

Editorial

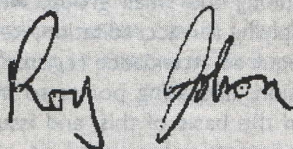
It's tempting to start prescribing a new drug – especially when its advantages are presented in a logical and persuasive way, backed up with articles from reputable journals. When one is presented with a bewildering array of figures, 'p' values, odds ratios, 95% confidence intervals and other calculated data, it's sometimes difficult to know quite what is relevant and what is not. I am not going to do this.

Can you always remember how to work out the sensitivity or specificity of a test for example – and which represents false negatives or false positives? Can you always remember how the 'positive predictive value' is calculated?

Most people who are not working with these figures on a daily basis are probably going to need a reminder of what they mean and how they are derived. I am not going to do this.

I have borrowed heavily from the Therapeutics Letters in this edition – they are published by the Therapeutics Initiative of the University of British Columbia, Vancouver, Canada. The banner on their website reads: 'Evidence Based Information on Drug Therapy' see: <<http://www.ti.ubc.ca/index.html>> [Accessibility verified 25/02/2002]

If you would like to subscribe to the 'Druginfo' list to which I refer – it is hosted by healthlink.org.za. Follow the instructions on the webpage <<http://www.hst.org.za/info/hllists.htm>> [Accessibility verified 25/02/2002]. You will find a number of interesting e-mail lists in which you can participate should you wish to.



Roy Jobson

“TO PRESCRIBE OR NOT TO PRESCRIBE?”

The advent of evidence based medicine has brought some new terminology and new calculations which Family Physicians are likely to encounter. But do they make any difference to the way we practice?

Consider the following three choices for drugs that reduce a cardiac risk factor (e.g. hypercholesterolaemia) with minimal side-effects, over five years.

Choice A.

Patients taking this drug for 5 years have 34% fewer heart attacks than patients taking placebo;

Choice B.

2.7% of the patients taking this drug for 5 years had a heart attack, comparing to 4.1% taking a placebo, a difference of 1.4%;

Choice C.

If 71 patients took this drug for five years the drug would prevent one patient from having a heart attack. There is

no way of knowing in advance which person that might be.

Question 1

Which of the above drugs would you choose if you had a cardiac risk factor (e.g. hypercholesterolaemia) that needed drug therapy?

Answer 1

This is actually a trick question. These are just three different ways of presenting the same information about the same drug from the same trial.

The first choice is presented as the 'relative risk reduction' (RRR).

The second choice is presented as the 'absolute risk reduction' (ARR)

The third choice is presented as the 'number needed to treat' (NNT)

If we go back to the original trial (a randomised double blind study) and look at the actual numbers, we find that a total of 4081 patients were divided into two groups: 2030 received placebo and 2051 received the active drug. Of the placebo group, 84 had a heart attack after 5 years; and of the treatment group 56 had a heart attack after 5 years. So in simple percentage terms, 4.1% of the placebo group had a heart attack, compared to 2.7% of the active treatment group. By subtracting we get a figure of 1.4% – the ARR. (Choice B) However if we divide the active group by the placebo group we get the ‘relative risk’: in this case ‘0.66’, or 66%. The ‘RRR’ is therefore 34% (Choice A). So how do we derive the NNT? This is done by dividing the percentage ARR (1.4%) into 100 and rounded off to the nearest whole number (= 71, Choice C).

In simplified terms:

- (a) Relative risk (RR) = Event rate (Drug A) / Event rate (Drug B)
- (b) Relative risk reduction (RRR) = 1 – relative risk x 100
- (c) % Absolute risk reduction (ARR) = %Event rate (Drug B) – %Event rate (Drug A)
- (d) Number needed to treat (NNT) = 100/ %absolute reduction

Note:

- 1. ‘Drug B’ in these examples could be placebo.
- 2. If the RRR is a negative number, then in fact it is a ‘relative risk increase’ (RRI), and likewise a negative %ARR would become the ‘% absolute risk increase’ (ARI).
- 3. These are not actuarial calculations.
- 4. Benefits in clinical trials are often presented in trial reports and advertisements as RR (relative risk) or RRR: these can often be misleading to clinicians and patients.¹

The NNT is becoming an increasingly useful way of thinking about and describing results of clinical trials and of systematic reviews or meta-analyses. But don’t be fooled by the word ‘treat’ – in Family Medicine language we would probably use the word ‘manage’ because of its broader perspective.

