*short report*
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# HEPARIN-INDUCED THROMBOCYTOPENIA WITH ARTERIAL THROMBOSIS: AN UNUSUAL CASE

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**ABSTRACT**

**A case of heparin-induced thrombocytopenia with thrombosis (HITT) is described. The patient, treated for several days with porcine Ca-heparin at a dosage of 10,000 IU/day, presented severe thrombocytopenia (Plt $36\times10^9$/L), intermittent right leg ischemia, and a positive heparin-induced platelet aggregation assay. We promptly discontinued heparin and started picotamide, an antiplatelet drug. Rapid clinical improvement was observed in a few days. We stress the unusual features of the reported case (HITT during prophylactic therapy with low doses of porcine heparin; intermittent thrombosis), and we suggest picotamide represents a rational therapy for HITT on the basis of clinical and pathogenetic considerations.**

*Key words: heparin, thrombocytopenia, thrombosis, picotamide*



Heparin-induced thrombocytopenia (HIT) is the most important form of drug-induced thrombocytopenia because of its high frequency. It is the only drug-induced thrombocytopenia that can be complicated by arterial thrombosis.[1]

We report an unusual case of HIT and arterial thrombosis arising during therapy with low doses of porcine heparin and treated with an anti-platelet drug (picotamide).

## *Case report*

A 61-year-old man was admitted to our Internal Medicine Unit because of recurrent right leg pain lasting for two days.

He had been well until 15 days earlier, when he was admitted to another hospital because of a traumatic stable fracture of two vertebral bodies (L1 and L3). Three to 4 weeks of immobilization were recommended. Porcine Ca-heparin (5,000 IU twice daily) was also prescribed. After 12 days of heparin therapy the patient experienced recurrent right leg pain and was then admitted to our Unit.

On physical examination, performed during a painful attack, the right leg and foot were pale and cold. The popliteal, posterior tibial and dorsalis pedis pulses were absent and Doppler examination showed no arterial flow. During periods of clinical remission the pulse amplitude was felt to be decreased, and Doppler examination revealed a flow rate reduced by 50%.

The lungs were clear and the heart was normal. No abdominal masses or tenderness were present. Neurologic examination was negative. Pulse rate was 80/min and blood pressure 135/70 mmHg. Axillary temperature was 36.3 C.

Hematologic values included: hematocrit 47%, white blood cells $5\times10^9$/L and platelets $36\times10^9$/L (confirmed by inspection of peripheral blood smears). On his previous admission platelets were $222\times10^9$/L.

Prothrombin time, partial thromboplastin time and fibrinogen were all normal. Fibrinogen degradation products (X-DP) were absent and a test for phospholipid antibodies was negative. The blood cultures were also negative. The platelet aggregation test in the presence of heparin was performed as described by King *et al.*,[2] using a final heparin concentration of 0.1 IU/mL and monitoring the resultant aggrega-

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tion within 15 minutes; 58.5% platelet aggregation was measured.

Heparin was promptly discontinued when thrombocytopenia was documented, and picotamide was started orally at a dose of 300 mg three times daily. After two days the patient complained of less frequent and less intense pain, and it completely disappeared the next day. At that time Doppler examination revealed a normal arterial flow. Platelet count was $67\times10^9$/L after 3 days and $147\times10^9$/L after 7 days of therapy.

### *Discussion*

Our patient presented the clinical features of HIT complicated by arterial thrombosis, in agreement with diagnostic criteria reported in the literature: 1) thrombocytopenia with platelets less than $100\times10^9$/L during heparin therapy; 2) normalization of platelet count after discontinuation of heparin therapy; 3) the presence of thrombotic complications; 4) exclusion of other causes of thrombocytopenia (bacteremia, disseminated intravascular coagulation, use of other medications).[3]

We could consider this case a type II HIT, the type in which thrombocytopenia is severe and can be complicated by thrombosis.[1] Moreover, type II HIT thrombocytopenia typically occurs after six or more days of heparin therapy (unless there has been a previous exposure to the drug), which is what probably happened in our patient since the thrombotic episode usually begins at the time thrombocytopenia is documented.[2]

HIT onset is rare in patients receiving low doses of subcutaneous porcine heparin, with an incidence of about 0.3% in prospective studies; moreover, only sporadic cases with severe thrombocytopenia ($<50\times10^9$/L) and/or thrombotic complications have been reported.[4]

The clinical manifestation of the thrombotic complication was also unusual in our patient. Heparin-associated thrombosis is fatal in 29% of cases and leads to limb amputation in 21% of affected patients.[2] However, our patient showed a benign clinical course due to the intermittent nature of the thrombosis.

Despite significant progress in understanding the mechanisms underlying HIT, the exact pathways leading to heparin-induced platelet activation are poorly understood. *In vitro* studies performed in patients with type II HIT showed that heparin can be a weak agonist inducing thromboxane-dependent platelet aggregation; however, in other cases it is a strong agonist inducing platelet aggregation irrespectively of thromboxane A2 (TxA2) synthesis. Furthermore, only TxA2-dependent platelet aggregation was prevented by cyclooxygenase inhibitors like aspirin.[6] It should also be noted that not only heparin but also fibrinolytic drugs may have prothrombotic effects.[7] In our case the fluctuant course of the thrombosis could have been the consequence of unstable thrombi formation (being composed mainly of platelets) and vasospasm, both probably the result of increased TxA2 synthesis. On the basis of these observations we considered it proper to use picotamide since this antiplatelet drug inhibits TxA2 synthetase and blocks platelet receptors for TxA2.[8]

We suggest administering picotamide in selected patients with type II HIT, in whom thrombosis could be attributable to TxA2 activation. However, further studies are needed to support our observation.



### *References*


1. Warkentin TE, Kelton JG. Heparin-induced thrombocytopenia. Annu Rev Med 1989; 40:31-44.
2. King DJ, Kelton JG. Heparin associated thrombocytopenia. Ann Intern Med 1984; 100:535-40.
3. Aburahma AF, Malik FS, Boland JP. Heparin-induced thrombocytopenia with thrombotic complications. W V Med J 1992; 88:95-100.
4. Warkentin TE, Kelton JG. Heparin-induced thrombocytopenia. Progr Hemost Thromb 1991; 10:1-34.
5. Chong BH. Heparin-induced thrombocytopenia. Aust NZ J Med 1992; 22:145-52.
6. Kappa JR, Fisher CA, Addonizio VP. Heparin-induced platelet activation: the role of thromboxane A2 synthesis and the extent of platelet granule release in two patients. J Vasc Surg 1989; 9:574-9.
7. Grignani G, Zucchella M, Brocchieri A, Saporiti A. Current concepts in coronary thrombolysis. Haematologica 1994; 79:475-82.
8. Gresele P, Deckmyn H, Arnout J, Nenci GG, Vermylen J. Characterization of N,N'-bis(3-Picolyl)-4-Methoxy-Isophthalamide (Picotamide) as a dual thromboxane synthase inhibitor/thromboxane A2 receptor antagonist in human platelets. Thromb Haemost 1989; 61:479-84.