

Ticlopidine as a Safe Alternative for Clopidogrel-associated Arthritis

To the Editor:

Clopidogrel and ticlopidine are both antiplatelet thienopyridine derivatives that inhibit the binding of adenosine diphosphate to its receptor on platelets. Clopidogrel is more effective than aspirin in reducing the combined risk of ischemic stroke, myocardial infarction, and vascular death¹. Dual antiplatelet therapy with aspirin and a thienopyridine reduces the incidence of thrombosis post-stent implantation. Due to its superior safety profile, clopidogrel has replaced ticlopidine as the dominant thienopyridine prescribed, although given the structural similarity between the 2 drugs, cross-reactivity is possible. We describe a case of acute arthritis related to clopidogrel, subsequently resolved when clopidogrel was stopped and replaced with ticlopidine.

A 50-year old man presented with 25 minutes of central chest pain. Electrocardiogram showed ST segment depression in leads I and AvL, and he was treated as for acute coronary syndrome with aspirin, β -blocker, and low molecular weight heparin. Cardiac risk factors included previous ischemic heart disease (IHD), a 35-pack-year smoking history, and a strong family history of IHD.

The peak troponin I was 13.3 $\mu\text{g/l}$ (normal 0–0.03) and creatinine kinase 609 U/l (normal 25–175), confirming a non-ST elevation myocardial infarct. On Day 2 he was given a stat dose of clopidogrel 600 mg prior to coronary artery stenting, with a view to continuing therapy for at least 6 months. He remained well and was discharged.

Three days after discharge he re-presented with a urticarial macular rash on his limbs and trunk associated with an oligoarthritis affecting his shoulders and right hand with morning stiffness. On examination, he was febrile and had a macular rash on his upper limbs. Both shoulders and right first metacarpophalangeal (MCP) joint were tender and swollen. Investigations showed C-reactive protein 21 mg/l (normal < 5), urate 0.45 mmol/l (normal 0.20–0.42), gamma-glutamyl transferase 62 U/l (normal 10–50), ALT 43 U/l (normal < 40), and eosinophils $0.10 \times 10^9/\text{l}$ (normal 0.0–0.5). Autoimmune serology including antinuclear antibodies, HLA-B27, rheumatoid factor, anti-cyclic citrullinated peptide antibodies, myeloperoxidase, and PR3 antibodies were negative. Streptococcal, hepatitis B and C, HIV, rubella, and parvovirus serology were also negative.

His shoulder and right first MCP joint pain settled with ibuprofen 400 mg tds and he was discharged. He re-presented within 24 hours with sudden onset of painful, red, swollen wrists. There was no evidence of chondrocalcinosis on radiograph. His left wrist was aspirated and revealed $107,700 \times 10^6/\text{l}$ white blood cell count, no crystals, and no organisms. The wrist was injected with 20 mg triamcinolone with good effect. A few days later he developed a tender swollen left ankle and was started on prednisone 15 mg daily, with resolution of symptoms. The arthritis returned soon after discontinuing the 7-day course of prednisone and therefore prednisone was restarted.

Given the temporal relationship between starting clopidogrel and onset of joint symptoms it was considered most likely that the arthritis was an adverse effect of clopidogrel therapy. The clopidogrel was discontinued and ticlopidine was started. The arthritis diminished rapidly after cessation of clopidogrel and he was able to discontinue prednisone. Ticlopidine was continued for the required 6 months post-stenting and no further episodes of arthritis occurred.

In the CAPRIE study over 9550 patients received clopidogrel, and arthritis was not recognized as an adverse effect¹. Since the more widespread use of clopidogrel there have been reports of acute arthritis associated with it^{2–7}. In the majority of cases the arthritis developed within 10–14

days after starting clopidogrel, was associated with a rash and elevation of inflammatory markers, and symptoms resolved with cessation of clopidogrel. In one case the arthritis resolved despite continuing clopidogrel².

While there have been concerns that there were alternative causes for the arthritis in some cases⁸, there was no evidence of an alternative diagnosis in our case. In particular there was no evidence of viral or crystal-induced arthritis. Given the severity of the arthritis and the response to cessation of drug we did not believe it was reasonable to rechallenge with clopidogrel.

Ticlopidine, another thienopyridine drug, is used less frequently because of adverse effects including agranulocytosis, pancytopenia, and thrombotic thrombocytopenic purpura. Given the structural similarity between clopidogrel and ticlopidine there is the potential for cross-reactivity for adverse effects. Indeed, a similar acute arthritis with ticlopidine has been reported⁹. However, the few reports of cross-reactivity between clopidogrel and ticlopidine appear to be a thienopyridine-associated rash¹⁰.

There are concerns about stopping clopidogrel due to the risk of stent thrombosis and further cardiac events⁸. However, our case report demonstrates that ticlopidine may be tolerated without recurrence of arthritis and can be considered as an alternative therapy in patients with clopidogrel-associated arthritis.

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