CRA Diclofenac Position Statement

Preamble

On October 6, 2014 (updated October 14, 2014) Health Canada issued a Summary Safety Review concerning diclofenac and the risk of major heart and stroke related adverse events.[1] The review covers diclofenac-containing products in tablet and suppository forms (Voltaren, Voltaren SR, Voltaren Rapide, Arthrotec, and generic equivalents). The review was prompted by "the results of a study published in the scientific journal, The Lancet (Bhala et al, 2013). This study indicated that diclofenac increases heart and stroke related adverse events more than other non-steroidal anti-inflammatory drugs (NSAIDs) and comparably to cyclooxygenase 2 (COX-2) inhibitors, a subgroup of NSAIDs which includes celecoxib."

Health Canada's review concludes that diclofenac is associated with an increased risk of heart and stroke related adverse events that is comparable to COX-2 inhibitors, and that this risk should be considered when prescribing or taking diclofenac. To reduce this risk, Health Canada has added additional information to prescribing information:

1) Specifying that diclofenac at a higher dose (150 mg per day) is associated with an increased risk of heart and stroke related adverse events that is comparable to COX-2 inhibitors;

2) Reducing the maximum daily dose for diclofenac from 150 mg to 100 mg for all indications, excluding VOLTAREN RAPIDE which allows for a 200 mg dose only on the first day of treatment for dysmenorrhea; and,

3) Recommending that for patients with a high risk of developing a heart and stroke related adverse events, other treatment options that do not include NSAIDs, particularly COX-2 inhibitors and diclofenac, should be considered first.

Summary of Study Reported by Bhala et al.[2]

This metanalysis deals with the risks of cardiovascular and gastrointestinal events and deaths with the use of high-dose COX-2 inhibitors, diclofenac, and naproxen compared to placebo. The authors relied on randomized, placebo-controlled trials in which at least 4 weeks of drug use were included. However, the trials compared COX-2 inhibitors to placebo and COX-2 inhibitors to a traditional NSAID (tNSAID), either diclofenac 75 mg twice daily or naproxen 500 mg twice daily. In order to estimate the rate ratios for cardiovascular and gastrointestinal events and deaths for diclofenac or naproxen versus placebo, the authors first determined the rate ratios for cardiovascular and gastrointestinal events and deaths for COX-2 inhibitors versus placebo, and then for COX-2 inhibitors versus diclofenac or naproxen. With these rate ratios determined, they indirectly calculated the rate ratio for diclofenac versus placebo and naproxen versus placebo. They show the formula used, and the justification for its use, in their Statistical Analysis.

To these indirectly determined rate ratios for diclofenac versus placebo and naproxen versus placebo, they added any available directly determined rate ratios. That is, the final rate ratios were determined by combining estimates obtained directly (from the small number of trials including this comparison) with these rate ratios estimates obtained indirectly (from the comparison of trials of COX-2 inhibitors versus tNSAID with trials of COX-2 inhibitors versus placebo).

In absolute terms, using this methodology, the authors state that there is an absolute increase of 3 additional cardiovascular events per 1000 patients using high-dose diclofenac versus placebo. They found no increased risk with high-dose naproxen versus placebo. Of these 3 additional events, they found an absolute risk also of 1 fatal event. The authors also report that most of the risk was mainly attributable to an increase in major coronary events. Contrary to the assertion from the Health Canada Summary Safety Review, Bhala et al. report that there was no increased risk for stroke with any of the NSAIDs studied.

The authors do state that this major vascular event risk can be stratified. They demonstrate this by examining the increased number of events expected (annual excess risk) according to baseline cardiovascular risk. They report, for example, that in a cohort of patients with a 2.0% baseline risk per annum of a major vascular event, the use of high-dose diclofenac confers a risk of an additional 10 major vascular events per 1000 patients. On the other hand, in a cohort of patients with a 0.5% baseline risk per annum of a major vascular event, the use of high-dose diclofenac confers a risk of only an additional 2 major vascular events per 1000 patients.

What this Study Adds

1. The absolute excess risk with high-dose diclofenac is small. It is an increase of 3 major vascular events per 1000 patients versus the number of events expected with placebo. That is, there is a 99.7% chance that the patient on diclofenac will experience *no* increased number of events compared to having been on placebo.

2. The absolute risk can be further reduced by avoiding diclofenac usage in those with a higher baseline risk of major vascular events.

3. Naproxen 500 mg bid was not associated with an increased risk of major vascular events.

4. There was no increased risk for stroke with any of the NSAIDs studied.

What This Study Does Not Add

1. The rate ratio estimates for cardiovascular and gastrointestinal events and deaths with the use of high-dose diclofenac and naproxen are not directly determined in this study. They are, for the most part, derived by indirect means, as described above.

2. There is no determination of whether the increased risk of events is different for different diclofenac preparations, though observational studies suggest that there is no difference.[3]

3. There is no determination of whether there is an effect of total cumulative dosage, duration of use, or continuous versus intermittent use of diclofenac on the risk of events.

4. There is no determination in this study of a dose-dependent relationship between events and diclofenac usage. That is, it has not been shown in analysis of randomized controlled trials that 100 mg per day of diclofenac is safer than 150 mg per day. However, observational studies have indicated that the risk is indeed dose-dependent.[3]

Incorporating the Data into Practice

Accepting the limitations of the methodology used, and the questions that remain unanswered, below is a suggested approach to the use of diclofenac in chronic pain patients (also see algorithm).

1. Ask patients who are using diclofenac for at least 4 weeks if they feel they derive benefit from the usage. If not, discontinue usage and reassess if there truly remains a need for diclofenac.

2. Review and ensure that there has been optimal use of evidence-based non-pharmacological treatments (including application of heat or cold, exercise, weight-loss or self-management programs, braces and orthotics), corticosteroid injections, NSAID or non-NSAID topical treatments, or NSAID regimens that minimize risk, using the lowest-risk agents at lowest dose for short periods.

3. Assess baseline major vascular event risk. If the baseline risk is 0.5% per annum or lower, the additional risk with high-dose diclofenac usage is much lower. Bhala et al. consider this observation to be a key objective of their study. For higher baseline risks, the patient should either be informed of the absolute excess risk of high-dose diclofenac should they wish to continue it, or they should discontinue usage.

   There is no evidence from metanalyses of randomized controlled trials yet that reducing the diclofenac dosage protects the patient, though there are observational studies that support this approach in the sense that they show that risk ratios for low-dose diclofenac use are intermediate (between the risk ratios for placebo and high-dose diclofenac).[3] Thus, reducing the diclofenac dose to a total of 100 mg daily is an option. An alternative choice, further supported by the study by Bhala et al., is naproxen 500 mg twice daily.

References

1. http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/review-examen/diclofenac-eng.php

2. Coxib and traditional NSAID Trialists' (CNT) Collaboration, Bhala N, Emberson J, Merhi A, et al. Vascular and upper gastrointestinal effects on non-steroidal anti-inflammatory drugs: meta-analyses of individual participant data from randomised trials. Lancet 2013; 382(9894):769-79.

3. McGettigan P, Henry D. Cardiovascular risk with non-steroidal anti-inflammatory drugs: systematic review of population-based controlled observational studies. PLoS Med 2011; 8: e1001098.