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Gliclazide-induced severe thrombocytopenia

Nagaraja Moorthy, P. N. Venkatarathnamma, N. Raghavendra

Department of General Medicine, Sri Devaraj Urs Medical College and RLJ Hospital and Research Centre, Kolar, Karnataka, India

A wide range of drugs and chemicals can induce thrombocytopenia and platelet dysfunction. Gliclazide, a second-generation sulfonylurea, is used to control glycemic levels in non-insulin-dependent diabetes mellitus. It has been recommended for use on the basis of both its metabolic and nonmetabolic effects. It has a clear beneficial effect on metabolic control in type 2 diabetes. Numerous studies have demonstrated that gliclazide reduces platelet hyperadhesion and platelet hyperaggregability. We report an adult male diabetic who developed severe bleeding secondary to severe thrombocytopenia during treatment with gliclazide. To the best of our knowledge, gliclazide-induced thrombocytopenia, warranting withdrawal of the drug, has not been previously reported in the literature. Both the physician and the patient should be aware of this dangerous side effect. Immediate discontinuation of gliclazide is recommended in case of bleeding.

KEY WORDS: Gliclazide, sulfonylurea, thrombocytopenia

Introduction

A wide range of drugs can induce thrombocytopenia. Numerous drugs and chemicals affect the functioning of human blood platelets. We report an adult male diabetic who developed severe bleeding secondary to severe thrombocytopenia during treatment with gliclazide, a second-generation sulfonylurea.

Case Report

A 30-year-old male who was diagnosed to have type-2 diabetes mellitus and was prescribed oral gliclazide 40 mg/day since 3 months presented with epistaxis of

spontaneous onset and severe bleeding from the gums of 1 day's duration. The patient had also noticed purpuric lesions and ecchymotic patches over his arms, chest, and back. The bleeding had been continuous for more than one day before admission. There was no history of fever or any evidence of infection, alcohol intake, or consumption of any other medications. At presentation to the emergency department the patient had profuse bleeding from the gums and nose. He also had purpuric and ecchymotic patches over his arms [Figure 1] and back and in the oral mucosa. No evidence of bleeding from any other sites was noted clinically. The hemogram showed Hb: 15.2 g/dl and TLC: 9800 cells/cu mm, with a normal differential count. The platelet count was 42000 cells/cu mm. The bleeding time was very prolonged (>10 min); the clotting time was normal (5 min). PT and aPTT were within normal limits. Workup for the common infections that can result in thrombocytopenia, including HIV serology, yielded negative results. Bone marrow biopsy showed normal erythroid and myeloid series with increased megakaryocyte numbers. Initially, a provisional diagnosis of ITP was considered and oral prednisolone was started. Bleeding continued over next one day; the platelet count dropped to 30000 cells/cu mm. The possibility of gliclazide-induced thrombocytopenia



Figure 1: Image showing ecchymotic lesions over the patient's arm

Correspondence to Dr. Nagaraja Moorthy, Department of General Medicine, Sri Devaraj Urs Medical College and RLJ Hospital and Research Centre, Kolar, Karnataka, India.
E-mail: drnagaraj_Moorthy@yahoo.com

was considered and both prednisolone and gliclazide were stopped and insulin was started. There was dramatic improvement in the platelet count over next few days (1st day: 46000/cu mm; 2nd day: 72000/cu mm; 5th day: 183000/cu mm) and bleeding completely stopped. This improvement in the platelet count was sustained during follow-up and was maintained within the normal range. There was no evidence of any other etiological factors that may have caused the thrombocytopenia. Additionally, dramatic improvement following withdrawal of the drug indicates the possibility of gliclazide-induced severe thrombocytopenia.

Discussion

A wide range of drugs and chemicals can induce thrombocytopenia and platelet dysfunction. The drugs used to treat diabetes mellitus are diverse and include several classes. Gliclazide, a second-generation sulfonylurea, is widely used to control glycemic levels in type 2 diabetes mellitus. It has been recommended for use on the basis of both its metabolic and nonmetabolic effects. It has a clear beneficial effect on metabolic control in type 2 diabetes.^[1] Studies with gliclazide have demonstrated that it exerts hemovascular effects, which can be valuable to patients. Thus, treatment with gliclazide leads to a decrease in platelet adhesiveness and aggregability. It also reduces thromboxane levels and increases TPA levels. The mechanisms of these actions of gliclazide are not fully known but it has been demonstrated that its antiplatelet action is independent of its hypoglycemic activity and is not accompanied by clinical abnormalities of blood clotting. Inhibition of activated glycogen synthetase, activation of adenylate cyclase, modulation of arachidonic acid release from platelet membranes, stimulation of PGI₂ production and inhibition of the proaggregant action of TXA₂ may mediate its direct action on platelet activity. Thus, gliclazide not only has a hypoglycemic action but it also improves hemovascular parameters in type 2 diabetes when used at normal therapeutic doses.^[2] Numerous studies have demonstrated that gliclazide reduces platelet hyperadhesion and platelet hyperaggregability. With regard to platelet function, several groups have demonstrated a significant reduction in serum and intraplatelet β -thromboglobulin and thromboxane B₂. In animal models, *in vitro* and *in vivo* gliclazide stimulates endothelial prostacyclin synthesis.^[3-5] A huge number of large-scale trials suggests that gliclazide is a potent

sulfonylurea with a low rate of secondary failure and a low incidence of side effects and may be a good choice in long-term sulfonylurea therapy.^[6-8] Gliclazide-induced severe thrombocytopenia, warranting drug withdrawal, was not reported in any of these trials.

In conclusion, this case strongly suggests that gliclazide can induce severe thrombocytopenia and bleeding, warranting immediate withdrawal of the drug. Our purpose is to draw attention to the severity of gliclazide-induced thrombocytopenia. To the best of our knowledge, gliclazide-induced thrombocytopenia, warranting withdrawal of the drug, has not been previously reported in the literature. Both the physician and the patient should be aware of this dangerous side effect and immediate discontinuation of gliclazide is recommended in case of bleeding.

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