

## EDITORIAL

### Nonsteroidal anti-inflammatory drugs in Juvenile Idiopathic Arthritis: What's the real risk?

#### Introduction

Given the known pharmacology of nonsteroidal anti-inflammatory drugs (NSAIDs), it should come as no surprise to us that such drugs may be associated with cardiovascular effects (both “good” and “bad”); after all, these effects are why acetylsalicylic acid in low doses is given to individuals at increased risk of thrombosis.

As Harry Gewanter recently pointed out on the Pediatric Rheumatology Listserv, for any intervention we have to balance the *potential* benefits of the intervention with the *potential* side effects of the intervention, and the *potential* effects of not intervening. Therefore the issue for us prescribing these drugs, and our patients taking them, revolves around the risk/benefit ratio of using these drugs, and the risk/benefit ratio of not using these drugs. As Harry noted, people tend to forget that not taking a drug is also an active therapeutic decision

#### Pharmacology of NSAIDs

NSAIDs have the potential for cardiovascular effects because a significant part of their antiinflammatory mechanism of action is to inhibit cyclooxygenase thereby decreasing the production of prostaglandins which have potent vascular activities (1). It has been postulated that whether or not an NSAID is associated with an increased or decreased cardiovascular risk may depend in large part on the resulting balance between the inhibition of cyclooxygenase 2 COX-2 and the inhibition of cyclooxygenase 1 (COX-1) caused by any particular NSAID (2). In this hypothesis the more a drug is specific for COX-2, the greater will be the inhibition of prostacyclin with its vasodilating/antithrombotic effects. Similarly, the more a drug is specific for COX-1, the greater will be the induced inhibition of thromboxane with its platelet aggregating effects. Consequently the more specifically the drug inhibits COX-2, the greater the likelihood of a vascular occlusive event occurring. This hypothesis is not the whole story however as other factors affecting vascular wall integrity such as systemic inflammation and atherosclerosis are undoubtedly important. There is also good evidence that there are differences between individual COX-2 inhibitors in where they locate in the cell membrane lipid bilayer; these differences may help explain differences in the vascular toxicity of celecoxib compared to rofecoxib (3). For more details about this controversial area the reader is referred to a recent excellent Medscape review (4).

#### Cardiovascular Toxicity of NSAIDs in adults

It has been known for many years that elderly individuals on NSAIDs or individuals with known renal disease are more likely to develop hypertension and cardiac failure (5,6). Given this knowledge, although it is not clear at the time of writing this editorial what were the cardiovascular events that lead to the discontinuation of

naproxen in the prevention of Alzheimer's trial, it does not seem greatly surprising that an increase in cardiovascular events was found given the presumed advanced age of individuals at risk for Alzheimer's disease. Fries and colleagues in 1991 evaluated the relative toxicity of NSAIDs (COX non-specific) using a sophisticated toxicity index (7). Using the ARAMIS data bank they studied 2747 patients with rheumatoid arthritis and 5,642 courses of the 11 most frequently used NSAIDs with the study period encompassing 8,481 patient-years. They found substantial differences between the individual NSAIDs, but cardiovascular toxicity was not a finding in this study.

In 2002 Ray et al. (8) performed a retrospective cohort study of individuals on the expanded Tennessee Medicaid program involving 202916 non-users, 24132 users of rofecoxib, and 151728 users of other NSAIDs. The study provided fairly convincing evidence that rofecoxib at doses in excess of 25 mg daily had an increased risk of serious coronary heart disease (RR 1.7 95% CI 0.98-2.95,  $p=0.058$ ) compared to non-use). Among new users the RR increased to 1.93 (95% CI 1.09-3.42,  $p=0.024$ ). There was no such increased risk for rofecoxib at doses of 25 mg or less, or for other NSAIDs.

In the Medscape review (4) Ray looked at data from 5 recent trials. The evidence from these trials is that naproxen is not associated with an increased RR for coronary heart disease compared to non NSAID use. Celecoxib is associated with a slightly decreased risk while the RR for rofecoxib is  $>1$  with the RR increasing with doses greater than 25 mg. He also concludes in this review that: “- one of the fortunate by-products perhaps of the rofecoxib debacle is that naproxen has become very well studied, and there is little evidence of its cardiotoxicity”.

Further data concerning the cardiovascular risks of rofecoxib is well presented in reference 4, and there seems little doubt that it is associated with significantly increased risk of cardiovascular disease compared to non-specific NSAIDs or to celecoxib, particularly when given in doses greater than 25mgs.

The data on celecoxib released by Pfizer on December 17<sup>th</sup> 2004 that led to the halting of a clinical trial investigating the role of celecoxib in preventing colon polyps, indicates that patients taking larger doses than is normally prescribed for rheumatoid arthritis (400 mg twice a day) had a 3.4 times greater risk of cardiovascular events compared to patients taking placebo (9). For patients taking 200 mg twice a day the RR was 2.5. The implications of these findings for adults with RA or OA taking celecoxib at lower doses are unknown.

There is now good epidemiological evidence that both RA and OA are associated with increased cardiovascular events, with relative risks of about 1.5 to 2 for various events (10,11). What role, if any, NSAIDs play in this increased risk is unclear. It may be that joint inflammation per se is the main factor associated with the increased risk.

