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White clot syndrome

A serious complication of heparin therapy

Jae C. Chang, MD

Thrombocytopenia develops in about 5% of all patients treated with heparin, usually 6 to 13 days after initiation of therapy.^{1,2} Some patients with heparin-induced thrombocytopenia progress further to paradoxical thrombosis.^{1,3,4} In these patients, pathologic examination always shows that the thrombi consist of platelet aggregates and are white. Therefore, they are called platelet thrombi, or white clots,^{1,3} giving rise to the name white clot syndrome. The clinical course of this condition is life-threatening, and early recognition is of paramount importance for a favorable outcome.

MECHANISM—The exact mechanism of white clot syndrome is unknown. However, in certain circumstances, heparin (either bovine or porcine) provokes an immune response, resulting in production of heparin antibodies belonging to the IgG class.⁵ This can happen even with very low doses. If treatment is continued, immune complexes of heparin and heparin antibodies are formed. These, in turn, bind to platelets via platelet Fc receptors, causing in vivo aggregation of platelets.

Clinically, in vivo platelet aggregation is manifested initially as thrombocytopenia. This usually occurs more than 5 days after initiation of heparin treatment, which is presumably the time required for antibody response. If heparin-induced thrombocytopenia is not recognized and if treatment is continued, intravascular aggregation of platelets will cause rapid development of multiple thrombotic diseases in some patients.

Support for this pathogenesis is provided by (1) the pathologic finding of white clots that show massive platelet thrombi on specimens obtained during surgery or at autopsy and (2) the observation of in vitro

aggregation of platelets when heparin is combined with the patient's plasma.¹ This in vitro effect has been utilized in the heparin-induced platelet aggregation test, which establishes the diagnosis of white clot syndrome.

CLINICAL ASPECTS—Although mild to modest thrombocytopenia is not a major clinical concern, since serious bleeding may not occur until the platelet count falls below 20,000/ μ L, thrombotic complications can be very serious. The spectrum of white clot syndrome includes arterial, venous, cerebral, and pulmonary thrombosis and acute myocardial infarction.^{1,6}

Since I first observed this syndrome in 1979, I have diagnosed more than 40 cases. Initially, when the diagnosis was not well recognized and appropriate diagnostic criteria were not available, the mortality rate at Good Samaritan Hospital, Dayton, Ohio, was 40% and the morbidity was considerable. However, once the syndrome was recognized and diagnostic criteria were developed, the mortality and morbidity rates were reduced to less than 10%. Most recently, both heparin-induced thrombocytopenia and white clot syndrome have been uncommon at Good Samaritan Hospital, after elimination of heparin products from certain manufacturers.

Typical clinical features of white clot syndrome are acute-onset thrombocytopenia and rapid development of gangrene in an upper or lower extremity, symptoms and signs of pulmonary emboli, and stroke in a patient who is receiving heparin.

THE ROLE OF HEPARIN MANUFACTURE—Because of periodic clustering of cases of white clot syndrome at Good Samaritan Hospital (personal observation) and other institutions,⁷ I suspected that the heparin product itself—not the patient's idiosyncrasy—was responsible. To check this theory, I painstakingly examined every patient's heparin records whenever possible. Interestingly, I found that this syndrome has been commonly observed in patients receiving heparin from certain lots and manufacturers. Once, within a 4-week span, I diagnosed it in four patients who had received

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CONTRAINDICATIONS Use in patients with cardiac arrhythmias associated with tachycardia is contraindicated.

Although rare, immediate hypersensitivity reactions can occur. Therefore Alupent® (metaproterenol sulfate USP) is contraindicated in patients with a history of hypersensitivity to any of its components.

WARNINGS Excessive use of adrenergic aerosols is potentially dangerous. Fatalities have been reported following excessive use of Alupent® (metaproterenol sulfate USP) as with other sympathomimetic inhalation preparations, and the exact cause is unknown. Cardiac arrest was noted in several cases. Paradoxical bronchoconstriction with repeated excessive administration has been reported with sympathomimetic agents. Therefore, it is possible that this phenomenon could occur with Alupent. Patients should be advised to contact their physician in the event that they do not respond to their usual dose of a sympathomimetic amine aerosol.

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Carcinogenesis Long-term studies in mice and rats to evaluate the oral carcinogenic potential of metaproterenol sulfate have not been completed. Studies of metaproterenol sulfate have not been conducted to determine mutagenic potential or effect on fertility.

Pregnancy Teratogenic Effects: Pregnancy Category C. Alupent has been shown to be teratogenic and embryocidal in rabbits when given orally in doses 620 times the human inhalation dose and 62 times the human oral dose. There are no adequate and well-controlled studies in pregnant women. Alupent should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Oral reproduction studies in mice, rats and rabbits showed no teratogenic or embryocidal effects at 50 mg/kg, corresponding to 310 times the human inhalation dose and 31 times the human oral dose. Teratogenic effects in the rabbit included skeletal abnormalities and hydrocephalus with bone separation.

Nursing Mothers It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Alupent is administered to a nursing woman.

Pediatric Use Consult package insert for age limit.

ADVERSE REACTIONS Adverse reactions are similar to those noted with other sympathomimetic agents. Adverse reactions such as tachycardia, hypertension, palpitations, nervousness, tremor, nausea and vomiting have been reported.

The most frequent adverse reactions to Alupent® (metaproterenol sulfate USP) Inhalation Solution are nervousness and tachycardia which occur in about 1 in 7 patients, tremor which occurs in about 1 in 20 patients and nausea which occurs in about 1 in 50 patients. Less frequent adverse reactions are hypertension, palpitations, vomiting and bad taste which occur in approximately 1 in 300 patients.

