Correspondence

Lessons in drug development

To the Editor:

There are indeed many implications arising from the recent problems surrounding the use of cyclooxygenase (COX) 2 inhibitors. However, it is an oversimplification to suggest that less selective non-steroidal anti-inflammatory drugs (NSAIDs) do not increase cardiovascular risk with long term use.¹

The literature is certainly complex and at times conflicting in its overall message - confounded by difficulties between studies of the patients' baseline cardiovascular risk, age, drug dosage, concomitant use of low-dose aspirin, duration of dosing, possible use of over the counter analgesic remedies and different underlying pathologies. Nevertheless some (reasonably) firm conclusions can be made:

1. Many studies have shown increased cardiac events,^{2,3} primarily thrombotic in nature, in patients taking COX 2 inhibitors compared to placebo or non-selective COX inhibitors.

2. Some studies have suggested that some COX 2 inhibitors are worse than others e.g., rofecoxib compared to celecoxib^{4,5} perhaps related to their degree of COX selectivity. Lumiracoxib seems not to be associated with increased cardiac risk.⁶

3. Many studies also show increased cardiovascular risk with the COX 1 inhibitors⁷⁻⁹ - at times comparable to the increased risk associated with COX 2 inhibitors.

4. Patients still die from gastrointestinal complications - more so with the less selective NSAIDs.

The imbalance created by the COX 2 mediated suppression of the vasodilator prostaglandin and the lack of suppression of the vasoconstrictor thromboxane A₂ (the major COX 1 product of platelets causing platelet aggregation and vasoconstriction) has been suggested to explain the increased thrombotic complications, but this in itself does not explain the increased risk seen with non selective drugs. Other cardiac effects may do so. All NSAIDs are associated with worsening of hypertension control and probably increased risk of developing hypertension. In addition, fluid retention, renal dysfunction and increased edema will increase the likelihood of developing or worsening heart failure.

Lessons in drug development to be learned should include rigorous evaluation or reevaluation of the risks *vs* benefits of *all* NSAIDs, not just the COX 2 group. In the perioperative setting this should include sensible guidelines on duration of therapy, caution in elderly patients - especially those with heart disease, hypertension or heart failure, possible use of concomitant low-dose aspirin, and an understanding that non-selective COX inhibitors are not necessarily safer.

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References

- 1 *Stafford-Smith M.* Hurry up and slow down: Lessons in drug development from the COX-2 inhibitors. *Can J Anesth* 2006; 53: 973-7.
- 2 *Solomon SD, McMurray JJ, Pfeffer MA, et al.* Adenoma Prevention with Celecoxib (APC) Study Investigators. Cardiovascular risk associated with celecoxib in a clinical trial for colorectal adenoma prevention. *N Engl J Med* 2005; 17: 1071-80.
- 3 *Juni P, Nartey L, Reichenbach S, Sterchi R, Dieppe PA, Egger M.* Risk of cardiovascular events and rofecoxib: cumulative meta-analysis. *Lancet* 2004; 364: 2021-9.
- 4 *Graham DJ, Campen D, Hui R, et al.* Risk of acute myocardial infarction and sudden cardiac death in patients treated with cyclo-oxygenase 2 selective and non-selective non-steroidal anti-inflammatory drugs: nested case-control study. *Lancet* 2005; 365: 475-81.
- 5 *Solomon DH, Schneeweiss S, Glynn RJ, et al.* Relationship between selective cyclooxygenase-2 inhibitors and acute myocardial infarction in older adults. *Circulation* 2004; 109: 2068-73.
- 6 *Matchaba P, Gitton X, Krammer G, et al.* Cardiovascular safety of lumiracoxib: a meta-analysis of all randomized controlled trials > or =1 week and up to 1 year in duration of patients with osteoarthritis and rheumatoid arthritis. *Clin Ther* 2005; 27: 1196-214.
- 7 *Helin-Salmivaara A, Virtanen A, Vesalainen R, et al.* NSAID use and the risk of hospitalization for first myocardial infarction in the general population: a nationwide case-control study from Finland. *Eur Heart J* 2006; 27: 1657-63.

