

Iatrogenic Effects of COX-2 Inhibitors in the US Population

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FROM ABSTRACT:

Background: Selective cyclo-oxygenase 2 inhibitors ('coxibs') have been demonstrated to increase cardiovascular risk, but the cumulative burden of adverse effects in the US population is uncertain.

Objective: To quantify cardiovascular and gastrointestinal (GI) haemorrhage disease burden from coxibs and traditional 'non-selective' non-steroidal antiinflammatory drugs (NSAIDs) in the US population.

Design, setting and participants: Adult respondents from the US who were followed for 2 years.

Exposure was defined by two or more prescriptions of rofecoxib [Vioxx], celecoxib [Celebrex] or a traditional NSAID in the first year.

Main outcome measures: Acute myocardial infarction, stroke and/or GI haemorrhage in the year following exposure.

Results:

Exposure to rofecoxib [Vioxx] was associated with a 230% increased risk for acute myocardial infarction and 328% increased risk for GI haemorrhage.

Celecoxib [Celebrex] was associated with a 44% increased risk of acute myocardial infarction, a 143% increased risk for stroke and 398% increased risk for GI haemorrhage.

The group of traditional NSAIDs was associated with a 47% increased risk of acute myocardial infarction, a 26% increased risk of stroke, and a 138% increased risk for GI haemorrhage.

In the 1999–2004 period rofecoxib [Vioxx] was associated with 46,783 acute myocardial infarctions and 31,188 GI haemorrhages; celecoxib [Celebrex] with 21,832 strokes and 69,654 GI haemorrhages; resulting in an estimated 26,603 deaths from both coxibs.

The traditional NSAID group was associated with an excess of 87,327 GI haemorrhages and 9,606 deaths in the same period.

Conclusions: Iatrogenic effects of coxibs in the US population were substantial, posing an important public health risk. Drugs that were rapidly accepted for assumed safety advantages proved instead to have caused substantial injury and death.

THESE AUTHORS ALSO NOTE:

“The rapid introduction of selective cyclooxygenase-2 inhibitors (‘coxibs’) into clinical practice in the first half of this decade was intended to provide adequate anti-inflammatory action and analgesia with a reduction in the gastrointestinal (GI) adverse effects commonly experienced with traditional ‘non-selective’ nonsteroidal anti-inflammatory drugs.”

“However, an unpredicted increase in cardiovascular events, predominantly with a focus on acute myocardial infarction, led to the withdrawal of rofecoxib [Vioxx] and a ‘black box’ warning for celecoxib [Celebrex].”

Celebrex is used by more than 3.7 million Americans, and direct-to-consumer advertising suggests that the Celebrex market will expand.

“There is agreement from the literature that coxibs increase the risk of cardiovascular events in the form of acute myocardial infarction and stroke.”

This study used the 1999–2004 Medical Expenditure Panel Survey, which is the largest US population-based health survey available, to examine the population effects of the selected coxibs and traditional NSAIDs as a group on acute myocardial infarction, stroke and GI haemorrhage longitudinally, and to quantify the cost in terms of actual numbers of patients who have been harmed over that period (5 years) as a result of exposure to these drugs.

These authors classified individuals as having been exposed to rofecoxib, celecoxib or a traditional NSAID if at any time in calendar year 1 they had obtained two or more prescriptions or refills of the particular coxib or traditional NSAID.

RESULTS

“Exposure to two or more prescriptions of rofecoxib [Vioxx] resulted in a 3-fold increase in acute myocardial infarction risk” and a 328% increased risk for GI haemorrhage.

Celebrex’s effect on acute myocardial infarction was a 44% increased risk and the “stroke risk was approximately doubled and was also associated with a 5-fold increase in GI haemorrhage risk.”

Traditional NSAIDs were associated with a 138% increased risk for GI haemorrhage.

For the US adult population (190 million individuals), the cumulative risk from coxibs over a 5-year period of time (1999-2004) was 46,783 acute myocardial infarctions, 21,832 strokes and 100,842 excess GI haemorrhages.

Traditional-NSAIDs were associated with an excess of 87,327 GI haemorrhages.

In their analysis, in a 4-year period of time, coxibs resulted in 26,603 excess deaths and traditional NSAIDs were associated with 9,606 deaths.

DISCUSSION

“In this study, we used population-level data and estimated that coxibs were associated with an excess of nearly 50,000 myocardial infarctions and 21,832 strokes. These figures included almost 30,000 deaths in the US over a 4-year period.”