### **Cardiovascular Toxicity of NSAIDs in Children**

Although it is well recognized that cardiovascular disease can occur in some forms of juvenile idiopathic arthritis (JIA) (notably myocarditis and pericarditis in systemic arthritis, and aortitis in rheumatoid factor positive arthritis and enthesitis-related arthritis), there is little if any convincing evidence that NSAIDs are associated with any increased risk of cardiovascular disease. The first major report evaluating the toxicity of NSAIDs in juvenile rheumatoid arthritis was by Barron and colleagues in 1982 (12). They found a high frequency of toxicity

necessitating discontinuation of the NSAID in 79 of 101 (78%) children who had received more than one NSAID. Acetylsalicylic acid appeared to be the major culprit; none of the side effects appeared to be cardiovascular in origin.

A study by Flatø et al. in 1998 (13) used a toxicity index similar to that used by Fries et al. (7) in adults. They did not demonstrate any definite cardiovascular toxicity in 117 children (72 with JIA) followed for a mean of 8.6 years.

There is a known increase in mortality in children with JIA, and an increased mortality among adults with a history of JIA. There is very little evidence that any of this increased mortality is due to cardiovascular disease. In a recent national study from Scotland, Thomas and her colleagues investigated cause-specific mortality in rheumatoid arthritis, juvenile chronic arthritis, and other rheumatic conditions over a 20 year (1981-2000) period (14). They found significantly increased standardized mortality ratios in patients with juvenile chronic arthritis for both males (3.39, 95% CI 1.97-5.46) and females (5.09, 95% CI 3.19-7.75). In the 1246 patients admitted to hospital during the 20 year period there were 39 deaths and 8 deaths were described as due to circulatory causes. Unfortunately no further information is available so it is difficult to draw any inferences from this, except to be aware that cardiovascular toxicity due to longterm NSAID therapy cannot be excluded as contributing to this excess mortality.

Finally, although the Evidence-Based Medicine gurus would probably sneer, I believe that the huge combined wealth of experience of pediatric rheumatologists is critical to this discussion. There seems to be no concern from pediatric rheumatologists around the world that cardiovascular disease is a significant problem despite over 30 years of experience with NSAIDs therapies.

### **Re-evaluating the decision to intervene with NSAIDs**

So what is the *potential* cardiovascular risk of treating a child with an NSAID? My assessment of the data presented above is that the risk of cardiovascular events for children treated with the classical NSAIDs is vanishing small—certainly during their childhood years. It may be that cardiovascular mortality is increased for adults who had, or who continue to have active JIA, but whether or not this is so is unclear, and it is even less clear if NSAIDs contribute to this possible increased mortality.

Even if we assume that there is an increased risk for cardiovascular events in children with JIA on NSAIDs, and even assuming a preposterously high relative risk of 2.0 (about the level of risk for high dose rofecoxib in adults), given childhood cardiac mortality rates of about one in 100,000 (15), only about one child with JIA per year would have an NSAID-related cardiovascular death for every 100,000 children treated with long term NSAIDs. Therefore the *potential* cardiovascular risk of using NSAIDs in our population is tiny.

What is the *potential* benefit of treating a child with an NSAID? There is no doubt that NSAIDs are moderately effective at minimizing inflammation in JIA (16,17). However I suspect only a relatively small number of patients—perhaps 20-25% has complete resolution of their arthritis with NSAIDs alone. In other words NSAIDs monotherapy is relatively ineffective at inducing remission, and the majority of children with JIA require the addition of a second-line agent (usually methotrexate). So to truly assess the *potential* benefits of treating a child with an NSAID we really need to know what is the marginal benefit of adding an NSAID to methotrexate monotherapy. An

RTC comparing methotrexate alone as initial therapy to methotrexate and an NSAID is needed. This might be a useful trial for CARRA or PRINTO to undertake. However, how easy it would be to recruit patients in this present climate is unclear. Given our present knowledge it is probably fair to say that the *potential* benefit of NSAID therapy in JIA is moderately high.

What is the *potential* risk of not treating a child with an NSAID? Younger pediatric rheumatologists will not know the awful damage wreaked by chronic arthritis in the days before the modern NSAIDs, intra-articular Triamcinolone, and methotrexate became available (see figure). Juvenile Idiopathic Arthritis can still occasionally cause severe joint damage, but much, much less frequently than 20 or so years ago. The risk of not effectively suppressing joint inflammation is huge! As mentioned above, it is unclear what is the relative importance of NSAID therapy, compared to particularly methotrexate, in decreasing this risk; however until we have evidence to the contrary, NSAIDs must remain central to our treatment regimens.

### **What should we say to our patients?**

Based on the present evidence there is no doubt that, for the vast majority of children with JIA, anti-inflammatory therapies (including NSAIDs) should be instituted early in the disease course, and used aggressively to try and fully suppress joint inflammation. Our job as pediatric rheumatologists is to explain as clearly as possible to patients and parents that this approach has the most favourable risk/benefit ratio. Unfortunately, all the evidence is that most human beings are not good at risk assessment. The use of examples such as the approximately one in three life time risk of cancer, or the fact that the child has a hugely higher risk of being killed in a motor vehicle accident may help. If the family wish to discontinue NSAIDs that the child is already taking, or in the case of a newly diagnosed patient, it might be best to use conventional therapies without NSAIDs, the use of a second-line agent (methotrexate, or for enthesitis-related arthritis, sulfasalazine) alone is probably an acceptable compromise. Only for a tiny minority of children is no treatment an acceptable option.

### **Conclusions**

The cardiovascular risk of NSAIDs in childhood is almost non-existent. The risk of continued use into adulthood is also extremely small. The benefits of such treatment for children with JIA far outweigh the risks.

### **References**

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