- 8 Hernandez-Diaz S, Varas-Lorenzo C, Garcia Rodriguez LA. Non-steroidal antiinflammatory drugs and the risk of acute myocardial infarction. *Basic Clin Pharmacol Toxicol* 2006; 98: 266–74.
- 9 Kearney PM, Baigent C, Godwin J, Halls H, Emberson JR, Patrono C. Do selective cyclo-oxygenase-2 inhibitors and traditional non-steroidal anti-inflammatory drugs increase the risk of atherothrombosis? Meta-analysis of randomised trials. *BMJ* 2006; 332: 1302–8.

Reply:

Dr. McConachie highlights many important additional issues regarding the current low confidence (internationally) in the safety evaluation process as part of drug development that was reviewed in the recent issue of the *Journal*.¹ These concerns exist not just for COX-2 inhibitors and, as pointed out in the letter, the line is blurred where acceptable side effects merge with unacceptable safety issues (e.g., gastrointestinal bleeding with aspirin). While the COX-2 inhibitor story continues to develop,² national institutions charged with drug development are beginning to respond. Subsequent to publication of the editorial, a report from the United States Food and Drug Administration lists eight major problem areas and makes five recommendations to improve drug safety evaluation.³ The proposed reforms focus upon empowering the agency with legislation, expertise and funding, and improvements in the process of drug safety review, including instituting a "conditional approval" or probationary period, that would place expectations on the company for completion of required studies before full endorsement. The European Medicine Evaluation Agency is contemplating a similar one-year conditional approval, while France, Japan and Norway have instituted two and four-year post-approval safety reviews for all drugs.³ Hopefully, public health and public trust will be improved by these changes in the drug development process.

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References

- 1 Stafford-Smith M. Hurry up and slow down: Lessons in drug development from the COX-2 inhibitors/Se hater et ralentir: les leçons à tirer de la production des inhibiteurs de la COX-2. *Can J Anesth* 2006; 53: 973–7.
- 2 Furberg CD. The COX-2 inhibitors--an update. *Am Heart J* 2006; 152: 197–9.
- 3 Furberg CD, Levin AA, Gross PA, Shapiro RS, Strom BL. The FDA and drug safety: a proposal for sweeping changes. *Arch Intern Med* 2006; 166: 1938–42.

Tracheal intubation using the GlideScope® with a combined curved pipe stylet, and endotracheal tube introducer

To the Editor:

The GlideScope® (Diagnostic Ultrasound, Bothell, WA, USA) videolaryngoscope provides an enhanced view of the glottis, and increases the likelihood of tracheal intubation compared with direct laryngoscopy in patients with a difficult airway.¹ However, it has been well demonstrated that providing a good view of the glottis does not always correlate with successful airway instrumentation. The limitation of the GlideScope® in advancing the endotracheal tube (ETT) through the vocal cords into the trachea has been well described.^{2,3} The manufacturer recommends using a stylet to curve the ETT and guide it into the larynx, but it remains difficult on occasion to negotiate the ETT through the vocal cords into the trachea. The bevel of the ETT may become stuck at the arytenoids, or impact on the anterior wall of the larynx. It has been suggested that a flexible stylet which would allow for the adjustment of the tube might decrease intubation times and increase the success rate.⁴

It has been shown previously that the Muallem ETT introducer (METTI; VBM Medizintechnik GmbH, Sulz, Germany), which is characterized by a semi rigid flexible body and a soft curved tip, is effective in guiding the ETT into the glottis and facilitating tracheal intubation.⁵ A curved brass pipe stylet (5 mm internal diameter) is made through which the METTI size 12 F is introduced. The ETT is slipped over the pipe stylet, thus making an assembly of an introducer, stylet, and tube, as shown in the Figure.

When the glottic inlet is visualized by the GlideScope®, the combined ETT, pipe stylet, and introducer are introduced into the pharynx facing the glottis. The METTI introducer is advanced inside the pipe stylet to target the glottis. Because it has a soft curved tip and semi rigid body, the introducer tip can be easily rotated and pushed via the glottis into the trachea. Once the introducer is pushed deep within the trachea, the ETT is railroaded over the introducer into the trachea. If the ETT becomes stuck at the arytenoids, it can be rotated 90° counter clockwise so that its bevel faces posteriorly, after which it is railroaded over the introducer into the trachea.⁶

We have successfully used the technique described to facilitate tracheal intubation in four patients with difficult airways (Cormack-Lehane laryngeal grades