

## ADVERSE DRUG REACTION

# Fatal haemorrhagic pulmonary oedema and associated angioedema after the ingestion of rofecoxib

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Angioedema is a recognised side effect of rofecoxib, a cyclo-oxygenase-2 (COX-2) inhibitor. But death resulting from a haemorrhagic pulmonary oedema after its ingestion has not been recorded. The case of a 60 year old man who died from haemorrhagic pulmonary oedema in the presence of angioedema after the ingestion of two doses of 12.5 mg of rofecoxib is reported.

Non-steroidal, anti-inflammatory drugs (NSAIDs) are widely used in the treatment of inflammatory joint disease and osteoarthritis. The anti-inflammatory effects of non-selective NSAIDs are mediated through the inhibition of cyclo-oxygenase-2 (COX-2)<sup>1</sup> whereas their harmful effects on the gastric mucosa appear to be mediated through the inhibition of COX-1.<sup>2</sup> Rofecoxib, a recently introduced NSAID licensed for symptomatic treatment of osteoarthritis, is an orally active COX-2 selective inhibitor. It is used increasingly for this condition and reported side effects include urticaria, facial oedema, and occasionally cardiac failure and angioedema.<sup>3</sup>

### CASE REPORT

A 60 year old man was admitted with the sudden onset of swollen lips, anxiety, breathlessness, sweating, and vomiting after taking two doses of 12.5 mg rofecoxib 18 and 12 hours earlier. He had a past medical history of rheumatoid and osteoarthritis, insulin treated diabetes mellitus, and fibrotic lung disease. Other medication was prednisolone 10 mg once daily (he had been taking this for three years at varying doses), intramuscular methotrexate 12.5 mg weekly for four months, paroxetine 20 mg once daily for one year, frusemide (furosemide) 40 mg once daily for nine months, and Human Mixtard 30 (Novo Nordisk) insulin 34 units am and 18 units pm. There was no family history of angioedema or allergy. Examination revealed swollen lips and tongue, raised respiratory rate, a heart rate of 120/min regular, blood pressure of 162/81 mm Hg, and fine inspiratory basal crackles bilaterally on chest examination. A diagnosis of angioedema was made.

He was given hydrocortisone 200 mg along with chlorpheniramine 10 mg by the intravenous route, subcutaneous adrenaline (epinephrine) 1/1000: 1 ml, together with intravenous fluids. He was transferred to the intensive care unit where his face and tongue became more swollen and he developed pulmonary oedema which was confirmed on chest radiography. His initial chest radiograph showed evidence of fibrotic lung disease and the electrocardiogram (ECG) was normal. His ECG remained unchanged. Despite being supported by artificial ventilation and inotropes, diuretics, and vasodilators he died on the day after admission.

On admission his full blood count and urea and electrolytes were normal and the blood glucose was 9.1 mmol/l. The next day his C3 level was 0.41 g/l (normal range 0.75–1.65) and C4

level was 0.05 g/l (0.2–0.65), haemoglobin was 109 g/l, and packed cell volume was 0.34. Serum tryptase was 4.8 ng/ml (normal range 2–14) and urine methylhistamine levels were 5.5 ng/μmol (normal range 5–20). The last two samples were taken approximately eight hours after admission to the hospital and no serial measurements were done. Serum lupus anticoagulant levels were in the normal range. C1 esterase inhibitor levels were not measured.

Postmortem examination revealed ulcerations of the mouth, haemorrhagic tracheal mucosa, petechiae, and ecchymoses on the epicardial surface and haemorrhagic pulmonary oedema.

### DISCUSSION

The timing of events suggests that rofecoxib was the cause of this fatal series of clinical events. The Committee on Safety of Medicines (CSM) has received four reports of angioedema, 23 of facial oedema, one of giant urticaria, three of periorbital oedema, six of tongue oedema, and 13 of urticaria associated with rofecoxib (personal communication with CSM, December 2000). There have been no reported cases of haemorrhagic pulmonary oedema.

While there is some evidence that rofecoxib lessens the risk of serious upper gastrointestinal events when compared with conventional NSAIDs, there are also data suggesting an increased risk of cardiovascular events.

Atherosclerosis is a process with inflammatory features and COX-2 inhibitors may potentially have antiatherogenic effects by virtue of inhibiting inflammation. However, by decreasing vasodilatory and antiaggregatory prostacyclin production, COX-2 antagonists may cause increased prothrombotic activity.<sup>4</sup> Results from the VIGOR study showed that the relative risk of developing a confirmed cardiovascular event with rofecoxib treatment compared with naproxen was 2.38 (95% confidence interval 1.39 to 4.00;  $p = 0.0020$ ).<sup>5</sup> It has been suggested that a prospective randomised trial is required to establish the size of the risk of such cardiovascular adverse effects to patients taking COX-2 inhibitors. Until then prescribers should be cautious particularly in patients at risk of cardiovascular morbidity.<sup>4</sup> Our patient had no pre-morbid evidence of heart disease, although he was known to have fibrotic lung disease.

The cause of angioedema in this case is unclear, but allergy is less likely with normal tryptase and methyl histamine levels. However, the serum tryptase level in our patient was measured about eight hours after the onset of the symptoms. Serum tryptase levels in an allergic situation begin to rise 15 to 30 minutes after an event, peak at one hour, and then fall with a half life of approximately two hours.<sup>6</sup> A study looking at

**Abbreviations:** COX-2, cyclo-oxygenase-2; CSM, Committee on Safety of Medicines; ECG, electrocardiogram; NSAIDs, non-steroidal, anti-inflammatory drugs

tryptase fluoroimmunoassay in the diagnosis of anaphylaxis established the best cut off of tryptase levels was 8.23 ng/ml with 94% sensitivity and 93% specificity.<sup>7</sup>

On the other hand, the urine methylhistamine levels using six hour urine collections seems to give a good indication of an anaphylactic reaction.<sup>6</sup> Moreover the patient was taking prednisolone on admission and did not respond to the usual treatment for an allergic emergency. A negative family history and the absence of previous attacks in a 60 year old argues against this being hereditary angioedema. Low C4 levels can be a useful screening test for hereditary angioedema.<sup>8</sup> In this case, however, it was felt that the low C4 level may have been related to haemodilution (intravenous fluids and a low packed cell volume). Active rheumatoid arthritis could also explain a low C4 (but not a low C3).<sup>9</sup>

Acquired angioedema is unlikely in the absence of lymphoproliferative disease and a low C3.<sup>10</sup>

Older NSAIDs have been associated with angioedema.<sup>11</sup> A proposed explanation is that COX inhibition results in the diversion of arachidonic acid synthesis to lipo-oxygenase pathways with the formation of leukotrienes, which increase vasopermeability resulting in angioedema.<sup>12</sup> These may also feed through to give complement activation resulting in lowered C3 and C4 levels. We suggest that this mechanism may pertain in this case.

This adverse event has been reported to the CSM and to Merck, Sharpe and Dohme.

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