HOW SUPPLIED Inhalation Aerosol: Each canister of Alupent® (metaproterenol sulfate USP) Inhalation Aerosol contains 225 mg of metaproterenol sulfate as a micronized powder in inert propellants. Alupent Inhalation Aerosol with mouthpiece (15 ml), Alupent Inhalation Aerosol refill (15 ml). Store below 77°F (25°C). Avoid excessive humidity.

Inhalation Solution: Alupent Inhalation Solution is supplied as a 5% solution in bottles of 10 ml or 30 ml with accompanying calibrated dropper.

Store below 77°F (25°C). Protect from light. Do not use the solution if it is brown or has a precipitate. Alupent Inhalation Solution Unit-dose Vial is supplied as a 0.4% or 0.6% clear colorless or nearly colorless solution containing 2.5 ml with 25 vials per box. Store below 77°F (25°C). Protect from light. Do not use the solution if it is brown or has a precipitate.

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Tablets: Alupent is supplied in two dosage strengths as scored, round white tablets in bottles of 100. Tablets of 10 mg coded BI/74. Tablets of 20 mg coded BI/72.

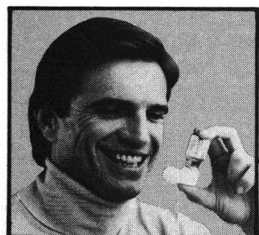
Storage for bottles: Store below 86°F (30°C). Protect from light.

Storage for blister samples: Store below 77°F (25°C). Protect from light.

Consult package insert before prescribing.

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VIEWPOINT CONTINUED

heparin from the same lot. When the hospital pharmacy removed that manufacturer's heparin products from the shelf, no further cases were observed for more than 2 years.

Since heparin is a heterogeneous group of straight-chain anionic mucopolysaccharides, it is possible that certain manufacturers' heparin, depending on its basic molecular structure and treatment during manufacture, is more antigenic than others. It has been shown that the platelet-aggregating activity of heparin can be directly related to its molecular weight.⁸

DIAGNOSTIC CRITERIA—I use the following criteria to diagnose white clot syndrome.

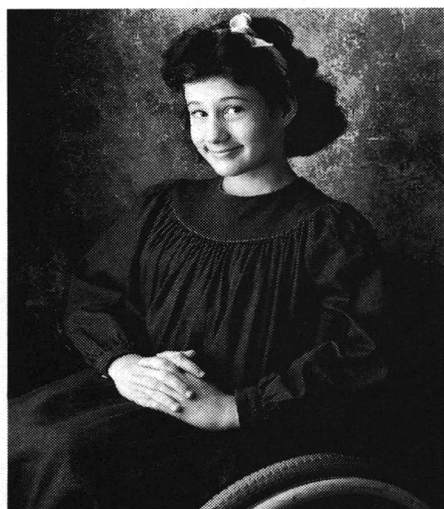
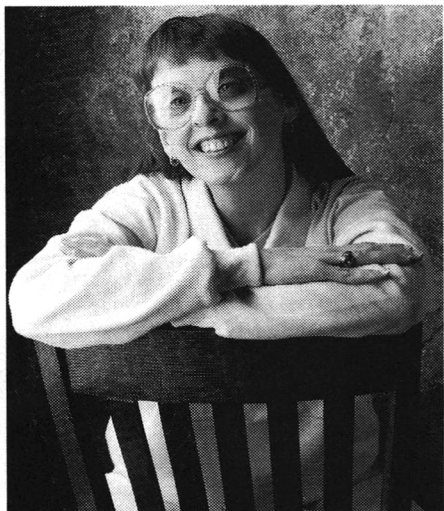
- Development of thrombocytopenia in the presence of a platelet count of less than 120,000/ μ L during heparin therapy
- Normalization of the platelet count after an interruption in heparin therapy
- Detection of white clots on pathologic examination of thrombectomy specimens or the presence of symptoms and signs indicating thrombosis
- Exclusion of other causes of thrombocytopenia
- Adequate or increased number of megakaryocytes in bone marrow
- Positive results on heparin-induced platelet aggregation test

A critical aspect of the heparin-induced platelet aggregation test is the pooling of normal platelet-rich plasma from multiple donors, usually five. Multiple donors are needed because the platelets from only about 50% of random normal donors would react to a heparin-dependent platelet aggregating factor.⁹ When multiple donors are used, the test result has high specificity (95%) and sensitivity (> 90%).

MANAGEMENT—The importance of early recognition of white clot syndrome cannot be overemphasized, since a missed or delayed diagnosis can have grave consequences. Awareness of the syndrome and close monitoring of the platelet count during heparin administration are critically important. I recommend that in an institution where heparin-induced thrombocytopenia has been seen, a platelet count at least once every

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VIEWPOINT CONTINUED

2 days for 14 days be performed while the patient is receiving heparin.¹

If heparin-induced thrombocytopenia is strongly suspected, heparin use should be discontinued immediately and a heparin-induced platelet aggregation test should be performed. If the test is positive, therapy with an alternate antithrombotic drug should be initiated. Possible alternatives include warfarin sodium, acetylsalicylic acid, dipyridamole (Persantine), dextran, and streptokinase (Kabikinase, Streptase). If massive arterial thrombi have already developed in an extremity but are still in an early stage, emergency thrombectomy may salvage the limb.

In my opinion, the hospital's most important decision when white clot syndrome is encountered in several patients who are receiving heparin from the same manufacturer is to remove all the heparin products from that particular source and replace them with another manufacturer's products. This precaution will probably prevent further occurrence of the syndrome in that hospital. In addition, the heparin manufacturer should be immediately informed of the problem. **FGM**

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