

CASE REPORTS

Anticoagulation Strategies for Treatment of Ischemic Stroke and Antiphospholipid Syndrome: Case Report and Review of the Literature

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A 49-year-old Caucasian man with antiphospholipid syndrome who experienced an ischemic stroke required multidisciplinary decisions regarding acute and long-term care. The patient first received warfarin and unfractionated heparin, followed by low-molecular-weight heparin. However, he developed complications from these drugs (warfarin-induced necrosis and heparin-induced thrombocytopenia), resulting in thigh necrosis and multiple additional cerebral and peripheral infarcts. His condition improved after warfarin and the heparins were discontinued, and a direct thrombin inhibitor, argatroban, was given intravenously for acute treatment. Argatroban is the only anticoagulant known to be safe in patients who experience an acute ischemic stroke in the setting of heparin-induced thrombocytopenia. For long-term anticoagulation, fondaparinux, an indirect, selective factor Xa inhibitor, was given subcutaneously. The patient received intravenous dexamethasone, later changed to azathioprine, for immunomodulatory treatment. He had significant improvement in his neurologic deficits without recurrent events over the next 18 months. Management of anticoagulation therapy in patients with antiphospholipid syndrome is complex and challenging, and therapeutic strategies need to be evaluated further.

Key Words: ischemic stroke, antiphospholipid syndrome, warfarin-induced necrosis, heparin-induced thrombocytopenia, HIT, thrombosis, anticoagulation, argatroban, fondaparinux.

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Anticoagulation therapy is used for prophylaxis and treatment of arterial and venous thrombosis in a myriad of clinical settings. Comorbid conditions, as well as the benefit-to-risk profiles of

anticoagulation with respect to those conditions, influence therapeutic decision-making. For example, although the routine use of anticoagulation with heparins is not recommended for acute ischemic stroke,¹ up to 88% of neurologists in the United States see the clinical need for early anticoagulation in these patients.² Furthermore, treatment strategies may need to evolve if patients develop drug-related complications, such as warfarin-induced necrosis or heparin-induced thrombocytopenia (HIT). In the past, heparins and warfarin were the primary agents available for parenteral and oral anticoagulation, respectively. More recently, however, a variety of

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Table 1. Time Course of the Patient's Condition

Day	INR	Platelet Count ($\times 10^3/\text{mm}^3$)	Hematocrit (%)	Clinical Course	Drug Therapy
0				Aphasic episode	None
7				Hospitalized with aphasia	Heparin started
8	1.1	205	35		Heparin continued, warfarin started
14	1.5			Discharged	Heparin discontinued, warfarin continued, enoxaparin started
17	2.3				Warfarin and enoxaparin continued
18	11			Purpura	Vitamin K given
21	1.2	132	34	Admitted for necrosis	Warfarin and enoxaparin discontinued, argatroban started
26	1.1	206	32		Argatroban continued
35				Debridement surgery	Argatroban continued, erythropoietin started
36	1.1	112	27	Aphasia worsened	Argatroban continued, PRBC infusion given, dexamethasone course given
37	1.0	126	26	Transferred to tertiary care center	
39		93	34		
51		202		Transferred to rehabilitation facility	Argatroban discontinued, fondaparinux started
> 16 mo later		200		No further stroke events	Frequent noncompliance with fondaparinux; switched to aspirin 25 mg—extended-release dipyridamole 200 mg twice/day
				Complement levels low	Azathioprine started

INR = international normalized ratio; PRBC = packed red blood cells.

alternative anticoagulants, including direct thrombin inhibitors (e.g., argatroban, lepirudin, and bivalirudin) and indirect factor Xa inhibitors (e.g., fondaparinux) have become available. We describe alternative therapeutic strategies considered for both acute and long-term management to prevent recurrent thrombosis in a patient with antiphospholipid syndrome who developed serious complications related to warfarin and heparin exposure.

Case Report

A 49-year-old Caucasian man with a history of depression was admitted to the hospital with acute onset of aphasia. He had experienced a transient episode of aphasia 6 days earlier (Table 1). Carotid dopplers demonstrated less than 50% stenosis of the internal carotid arteries bilaterally. Transesophageal echocardiography revealed an atrial septal aneurysm and mitral valve prolapse. Laboratory data, including complete blood count, basic metabolic profile, hepatic function panel, C-reactive protein, protein C, protein S, homocysteine, and fluorescent treponemal antibody, were within normal limits. A heparin infusion was started for his stroke that occurred after a transient ischemic attack; after 1 day this was overlapped with warfarin for 6 days. The patient's symptoms improved nearly to baseline. The patient was discharged 7 days after

admission; warfarin therapy continued. Because he had a subtherapeutic international normalized ratio (INR) of 1.5 (target range 2.0–3.0), enoxaparin was added to his home drug regimen. Anticardiolipin antibody (ACLA) and other serologic profiles were pending at the time of discharge.

