Lepirudin Anaphylaxis and Kounis Syndrome

To the Editor:

In an ongoing lepirudin pharmacosurveillance program, Greinacher et al. reported that 4 patients experienced fatal anaphylaxis after reexposure to lepirudin and died shortly after the onset of the event. Three patients died from acute cardiorespiratory arrest and 1 from acute myocardial infarction. These cases are characteristic examples of drug-induced Kounis syndrome—the concurrence of allergic or hypersensitivity reactions with acute coronary syndromes. Kounis syndrome is caused by certain environmental exposures, poisons, and venoms; conditions such as angioedema, bronchial asthma, exercise-induced anaphylaxis, food allergy, idiopathic anaphylactic syndrome, serum sickness, urticaria, and mastocytosis; drugs via inflammatory mediators such as histamine, tryptase, and chymase; and arachidonic acid products such as leukotrienes. There are several categories of drugs that are capable of inducing Kounis syndrome. These include antibiotics, analgesics, antineoplastics, contrast media, corticosteroids, intravenous anesthetics, nonsteroidal antiinflammatory drugs, skin disinfectants, thrombolytics, and others. Apart from lepirudin, thrombolytics that have been reported, so far, to induce Kounis syndrome are streptokinase and urokinase. Although the overall risk/benefit assessment of lepirudin as a treatment for heparin-induced thrombocytopenia remains favorable, preventive and therapeutic measures should be considered before any reexposure to lepirudin. These measures should include the following: first, skin testing as a mainstay consideration (skin testing for most drugs, including lepirudin, should be studied at concentrations of \( \leq 10^{-3} \text{ mol/L} \)); second, antibody testing including ELISA and radioallergosorbent testing; and third, rapid epinephrine or other vasopressor administration.

As the authors of the above paper correctly concluded, lepirudin should only be given in an environment where treatment for any anaphylactic reaction is readily available.

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Response

Drs. Koutsojannis and Kounis suggest that the fatal anaphylactic reactions associated with lepirudin reexposure are typical examples of allergic acute coronary syndrome (ACS). Although there is no doubt that the cardiac events occurring in the lepirudin-treated patients are associated with an immune reaction, their clinical course differs from the typical cases of allergic ACS reported and referenced by Dr. Kounis. In allergic ACS, the delay between the onset of allergic symptoms and ACS ranges from 1 to 24 hours. In contrast, the reaction toward lepirudin occurred within minutes. The concept of allergic ACS is based on the release of enzymes from activated mast cells and leukocytes that digest the upper layer of the plaque, facilitating plaque rupture. Although this concept is certainly compatible with a delayed onset of cardiac symptoms after the start of the allergic reaction, it does not fit with the immediate onset of ACS in lepirudin-treated patients. The close correlation of anaphylactic reaction and ACS would be more compatible with cardiac decompensation during a hypotensive episode.

The authors recommend anti-lepirudin antibody testing and skin testing before lepirudin reexposure. In our opinion, this will not provide useful information. More than 40% of lepirudin-treated patients will develop anti-lepirudin antibodies of the IgG class, which persist for many months. Antibody testing would, therefore, have a very low predictivity for anaphylaxis. Furthermore, in 2 patients with anaphylactic reactions during lepirudin reexposure, the immunoglobulin class of the anti-lepirudin antibodies has been assessed. In both patients IgG antibodies were found, but no IgE anti-lepirudin antibodies were found, and in one of the patients, skin tests were negative despite a clear anaphylactic reaction during reexposure.

Clinically relevant is the fact that severe anaphylaxis to date has always occurred directly after a bolus of lepirudin. Patients receiving a lower dose or an intravenous infusion during hemodialysis had much milder symptoms. This observation supports the concept that in preimmunized patients, a large dose of antigen results in immune complexes that induce an acute reaction via Fc-receptor–dependent release of mediators of anaphylaxis, ie, a dose-dependent, IgG-mediated acute type of anaphylaxis. Therefore, we recommend that a bolus of lepirudin be avoided and that one should start with a reduced intravenous infusion (0.1 mg/kg bw/h). This should reduce the risk of severe anaphylaxis and also the risk of lepirudin overdosing in patients with renal insufficiency.

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