One way of clarifying the concept is to add a verb to the NNT. For example: The NNT ‘to cure/control’ a condition. This should logically be a small number if the management is effective. (E.g. I only need to treat one patient to achieve one cure. This would be particularly important in acute life-threatening diseases such as meningococcal meningitis.)

Another example would be the NNT ‘to prevent’ a condi-

tion, or a complication of a condition. This should logically be a large number. (E.g. Only one patient out of ‘x’ hundred or ‘y’ thousand will contract measles following measles immunisation.)

Every clinical trial records adverse events and serious adverse events (SAEs). In considering these, one would look at the NNT ‘to cause an adverse event or SAE’. The words ‘side effect(s)’ would also be used in this context. In these cases, they are sometimes referred to as the ‘number needed to harm’ or NNH.

Interesting NNT figures are provided in the Therapeutics Initiative ‘Therapeutics Letter’ #15 of 1996.¹ They are all derived from published articles in reputable journals and are specific to those particular trials. Note that extrapolations about other time periods of drug usage cannot reasonably be made from these statements. The original references have not been consulted or checked, but they are provided for those who wish to double check these results.

- 1. One would need to treat 10 patients who have congestive heart failure, with ACE-inhibitors for 6 months, to prevent 1 death or hospitalisation (for CCF).²
- 2. One would need to treat 11 ‘old’ patients who have hypertension, with diuretics and beta-blockers for 5 years, to prevent 1 death or cardiovascular event.³
- 3. One would need to treat 12 patients who have elevated cholesterol and coronary artery disease, with simvastatin for 5 years, to prevent 1 death or cardiovascular event.⁴
- 4. One would need to treat 26 patients who have had a previous myocardial infarction, with long-term beta-blockers for 6 months, to prevent 1 death or non-fatal myocardial infarction.⁵
- 5. One would need to treat 71 male patients who have high cholesterol, with gemfibrozil for 5 years, to prevent 1 cardiac event.⁶
- 6. One would need to treat 111 healthy male doctors with aspirin (dose not stated) for 5 years, to prevent 1 myocardial infarct.⁷
- 7. One would need to treat 263 rheumatoid arthritis patients taking NSAIDs, with misoprostol for 6 months to prevent 1 serious gastrointestinal complication.⁸

What is clear from these examples is that the outcome measure(s) (endpoints) have been clearly stated (e.g. death, hospitalisation, serious gastrointestinal complication, myocardial infarct). One of the problems with many clinical trials these days is that ‘surrogate endpoints’ are often used with the sometimes unproven assumption that the surrogate endpoint sufficiently represents an outcome. For example, in treating peptic ulcer disease with a

proton pump inhibitor, surrogate endpoints may be symptom assessment, reduction of gastric acid, or endoscopically assessed healing of mucosal lesions, but the outcome measures that may actually differentiate the PPI from a simple antacid might only be at the level of serious gastrointestinal complications such as haemorrhage or perforation of an ulcer. Another example is to measure lipid levels as a surrogate end point, when the outcome you're really interested in is the rate of myocardial infarction.

[Something to think about: What is the outcome measure for antiretroviral therapy? Are viral loads and CD4 counts surrogate endpoints or 'real' outcomes?]

The importance of the time-frame may make a significant difference to the results of trials. As a rule of thumb, the longer the trial and the more people enrolled as trial participants, the better the quality of the results will be. (This is in addition to issues of randomisation and blinding.) Part of the rationale for multicentre studies, and the increasingly important role of systematic reviews, is for this very reason.

