



## Amiodarone-induced lung disease

**To the Editor:** I read the Scientific Letter by Brian Rayner,<sup>1</sup> concerning amiodarone-induced interstitial lung disease, with interest.

Interpretation of high-resolution computed tomography (CT) scans of the lungs, such as those obtained in this case, is diagnostically challenging. By way of example, ground-glass opacification, one of the more commonly detected abnormalities that can be seen on high-resolution CT scanning, carries a differential diagnosis of more than a dozen different specific conditions. Interpretation is vitally dependent on correlating the high-resolution CT scan appearances with the chest radiographs and the clinical history and findings on clinical examination. With regard to the chest radiographs, review of all available previous radiographs that the patient might have had, as was done in this case, can provide important diagnostic clues. Conditions which are associated with interstitial fibrosis at the lung bases, such as asbestosis, usual interstitial pneumonia, scleroderma and rheumatoid lung, are commonly associated with a decrease in lung volume on the chest radiograph over time. The chest radiographs of the case presented in this instance show no reduction in lung volume when the current film is compared with a previous film, taken 10 years earlier. This could have provided a clue that the initial diagnosis of asbestosis should be treated with caution. Having said this, however, the reduction in lung volume is variable and not invariable. The absence of a decrease in lung volume is no more than a clue, but in the investigation of lung disease of obscure origin and the interpretation of high-resolution CT scans of the lungs, every clue is valuable.

**Donald Jan Emby**

AngloGold Ashanti Health  
Western Deep Levels Hospital  
Carletonville  
demby@anglogoldashanti.com

1. Rayner B. Clinical lesions from an elderly man with amiodarone-induced interstitial lung disease. *S Afr Med J* 2005; 97: 360-361.

## Non-steroidal anti-inflammatory drugs and cardiovascular risk

**To the Editor:** Chin and Commerford<sup>1</sup> suggest the imbalance between eicosanoids (prostacyclins and thromboxanes) as a possible cause for the observed increase in cardiovascular risk with the cyclo-oxygenase-2 (COX-2) inhibitors and traditional non-steroidal anti-inflammatory drugs (NSAIDs).<sup>1</sup> I would like to suggest that the drug-drug interaction between the traditional NSAIDs and aspirin in post-myocardial infarction (MI) patients may be another contributing mechanism.

In people who have already had an MI, aspirin is well known to reduce cardiovascular risk, by reducing the risk of further acute MI or sudden death by 25%.<sup>2</sup> It is quickly absorbed from the stomach and upper small bowel, with a peak level about 30 minutes after ingestion. It has a short half-life (15 - 20 minutes), being rapidly cleared by the liver.

Despite its short half-life, aspirin is able to have a profound clinical effect because it binds irreversibly to the COX enzymes of platelets. This antiplatelet effect lasts the lifespan of the platelet. This action on the platelet is particularly important in the portal system, where the concentration of aspirin is highest. Low-dose aspirin preferentially inhibits the COX-1 enzymes, compared with high-dose aspirin which inhibits both COX-1 and COX-2 enzymes.<sup>3</sup>

Most traditional NSAIDs also bind to the COX-1 enzyme on the platelets at the same site as aspirin, but in a reversible fashion. Therefore co-administration of NSAIDs and aspirin in the post-MI patient may prevent the binding of aspirin to the COX-1 enzyme. After the NSAIDs have disassociated from the platelet COX-1 enzyme, the platelet is 'free' to function as normal without the beneficial 'anti-platelet effect' of aspirin. This effect was shown in normal subjects, where single-dose ibuprofen was administered 2 hours before aspirin. It was noted that the inhibition of platelet aggregation that is normally found with aspirin use was antagonised. This effect was also noted with multiple daily doses of ibuprofen, but not when aspirin ingestion preceded a single dose of ibuprofen.<sup>4</sup> (Interestingly in this study, diclofenac was not shown to affect the pharmacodynamics of aspirin.)

This NSAID-aspirin drug interaction could be another mechanism to explain the observed increase in mortality in post-MI patients in the Danish registry study quoted by Chin and Commerford.<sup>5</sup>

Other studies have also suggested an increase in mortality when ibuprofen was used concomitantly with aspirin for secondary prevention of cardiovascular disease.<sup>6</sup> This led MacDonald and Wei in their review to recommend avoiding chronic ibuprofen use at the same time as using aspirin for cardiovascular protection, especially if cardiovascular risk is high.<sup>7</sup> While it is unclear whether the other NSAIDs have the same effect, MacDonald and Wei suggest that diclofenac at least may have a lesser effect.

**Brian Allwood**

Medical Registrar  
Groote Schuur Hospital  
Cape Town

**Marc Blockman**

Department of Clinical Pharmacology  
University of Cape Town and  
Groote Schuur Hospital  
Cape Town



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2. Opie LH, Gersh BJ. *Drugs for the Heart*. 6th ed. Philadelphia: Elsevier Saunders, 2005: 281.
3. Patrono CP, Rodriguez LAG, Landolfi R., Baigent C. Low-dose aspirin for the prevention of atherothrombosis. *N Engl J Med* 2005; 353: 2373-2383.
4. Catella-Lawson F, Reilly MP, Kapoor SC, et al. Cyclooxygenase inhibitors and the antiplatelet effects of aspirin. *N Engl J Med* 2001; 345: 1809-1817.
5. Gislason GH, Jacobsen S, Rasmussen JN, et al. Risk of death or reinfarction associated with the use of selective cyclooxygenase-2 inhibitors and nonselective nonsteroidal antiinflammatory drug after acute myocardial infarction. *Circulation* 2006; 113: 2906-2913.
6. MacDonald TM, Wei L. Effect of ibuprofen on the cardioprotective effect of aspirin. *Lancet* 2003; 361: 573-574.
7. MacDonald TM, Wei L. Is there an interaction between the cardiovascular protective effects of low-dose aspirin and ibuprofen? *Basic & Clinical Pharmacology & Toxicology* 2006; 89: 275-280.

