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Argatroban caused severe hypercholesterolaemia in a chronic haemodialysis patient with heparin-induced thrombocytopenia: an unreported adverse effect?

Sir,

Argatroban is a synthetic direct thrombin inhibitor that is used as an anticoagulant for haemodialysis (HD) in patients with type II heparin-induced thrombocytopenia (HIT) or with antithrombin III deficiency [1,2]. Although there has been no report of hypercholesterolaemia as an adverse effect of argatroban, I recently experienced a case in which severe hypercholesterolaemia was strongly suspected to be induced by argatroban.

I took charge of a 67-year-old female chronic-HD patient in September 2007. She received dialysis three times a week for 3.5 h with 40 mg of arogatroban on the basis of the diagnosis of HIT. Because her anti-heparin and platelet factor 4 complex antibody (HIT antibody) was still detected by ELISA [3] then, I continued to use argatroban in her HD. At that time, she was also suffering from severe hypercholesterolaemia. Her serum low-density-lipoprotein cholesterol (LDL-C) was 175 mg/dL in spite of taking simvastatin of 20 mg every day. But she has no familial history of hypercholesterolaemia and she said that she had never been diagnosed as with hypercholesterolaemia until the initiation of HD therapy.

I reviewed her hospital record in detail again. She started chronic HD with heparin sodium because her end-stage diabetic nephropathy had deteriorated in January 2007 at another hospital. During the first several HD sessions, her platelet count decreased from 318 000/μL to 82 000/μL and the HIT antibody was detected. She was diagnosed with HIT and the anticoagulant was changed to argatroban. Her platelet count quickly increased and reached to 185 000/μL in only 5 days. Since then, her platelet count has never decreased again. However, according to a series of her laboratory data, her serum total cholesterol, which had been <210 mg/dL until just before initiation of argatroban, began to increase obviously thereafter.

She was introduced to our clinic in March 2007. Her total cholesterol had reached 314 mg/dL and her LDL-C was 189 mg/dL at that time. The LDL-C value was extremely higher than 91 mg/dL just before using argatroban at the previous hospital. Soon her LDL-C increased to 210 mg/dL. This value was not reduced until the daily use of simvastatin of 20 mg, as mentioned above, and could not be reduced below 170 mg/dL even after that. (Her LDL-C rather increased a little by the change of the statin to pitavastatin afterwards.) Patients with this LDL-C level are at a high risk of developing coronary artery disease [4]. From her clinical courses, I suspected argatroban as the cause of her severe hypercholesterolaemia. Though I know the use of low-molecular-weight heparins (LMWHs) should also be discouraged in patients with HIT [1], for some reason, I dared to carefully change her argatroban to parnaparin sodium, an LMWH, in November 2007. After eight sessions of HD with 1000 international units (IU) of parnaparin sodium during 19 days, her LDL-C decreased to 87 mg/dL without thrombocytopenia. From that time until now, I have been using 1000 IU of parnaparin sodium in her HD, and her LDL-C has been always <90 mg/dL without thrombocytopenia or any sign of blood coagulation in spite of HIT antibody still being detected in January 2008.

She was given furosemide, asprin, candesartan cilexetil and acarbose orally, and also given epoietin beta intravenously at the time of initiation of HD. Later, other medications were given to her in addition. Cellulose triacetate dialyzer was used initially and changed to a polysulfone one afterwards. But none of these medications seemed to have had any direct effect on her hypercholesterolaemia except for argatroban.

I believe that argatroban could cause severe hypercholesterolaemia as a serious side effect, at least in HD patients with HIT.

Conflict of interest statement. None declared.

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Interaction between estradiol and tacrolimus in kidney-transplanted menopausal women

Sir,

Hormone replacement therapy for symptoms caused by oestrogen deficiency is often used by menopausal women. Transdermal administration is regularly used by means of a dermal application gel. Its active principle, the synthesis 17β estradiol, is a well-known substance known as an

inhibitor of the microsomial cytochrome P450 enzymatic system.

We present the case of a kidney transplant woman who faced a brutal degradation of her graft function consequent to an increase of her tacrolimus plasma level.

This 65-year-old patient had benefited from a kidney transplant as a consequence of renal insufficiency due to hyperuricaemia-induced interstitial nephropathy (uromoduline gene mutation). Her medical history also included hypertension, hysterectomy for fibroma and partial thyroidectomy. Her treatment included tacrolimus 9 mg/day, mycophenolic acid 540 mg/day, prednisolone 4 mg/day, lisinopril 20 mg/day, atorvastatin 10 mg/day, l-thyroxine 100 mg/day and alprazolam 0.5 mg/day. She had a normal post-transplant evolution with good renal function (creatinine 1.1 mg/dl, GFR estimated according to MDRD 53 ml/min/1.73 m^2, plasma tacrolimus trough levels ranging between 5.0 and 7.5 ng/ml).

Her renal function suddenly deteriorated 10 days after a gynaecological consultation, with a very high tacrolimus plasma level: creatinine increased to 1.6 and 2 mg/dl, GFR decreased to 28 ml/min/m^2 and tacrolimus plasma trough levels reached 14.2 and 18.3 ng/ml. No other cause of graft-function loss was detected: an echography with Doppler was normal; no urinary infection was found. A thorough investigation of her medication revealed a new oestrogen gel-based treatment (Estreva 0.1%, Merck, France) requesting daily application of 0.5 mg/day (one-third of the recommended doses). Despite the small estradiol doses, plasma tacrolimus concentrations apparently significantly increased because of medical interaction between tacrolimus and the oestrogen preparation. A drastic reduction (60%) in the daily doses of tacrolimus was necessary to reach the therapeutical plasma concentrations again: the tacrolimus plasma trough level reached 6.4 ng/ml, serum creatinine 1.3 mg/dl and eGFR 44 ml/min/m^2, 2 weeks after a progressive reduction in the tacrolimus dosage.

Both tacrolimus and estradiol are metabolized through the CYP450 3A4 enzyme complex [1,2,5]. Tacrolimus is a well-known strong inhibitor of the 2-estradiol metabolization phases (hydroxylation and glucuronidation) [2,4], delaying its elimination. While estradiol inhibits hepatic as well as intestinal CYP450 3A4 [3], it induces a lowering in the tacrolimus metabolism. This inhibition shows an inter-individual variability [3]. The transdermic administration avoids the hepatic '1st passage' phenomenon, which explains the fact that even small doses are sufficient to create a systemic effect.

Co-administration of tacrolimus with oestrogen is possible, but a close monitoring of tacrolimus trough levels and renal function is necessary. Even small doses of estradiol can create severe interactions with tacrolimus; therefore, clinicians should be aware of this harmful drug interaction in order to avoid potential renal graft dysfunction.

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