A real-life example

An article published in the Journal of the American Medical Association (JAMA) in September 2000 reported on 'Gastrointestinal Toxicity With Celecoxib vs Nonsteroidal Anti-inflammatory Drugs (NSAIDs) for Osteoarthritis and Rheumatoid Arthritis'.⁹ The main outcome measures were: *Incidence of prospectively defined symptomatic upper GI ulcers and ulcer complications (bleeding, perforation, and obstruction) and other adverse effects during the 6-month treatment period.* (My emphasis)

The conclusion states: *In this study, celecoxib, at dosages greater than those indicated clinically, was associated with a lower incidence of symptomatic ulcers and ulcer complications combined, as well as other clinically important toxic effects, compared with NSAIDs at standard dosages. The decrease in upper GI toxicity was strongest among patients not taking aspirin concomitantly.*

This is clearly an important study because of the general need for NSAIDs with a lower incidence of side-effects. Selective cyclo-oxygenase inhibitors (COX-2 inhibitors) would seem to fill this role, particularly considering the above conclusion.

Just over a year later, in the letters to the editor column of JAMA,¹⁰ it was pointed out that once all the data were considered, a different – possibly contradictory – picture was apparent. The data for the study are publicly available on the FDA website,¹¹ and quoting the FDA reports, the authors of the letters state that: (i) *[a]lthough complicated ulcers were the primary outcome in documents submitted to the FDA, the published study also included symptomatic ulcers.* [see above]

(ii) *the published CLASS trial differs from the original protocol in primary outcomes, statistical analysis, trial duration, and conclusions. In particular, the unpublished data show that by week 65, celecoxib was associated with a similar number of ulcer complications as diclofenac and ibuprofen* (iii) *[t]he trend toward an increased risk of serious adverse events, particularly with celecoxib long-term therapy, is particularly concerning. The unfortunate result of the selective and partial reporting of the CLASS study is that it could mislead physicians and patients. Until there is a better understanding of the risk of serious adverse events with COX-2 selective drugs, these drugs should be prescribed with caution.*¹⁰

As is customary, the authors of the original paper were asked to respond and in the concluding paragraph of their letter they state: *After adjusting for duration of exposure, the relative risk of all serious adverse events with celecoxib compared with NSAIDs at 12 to 16 months was comparable to the relative risk at 6 months.*¹⁰ (my emphasis)

So who and what do we believe?

Fortunately our colleagues of the Therapeutics Initiative did all the hard work for us, and have published their own critique of the study with their analysis of the results published on the FDA website.¹²

They state: *The FDA data reveal that the CLASS study as published in JAMA, ... reported only the first six months of data from two trials of longer duration. One of the trials was a 15-month trial comparing celecoxib with ibuprofen and the other was a 12-month trial comparing celecoxib with diclofenac. Both the six-month and full trial data are provided in the FDA review. The published VIGOR trial duration and GI outcome data are the same as that found on the FDA website, but the FDA report is more complete and provides overall serious adverse event data.*¹²

In tabulating their calculations, apart from the original category of 'complicated ulcers' there are two other categories of results to which the Therapeutics Initiative team draw our attention: 'total serious adverse events' and 'other serious adverse events'.

- a) In the data comparing celecoxib and other NSAIDs at 9 months, [CLASS trial] the difference between the groups in terms of
 - i) 'complicated ulcers' was non-significant (celecoxib was no better than other NSAIDs);
 - ii) 'total SAEs' was non-significant (celecoxib was no better than other NSAIDs);
 - iii) 'other SAEs' – showed an absolute risk increase (ARI) of 1% and the NNH (number needed to treat to cause one harmful event) was 100 (i.e. celecoxib was worse than other NSAIDs).

From the letters quoted we can deduce that the 'other NSAIDs' were ibuprofen and diclofenac.

- b) In the data comparing rofecoxib and naproxen at 9 months, [VIGOR trial] the difference between the groups in terms of
- 'complicated ulcers' – showed an ARR of 0.52% (rofecoxib was better than naproxen)
 - 'total SAEs' – showed an ARI of 1.5% and NNH of 67 for rofecoxib (rofecoxib was worse than naproxen);
 - 'other SAEs' – showed an ARI of 1.9% and NNH of 53.¹² (rofecoxib was worse than naproxen).