“Although the coxibs were marketed as having a lower risk of GI adverse effects, the frequency of GI bleeding in the US population was high and these agents were in fact associated with more GI bleeding than were traditional NSAIDs during this period.”

The risk of acute myocardial infarction increases with the longer one consumes coxibs.

The risk of GI bleeding also increases with the length of time one consumes traditional NSAIDs.

The increased GI haemorrhage potential with both Celebrex and Vioxx indicates that their widespread clinical use causes a significant burden of disease.

These authors estimated that Vioxx was responsible for 9,356 acute myocardial infarctions per year.

These authors estimated that Celebrex was responsible for 4,366 strokes per year.

These authors estimated that Vioxx was responsible for 31,188 GI bleeds per year.

These authors estimated that traditional NSAIDs are responsible for 21,832 GI bleeds per year.

Importantly, this study did not count the problems associated with those who took only one prescription of coxibs or NSAIDs, or those who took traditional NSAIDs such as low-dose aspirin or over-the-counter NSAIDs. "This leads to an underestimate of the exposure levels in the population and consequently the overall disease burden. Therefore, our estimates of disease burdens are conservative."

"Rofecoxib [Vioxx] was identified as the 14th most commonly implicated drug in causing death over the period 1998–2005."

In the period 1998-2005, Celebrex "was in tenth place for causing disability or other serious outcome." "These data, derived from voluntary reports, are likely to underestimate the true scale of the problem."

The design of this study is powerful because it represents 951,800,000 person-years.

"To put the coxib mortality figure of 26,603 in context, it is equal to the mortality of motorists in motor vehicle accidents in the USA over a 9-month period."

"The rapid diffusion of coxibs into clinical practice is likely to be at least partly responsible for the large mortality reported. Rapid diffusion has both benefits and costs and neither of these are the same across drugs. This suggests that society (and policy makers) ought to be making more informed and explicit determinations about the trade-offs between the benefits of faster diffusion and higher risks."

"Undoubtedly part of the reason for the rapid diffusion of the coxibs was the vigorous marketing campaign including high levels of sampling and direct-to consumer advertising."

CONCLUSIONS

"We found substantial morbidity and nearly 27,000 deaths associated with coxibs."

"The results presented here, and in particular the stroke risk, suggest that coxibs have potentially serious effects on patients and that very careful consideration by physicians and patients alike is needed before choosing coxibs over other analgesic and anti-inflammatory therapies."

KEY POINTS FROM DAN MURPHY

- 1) Selective cyclo-oxygenase 2 inhibitors ('coxibs'), specifically Vioxx and Celebrex, increase cardiovascular risk.
- 2) This study evaluated the incidence of acute myocardial infarction, stroke and/or GI haemorrhage in the year following after being given 2 or more

prescriptions of Vioxx, Celebrex, or a traditional NSAID.

3) "There is agreement from the literature that coxibs increase the risk of cardiovascular events in the form of acute myocardial infarction and stroke."

4) Because of the increase in cardiovascular events Vioxx has been removed from the market, and a 'black box' warning has been applied to Celebrex.

5) Celebrex is used by more than 3.7 million Americans, and direct-to-consumer advertising suggests that the Celebrex market will expand.

US Adverse Effects of coxibs and traditional NSAIDs over a 4-year period

	% increase of g.i. bleeding	# increase of g.i. bleeding	% increase of heart attack	# increase of heart attack	% increase of stroke	# increase of stroke	# of deaths
Celebrex	398%	69,654	44%	NA	143%	21,832	13,404
Vioxx	328%	31,188	230%	46,783	NA	NA	13,199
Traditional NSAIDs	138%	87,327	47%	NA	26%	NA	9,606

6) For the US adult population (190 million individuals), the cumulative risk from coxibs over a 4-year period of time (1999-2004) was 46,783 acute myocardial infarctions, 21,832 strokes and 100,842 excess GI haemorrhages.

7) Traditional-NSAIDs were associated with an excess of 87,327 GI haemorrhages.

8) In their analysis, in a 4-year period of time, coxibs resulted in 26,603 excess deaths and traditional NSAIDs were associated with 9,606 deaths.

9) "In this study, we used population-level data and estimated that coxibs were associated with an excess of nearly 50,000 myocardial infarctions and 21,832 strokes. These figures included almost 30,000 deaths in the US over a 4-year period."

