assigned to receive either rofecoxib, a COX-2-selective NSAID, or naproxen, a nonselective NSAID. In the VIGOR trial, the reduction in the relative risk of GI events was 67% in the rofecoxib group, a significant reduction. Surprisingly, the same degree of relative risk reduction was found in the rofecoxib subgroups who were at a higher baseline risk for major GI complications as well as subgroups at a lower baseline risk. *Absolute risk reduction* represents the actual reduction in adverse outcomes between the group of patients receiving treatment and the control group. It is calculated by subtracting the percentage of adverse outcomes in the treatment group from the percentage in the control group. Absolute risk reduction values resulting from the use of cotherapy with proton pump inhibitors or misoprostol vary greatly among patients taking NSAIDs, depending on the patient's baseline risk. For example, Silverstein et al² reported on the effectiveness of misoprostol for the prevention of major GI complications in patients who had experienced GI symptoms during NSAID therapy. In

the group who received NSAIDs alone, the risk of GI complications was 0.74%, compared with a 0.36% risk of major GI events over a 6-month period in the groups who received NSAIDs and misoprostol cotherapy. The absolute risk reduction for cotherapy is 0.38%, compared with a relative risk reduction of 50%.

The third factor, NNT, is the number of patients who must be treated with the therapy in question to prevent 1 additional adverse outcome over a given period of time. The NNT is the reciprocal of the absolute risk reduction value. Thus, in the misoprostol regimen trial,² where the absolute risk reduction was 0.38%, the NNT would be the reciprocal of 0.0038, or 263. That is, 263 patients taking NSAIDs would have to receive misoprostol cotherapy to prevent 1 major GI complication over a 6-month period.

Additionally, NNT can be used to perform a crude cost analysis of therapeutic alternatives. Based on the average wholesale price of misoprostol and naproxen therapy for a 6-month period, it would cost an additional \$250,000 to prevent 1 complication in this group of 263 patients.

Assessing Risk in NSAID Therapy

The US Food and Drug Administration estimates the annual incidence of a complication with NSAID therapy to be between 1% and 4%. For clinicians, issues arise as to how to assess the risk of complications not in an entire population but in an individual patient. Every patient has a different baseline risk, and only if that risk can be accurately assessed can risk stratification be safely applied.

Studies have identified several factors that increase the risk for a major GI complication in patients taking NSAIDs. Silverstein et al² identified 4 factors: patient age over 75 years, history of peptic ulcer disease, history of GI bleeding, and history of cardiovascular disease. In patients with none of these factors, the baseline risk of complications was 0.4%. With 1 factor, it increased to 1%, and for patients with all 4 factors, the risk rose to 9%. Another study of the risk of upper GI bleeding in patients taking NSAIDs found

the relative risk overall was 4.7.³ If the patient was taking high-dose NSAIDs, the relative risk rose to 7, and for those taking NSAIDs and anticoagulants, 6.4. If the patient was older than 70 years, the relative risk was 5.6, and with a history of a previous bleeding ulcer, 13.5. According to Garcia-Rodríguez and Jick,³ the risk factors are individual and independent, but not additive.

The duration of NSAID therapy does not appear to be of predictive value in determining if this patient is likely to be among the 1% to 4% of patients who will experience a complication in 1 year, or the 96% to 99% who will not.

To assess a patient's risk of GI complications from NSAID use, a clinician must first establish the presence or absence of 1 or more risk factors, which can be accomplished by taking an accurate history. Yet the process of taking a history has its limitations. Roter and Hall⁴ found that physicians manage to obtain accurate histories only about 50% of the time. Although increased training can improve their performance, patients may be unable or unwilling to provide the physician with accurate information. For example, in a study of patients with GI bleeding, the researchers sought chemical evidence of either aspirin or NSAID use⁵; 80% of the patients had such evidence, but, even with careful questioning, 20% of patients proven to have taken aspirin or NSAIDs denied such use.

The duration of NSAID therapy does not appear to be of predictive value in determining if this patient is likely to be among the 1% to 4% of patients who will experience a complication in 1 year, or the 96% to 99% who will not. Furthermore, upwards of 80% of NSAID-associated com-

plications are not preceded by any warning symptoms, making it impossible for the clinician to stop the NSAID before a complication occurs.

Undoubtedly, prescribing generic, non-specific NSAIDs for patients with low risk of complications would be an effective cost-saving measure. Unfortunately, however, an accurate assessment of an individual patient's risk, crucial to deciding who should receive generic NSAIDs, is difficult, if not impossible. Even without factoring in risk versus cost, healthcare professionals appear to have difficulty determining the appropriate use of NSAIDs.

Summary

With healthcare costs in the United States continuing to rise, researchers seek ways to reduce costs without negatively impacting patient outcome. Risk stratification may eventually be an effective tool to guide choices in NSAID therapy if and when physicians can confidently assess

their patient's risk. Until then, many would argue that all patients must be treated as if they are at risk for an NSAID complication.

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