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Non-steroid anti-inflammatory drug use and increased risk of cardiac arrest: is misrepresentation of information more harmful than no information, *primum non nocere*

Felix Ram, Elissa McDonald

Due to the recent media coverage¹⁻² in New Zealand of a Danish retrospective case-control study³ and the risks of out-of-hospital cardiac arrest (OHCA) with the use of non-steroidal anti-inflammatory drugs (NSAIDs) and COX-2 selective inhibitors, we felt obliged to highlight some of the fundamental shortcomings of this study to help alleviate the fear of prescribing NSAIDs.

When reading the Sondergaard article it is important to note the fact that no doses of NSAIDs are reported in the study. However, references used to discuss study results referred to trials investigating high-dose treatment only (ie, 2,400mg ibuprofen), which is considerably higher than dosages used in daily practice, and which is not recommended in the medicine datasheet available on the Medsafe website,⁴ with 1,200mg to 1,800mg being the maximum daily dose.

The authors have used odds ratios (OR) but interpreted the results as relative risks (RR). This is permissible if the event rate is relatively low (<10%) in both the case and control groups and when OR will approximate RR. However, Table 2 of the study shows very high event rates 21.8% (diclofenac), 51% (ibuprofen) and 14.2%

(other NSAID). Furthermore, the event rate in the naproxen, celecoxib and rofecoxib are relatively low, 3.1%, 5.6% and 4.5%, respectively. Not only are inappropriate statistics used to analyse this data, but the large imbalance in the event rate between groups makes direct group comparison nonsensical and can provide misleading results favouring the lower event rate outcome, in this case naproxen, celecoxib and rofecoxib. Reasons for this very low event rate are that naproxen is rarely used in Denmark and coxibs are also rarely used, especially after 2006 when coxibs were withdrawn from the market as trials showed unequivocally that they were associated with increased risk of atherothrombotic vascular events.^{5,6}

Furthermore, although the case event rates are reported, it is impossible from the data and additional online information supplied to track how the control event rate was calculated. This missing information has large implications on the findings reported as the risks reported are relative to the control population.

The authors have also failed to provide any power calculation as to the minimum number of patients required for cases and controls. As a result, one is unaware of the minimum number of patients that are

required to provide sufficient statistical power to detect a difference if one exists. Therefore, the possibility of type 1 error (ie, false positive) cannot be ruled out, and thus the study likely incorrectly concluded that NSAIDs appear worse and/or coxibs appear safer, when well conducted trials have convincingly demonstrated the dangers of prescribing coxibs.^{5,6} Due to the lower methodological quality and inherent assumptions of retrospective observational case-control studies (compared to higher methodological quality trials) it is fundamental that case-control studies are able to demonstrate causality. The authors failed to demonstrate causality of association between NSAID and risk of OHCA. That being increasing and/or decreasing doses of NSAID and its impact on effect size (risk of OHCA) has not been demonstrated. Authors attempt to defend the robustness of their results by conducting sensitivity analysis based on case-control analysis at different time points with OR decreasing with time as one would have expected due to the decreasing event rate after the initial hospital discharge. Nevertheless, this sensitivity analysis is not a substitute for demonstrating causality.

We believe that this study by Sondergaard and co-investigators³ has misrepresented information and data on the risk of NSAID's in favour of coxib's by providing incomplete and inappropriate data analysis with fundamental statistical and clinical shortcomings.

The harm to the public from misinformation in this case is much greater than no information. Previously published well-conducted high-quality studies have clearly highlighted the dangers of coxibs for more than 10 years. Systematic review and meta-analysis of randomised trials⁷ and another of observational studies⁸ showed similar increases in cardiovascular risks with coxibs and diclofenac but not Ibuprofen nor naproxen. Therefore, and for valid reasons, both the FDA⁹ and the European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP)^{10,11} had decided many years ago that coxibs (not NSAIDs) were contraindicated in patients with risk of coronary heart disease or stroke and to be used with caution in patients with risk factors for coronary heart disease.

We therefore recommend that prescribers continue to use NSAIDs as per the Medsafe medicine data sheet⁴ (ie, lowest possible dose for the shortest duration) and only as a second line drug after paracetamol for those seeking pain relief. In order to do no harm, we must remember that there are no harmless drugs and that the safest prescription is often no prescription—*primum non nocere*. It is incorrect to state that all patients who seek pain relief require medication; unless it impacts on their lives. Therefore, a careful assessment of the impact of pain is important before any prescription for pain relief is considered.

Competing interests:

Nil.

Author information:

Felix SF Ram, Clinical Pharmacologist, College of Health, Massey University, Auckland; Elissa M McDonald, Lecturer, Faculty of Medical and Health Sciences, University of Auckland, Auckland.

Corresponding author:

Dr Felix SF Ram, Clinical Pharmacologist, College of Health, Massey University, Auckland.
fsfram@yahoo.co.uk

URL:

<http://www.nzma.org.nz/journal/read-the-journal/all-issues/2010-2019/2017/vol-130-no-1456-2-june-2017/7269>

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