10) "Although the coxibs were marketed as having a lower risk of GI adverse effects, the frequency of GI bleeding in the US population was high and these agents were in fact associated with more GI bleeding than were traditional NSAIDs during this period."

11) The risk of acute myocardial infarction increases with the longer one consumes coxibs.

12) The risk of GI bleeding also increases with the length of time one consumes traditional NSAIDs.

13) Importantly, this study did not count the problems associated with those who took only one prescription of coxibs or NSAIDs, or those who took traditional NSAIDs such as low-dose aspirin or over-the-counter NSAIDs. "This leads to an underestimate of the exposure levels in the population and consequently the overall disease burden. Therefore, our estimates of disease burdens are conservative."

14) "Rofecoxib [Vioxx] was identified as the 14th most commonly implicated drug in causing death over the period 1998–2005."

15) In the period 1998-2005, Celebrex "was in tenth place for causing disability or other serious outcome." "These data, derived from voluntary reports, are likely to underestimate the true scale of the problem."

16) "The rapid diffusion of coxibs into clinical practice is likely to be at least partly responsible for the large mortality reported. Rapid diffusion has both benefits and costs and neither of these are the same across drugs. This suggests that society (and policy makers) ought to be making more informed and explicit determinations about the trade-offs between the benefits of faster diffusion and higher risks."

17) "Undoubtedly part of the reason for the rapid diffusion of the coxibs was the vigorous marketing campaign including high levels of sampling and direct-to consumer advertising." "We found substantial morbidity and nearly 27,000 deaths associated with coxibs."

18) "The results presented here, and in particular the stroke risk, suggest that coxibs have potentially serious effects on patients and that very careful consideration by physicians and patients alike is needed before choosing coxibs over other analgesic and anti-inflammatory therapies."

19) "Iatrogenic effects of coxibs in the US population were substantial, posing an important public health risk. Drugs that were rapidly accepted for assumed safety advantages proved instead to have caused substantial injury and death."

COMMENTS FROM DAN MURPHY

In light of this study, it seems superfluous that there is any discussion pertaining to the safety of chiropractic spinal adjusting. Recall these studies we have recently reviewed:

In patients with chronic pain attributed to spinal degenerative disease, 59% can become pain/drug free and 29% can reduce their drug dependence by taking omega-3 fatty acids for 75 days.

Joseph Charles Maroon, MD, Jeffrey W. Bost, PAC; Omega-3 Fatty acids (fish oil) as an anti-inflammatory: an alternative to nonsteroidal anti-inflammatory drugs for discogenic pain; Surgical Neurology; 65 (April 2006) 326– 331.

In the treatment of chronic neck and back pain, chiropractic spinal adjusting is better than 5 times more effective than Celebrex or Vioxx, and the benefits of 9 weeks of chiropractic was still present a year later. Unlike the drugs, chiropractic was associated with no adverse events.

Lynton G. F. Giles, DC, PhD; Reinhold Muller, PhD; Chronic Spinal Pain: A Randomized Clinical Trial Comparing Medication, Acupuncture, and Spinal Manipulation; Spine July 15, 2003; 28(14):1490-1502.

Reinhold Muller, PhD, Lynton G.F. Giles, DC, PhD; Long-Term Follow-up of a Randomized Clinical Trial Assessing the Efficacy of Medication, Acupuncture, and Spinal Manipulation for Chronic Mechanical Spinal Pain Syndromes; Journal of Manipulative and Physiological Therapeutics, January 2005, Volume 28, Number 1.

In a study of 50,276 consecutive chiropractic adjustments involving 19,722 patients, no serious adverse events occurred.

Thiel, Haymo W. DC, PhD; Bolton, Jennifer E. PhD; Docherty, Sharon PhD; Portlock, Jane C. PhD; Safety of Chiropractic Manipulation of the Cervical Spine; A Prospective National Survey; Spine; Volume 32(21), October 2007, pp 2375-2378.

The largest study to date concluded that chiropractic cervical spine adjusting is not associated with adverse vascular events.

Cassidy, J David DC, PhD; Boyle, Eleanor PhD; Côté, Pierre DC, PhD; He, Yaohua MD, PhD; Hogg-Johnson, Sheilah PhD; Silver, Frank L. MD; Bondy, Susan J. PhD; Risk of Vertebrobasilar Stroke and Chiropractic Care: Results of a Population-Based Case-Control and Case-Crossover Study; Spine; Volume 33(4S), February 15, 2008 pp S176-S183.