What this does not tell us is what the nature of the SAEs were. The authors conclude:

*The reason for the increased incidence of serious adverse events with the COX-2 selective inhibitors can not be completely answered from the available FDA data. SAEs are more completely reported in the FDA VIGOR report than the FDA CLASS report. Myocardial infarction (RR=4.9 [1.7-14.3], ARI=0.4%, NNH=250) and adjudicated thrombotic cardiovascular events (RR=2.38 [1.39-4.00], ARI=0.6%, NNH=167) are increased with rofecoxib as compared to naproxen. **However, none of the reported individual or combined outcomes explain the overall 1.0-1.9% absolute risk increase of other serious adverse events associated with either celecoxib or rofecoxib.** (Their emphasis) Before making a claim of a safety benefit over a comparator, the total % SAEs should be less than that observed with the comparator. For example, rofecoxib as compared to naproxen reduced complicated ulcers (ARR=0.5%) leading to a claim of a safety benefit, but the magnitude of this benefit is outweighed by the harm associated with rofecoxib in terms of other SAEs (ARI=1.9%).¹²*

Question 2

What would you tell your patient with osteo- or rheumatoid arthritis needing an NSAID based on this evidence?

Answer 2

- a) After taking celecoxib in preference to other NSAIDs for 9 months, she or he has the same chance of developing a complicated [peptic] ulcer, but more chance of a serious adverse event – which cannot clearly be defined at this stage.
- b) After taking rofecoxib in preference to naproxen for 9 months, she or he has less chance of developing a complicated [peptic] ulcer, but more chance of a serious adverse event, which may include a myocardial infarct or a thrombotic cardiovascular event.

Note: There is no significant improvement in efficacy of the COX-2 inhibitors compared to other NSAIDs.¹³

It's all very well looking at evidence from overseas countries published in international journals, but what is the situation in South Africa?

The following information was provided to the 'Druginfo' list by Dr Ushma Mehta of the National Adverse Drug Event Monitoring Centre – NADEMC:¹⁴

7 reports of adverse reactions associated with celecoxib and 40 reports associated with rofecoxib. (Please note that this does not mean that rofecoxib is more unsafe than celecoxib.)

The breakdown of reports are as follows:

Celecoxib:

- 3 reports of gastrointestinal bleeding (1 fatal due to cardiac arrest)
- 1 interaction with warfarin
- 1 nephrotic syndrome, proteinuria and ankle oedema
- 1 rash, oedema, urticaria
- 1 toothache

Rofecoxib:

- 3 deaths (1-sudden death, 1-pulmonary embolism & renal failure, 1-GIT bleed)
- 11 cardio vascular reports (including 2-hypertension, 1-chest pain, 2 TIA's, 1 cardiac arrest, 1 arrhythmia, 4 cases of cardiac failure with concomitant increased blood pressure in 3 cases) – these cases exclude the reported deaths.
- 6 gastrointestinal bleeding (1 epistaxis, 1 rectal haemorrhage, 2 peptic ulcer haemorrhages, 1 melana, 1 GIT bleed)
- 5 generalised oedema
 - 1 aggravated varicose veins
 - 1 asthma
 - 1 decreased hearing with tinnitus
 - 1 spasms
 - 1 confusion and hallucinations
 - 1 paraesthesias
- 4 abdominal distension, discomfort or pain or oral ulceration or heartburn (without report of bleeding)
 - 1 breath shortness and dizziness in a hypertensive patient
 - 2 dyspnoea with erythema in 1 case, and facial oedema in another

Please note that these reports do not necessarily suggest a direct causal relationship, nor do they provide any indication of frequency of the reaction occurring in our population.

So we don't really know what the situation is in South Africa, but this highlights the need for each of us to be alert to adverse drug reactions and to report them to the NADEMC!

The last cautionary word goes to our colleagues at the Therapeutics Initiative, and it is their final statement that we most need to take to heart:

- *Based on FDA data from the CLASS and VIGOR studies, **COX-2 selective inhibitors are associated with an increased incidence of serious (life-threatening) adverse events as compared to non-selective NSAIDs.*** (their emphasis)
- *Published versions of the CLASS and VIGOR trials focused on GI events and failed to report other serious adverse events fully.*
- ***In the interests of public safety, serious adverse event rates from all trials must be published.***¹² (their emphasis)

It is heartening to know that the monitoring of SAEs is one of a myriad of functions of the SA Medicines Control Council that is being actively addressed. A pharmacovigilance unit for SAEs is in the process of being established as a sister unit to the NADEMC (which specialises more particularly in 'adverse drug reactions' – ADRs).

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