Author's response to reviews

Title: Cyxlo-oxygenase-2 selective inhibitors and nonsteroidal anti-inflammatory drugs: balancing gastrointestinal and cardiovascular risk

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Version: 3 Date: 27 June 2007

Author's response to reviews: see over
Dear Editor

MS: 6953365811089668

Cyxlo-oxygenase-2 selective inhibitors and nonsteroidal anti-inflammatory drugs: balancing gastrointestinal and cardiovascular risk
R Andrew Moore, Sheena Derry and Henry J McQuay

We would like to thank Angel Lanas and Leslie Cleland for taking time again to look at this paper. While Angel was satisfied with our response to their original comments, Leslie was not. We have again tried to respond positively, but it is inevitable that we will again fail to satisfy him, for reasons that we hope will be clear in the paper and our response. In our responses we have included information from the MEDAL programme, and updated any calculations accordingly.

Leslie Cleland

There are a number of points mentioned, and the following outlines our answers:

1. Confounding factors in randomised trials are between-trial issues (differing patient populations, or level of comorbidity, or drug use). Since our approach compares absolute rates of two different events in essentially the same population, confounding is not really an issue. However, confounding could reflect on some differences between trials. Aspirin is known not to effect the balance of cardiovascular event rates between coxibs and NSAIDs from the Kearney meta-analysis in the BMJ in 2006. However, for completeness we have added a different analysis of myocardial infarction rates in the large RCTs with information from the MEDAL programme. With about 320 events in total, more than the Kearney, in predominantly longer duration trials than those in the meta-analysis, and with a single, simple, outcome, it could be regarded as better than the APTC outcome. Anyway, it gives the same result – no major effect of aspirin on the coxib/NSAID balance. There may be other arguments to be made, subject to all the problems associated with sub-group analysis, but this is not the place.

2. Whether the population in these trials has a low CV risk is an interesting question. The absolute risk was about 1% a year – or 10% over 10 years. The Kearney meta-analysis demonstrates that in populations with much higher risk (above 20% over 10 years) there was no difference between coxibs and NSAIDs in terms of cardiovascular risk, and if there was any difference it was in populations with lower cardiovascular risk (5% over 10 years). This confirms some observational studies, and perhaps the aspirin analysis above, where any excess risk was in those not taking low dose aspirin
with demonstrable lower risk. Again, though, these are fine points of
detail about which there is no agreement and much debate. Any effects
are in any case small and we do not think this is the place to rehearse
them.

3. Any “corruption” of the literature has been discussed elsewhere in
much detail and heat, and is not germane here, where the approach is
one of method – taking an absolute rather than relative risk approach.

4. There is no answer to the accusation of being somehow bought and
influenced by Pfizer. It’s an unanswerable accusation, used perhaps
where other arguments fail. We are content to rest with a policy we
have used for many years – that of working with funding organisations
where we have the absolute right to publish. We believe our record of
method development, of pointing out possible misbehaviour, and of
working with companies to bring otherwise unpublished data into the
public domain speaks for itself.

5. We make a point about the mortality of gastrointestinal versus
cardiovascular events. What we say about morbidity is this:
Subjectively, of course, heart attack or stroke may seem to be more
serious than gastrointestinal bleeding, but there is little objective
evidence that this is the case. We think that a conservative statement,
and would change it in the face of evidence to the contrary.

6. On fish oil, we refuse to be moved. Our intention was not a tour
d’horizon of all possible therapies, but a limited look at the singular
evidence for coxibs and NSAIDs where there is beginning to be a
sufficiency of evidence to look at rare but serious events in a different
way. For no other therapy are we aware of a sufficiency of information
to do this. Where events are rare, and differences between event rates
small, the number of subjects needed in studies to have any idea of the
direction let alone the size of the difference runs into the tens of
thousands. We do not have that information for fish oil, or rose hip
extract, or homeopathy, or acupuncture, or even most conventional
therapies. We do add some paragraphs and references to emphasise
that general point, but do not feel the need to change the whole tone of
the paper into a panegyric on fish oil, where Tom Chalmer’s 1995
meta-analysis which included 395 patients has only been added to by
fewer than 100 patients in RCTs subsequently. We do not think that we
need to spend much space on this point in the paper, and while Leslie
seems to want to pick a fight with us, we are not seeking to pick a fight
with him.

This paper was originally submitted in July 2006, and revised fairly promptly
in November 2006. It is now late June 2007, and while input from referees has
helped us improve the manuscript, and we are grateful for that, there is no
substantive change over the past year to justify what has been an
unconscionable delay. We understand the editorial dilemma, but at some
stage decisions have to be made; the situation of significant disagreement
between reviewers is not uncommon; and the peer review process has known flaws. We would have appreciated less delay.

We have updated the information in the paper to take account of publications that have occurred over the past year, none of which has substantially altered the thrust of the arguments. We are aware that several other papers have examined benefits and risks, though none, to our knowledge, has used the approach of absolute risk in RCTs.