**Dr Chin replies:** The pharmacodynamic interaction between the NSAIDs and aspirin is poorly understood. In the study by Catella-Lawson *et al.*,<sup>1</sup> the concomitant administration of ibuprofen but not rofecoxib, paracetamol or diclofenac antagonised the irreversible platelet inhibition induced by aspirin. Thus, in the limited evidence available, treatment with ibuprofen has been shown in an experimental trial to limit the cardioprotective effects of aspirin in patients with increased cardiovascular risk.<sup>1</sup> Currently the US Food and Drug Administration recommends that ibuprofen be given at least 30 minutes after aspirin or at least 8 hours before aspirin to limit this interaction.<sup>2</sup> No data exist for definitive conclusions to be drawn about the interactions between celecoxib, indomethacin, other traditional NSAIDs and aspirin. Clearly the mechanism of cardiovascular hazard and the use of NSAIDs is complex. Although limited trial evidence suggests that the pharmacodynamic interaction between aspirin and NSAIDs may be a potential mechanism, a substantial body of evidence indicates that suppression of COX-2-dependent prostacyclin formation initiates and accelerates atherogenesis.<sup>3</sup>

1. Catella-Lawson F, Reilly MP, Kapoor SC, et al. Cyclooxygenase inhibitors and the antiplatelet effects of aspirin. *N Engl J Med* 2001; 345: 1809-1817.
2. US Food and Drug Administration website. Concomitant use of ibuprofen and aspirin: potential for attenuation of the anti-platelet effects of aspirin. [http://www.fda.gov/cder/drug/infopage/ibuprofen/science\\_paper.htm](http://www.fda.gov/cder/drug/infopage/ibuprofen/science_paper.htm) (last accessed 5 December 2007).
3. Grosser T, Fries S, FitzGerald GA. Biological basis for the cardiovascular consequences of COX-2 inhibition: therapeutic challenges and opportunities. *J Clin Invest* 2006; 116: 4-15.

## Chris Barnard

**To the Editor:** With regard to John Terblanche's tribute to Barnard in the August *SAMJ*,<sup>1</sup> your readership might be interested in the following correspondence.

On 3 July 2006, I wrote to the Hunterian Museums at the Royal College of Surgeons, Lincoln's Inn Fields, London:

### Open Heart Surgery

Primarily, I would like to congratulate you on your magnificent museums. Any person who has studied medicine, or has contemplated its study, or indeed has an interest in biological sciences, should strive for the privilege of a visit.

The other purpose of this letter is as follows. In December 2005 I enjoyed a lengthy first sojourn in the Hunterian

Museum and noted in the *Open Heart Surgery* section:

*'In 1967 the first heart transplant was carried out' (full stop, paragraph).*

A separate preceding panel, containing a photograph of Cooley operating, stated: *'Denton Cooley is one of the pioneers of open heart surgery' – further paragraph, then: 'In 1968 Cooley performed the first successful heart transplant in the United States and in 1969 became the first heart surgeon to implant an artificial heart in a human patient.'*

One was a little puzzled that no mention was made of the surgeon who performed the first heart transplant nor of where the operation took place. I thought no more of it at the time, but was reminded of the omission when I watched a short documentary on the life of Christiaan Barnard on the plane back to South Africa a few days later. Since then I have discussed both the excellence of the museum and this observation with friends and medical colleagues at home and in the UK, and have been surprised at the almost uniform response. Most felt that one had a duty to query this historical/scientific/ethical anomaly.

Therefore I paid a brief second visit to the Royal College of Surgeons on Wednesday 28th June 2006 to confirm my facts and to establish via your most helpful information desk the appropriate recipient of this letter.

I look forward to your response and would be most grateful for comments on this small but possibly important issue.

Simon Chaplin, Senior Curator, replied on 6 July 2006:

Thank you for your email. I am glad you enjoyed your visit to the museum. Writing text for museum displays is always tricky: covering a broad topic (such as post-war heart surgery) in fewer than 160 words is something of a challenge. The decision I took as Curator was to try to avoid mentioning individual surgeons by name – I feared that otherwise the panels would become simply lists of names and dates. The addition of the separate panel on Denton Cooley's work was undertaken at the behest of our Trustees who felt that his overall contributions to the field of cardiac surgery (including, but certainly not limited to, his work in heart transplantation) were deserving of particular mention. This additional panel was added after the main text (with its brief reference to the 1967 breakthrough) had been installed, otherwise I would have added in Barnard's name to avoid any suggestion that his exclusion was in any way deliberate. Hopefully this is something that we will be able to correct in future, but for the meantime please be assured that our representation was not intended as any kind of slight towards Christiaan Barnard's work!