Four days after discharge, the patient was evaluated for purpura at a clinic visit. He was found to have an INR of 11 and was given vitamin K. Three days after that evaluation (day 21), he was admitted to the same hospital for right posterior thigh necrosis requiring surgical debridement. Warfarin was discontinued. Because his platelet count had fallen from $205 \times 10^3/\text{mm}^3$ (normal range $150\text{--}370 \times 10^3/\text{mm}^3$) during his first admission to $132 \times 10^3/\text{mm}^3$ at his second admission, HIT was suspected. Enoxaparin was discontinued, and argatroban was started at $2 \mu\text{g}/\text{kg}/\text{minute}$, titrated to achieve an activated partial thromboplastin time (aPTT) of 1.5–3.0 times the baseline value, as recommended for HIT.^{3,4} The patient's platelet count returned to $206 \times 10^3/\text{mm}^3$ on the fifth day.

Fourteen days into the patient's second admission (day 35), he underwent surgical debridement of his thigh. Argatroban treatment was continued. The day after surgery the patient was drowsy and aphasic, with a hematocrit of 27% and platelet count of $112 \times 10^3/\text{mm}^3$.

Treatment with erythropoietin was started, and the patient was transferred the next day to our tertiary care center for further management.

On admission to our facility (day 37), the patient was awake and alert but profoundly aphasic, with right lower facial weakness and moderate right hemiparesis and hyperreflexia. Right thumbnail necrosis, a large right posterior leg wound with healing granulation tissue, and livedo reticularis were present. Diffusion-weighted magnetic resonance imaging showed multiple bilateral bright regions suggestive of acute cortical ischemia, as well as a subacute infarct referable to the initial event.

Laboratory data from the first hospitalization became available, showing elevated anticardiolipin immunoglobulin (Ig) G (> 100 GPL) and anticardiolipin IgM (> 100 MPL). Low-density lipoprotein cholesterol level was elevated at 136 mg/dl (optimal goal < 100 mg/dl), erythrocyte sedimentation rate was elevated at 73 mm/hour (normal range 0–25 mm/hour), antinuclear antibody was positive with a 1:80 titer, levels of complement 3 and 4 were low, and HIT antibody was present.

In response to these findings, argatroban was continued and the patient was transfused with packed red blood cells. On day 39, his hematocrit rose to 34%. A short course of dexamethasone was started for the possible diagnoses of systemic lupus erythematosus and antiphospholipid syndrome. During this hospitalization, the patient required medical therapy for acute delirium, probably attributable to glucocorticoid-induced psychosis. His platelet count gradually normalized, and there was no evidence of new thromboses or worsening of the infarcts during argatroban administration.

Consultants from neurology, hematology, pharmacy, rheumatology, and critical care medicine jointly reviewed the patient's options for long-term antithrombotic treatment. Both oral (aspirin alone and aspirin with long-acting dipyridamole) and subcutaneous (lepirudin and fondaparinux) routes were considered. One month after argatroban treatment had started (day 51), the patient was given his first subcutaneous dose of fondaparinux; argatroban was discontinued 1 hour later. He was transferred to a rehabilitation facility that afternoon, with instructions to receive fondaparinux 5 mg subcutaneously in the morning and 2.5 mg subcutaneously in the evening.

Over the next 18 months, fondaparinux was stopped due to noncompliance, and aspirin 25

mg–extended-release dipyridamole 200 mg (combination product) twice/day was started. The patient had continuous improvement in his neurologic deficits, with motor function returning to baseline. His language function improved by approximately 50%, and he returned to driving. Although his ACLA titers remained high, his complete blood count results normalized. Because of recurrent angioedema, low complement levels, and polyarthritis, immunomodulatory therapy with azathioprine was added to the patient's drug therapy regimen.

Discussion

In this unusually complicated case, the patient had evidence of bilateral cortical infarcts, warfarin-induced necrosis, HIT, and persistently high ACLA titers. Acute treatment issues included management of the patient's HIT, necrosis, and elevated ACLA titers. Long-term treatment issues included secondary stroke and thrombosis prevention.

Acute Treatment Issues

Management of HIT

Argatroban. In 2003, two direct thrombin inhibitors—argatroban and lepirudin—were approved by the United States Food and Drug Administration (FDA) for use in patients with HIT. Argatroban, a synthetic molecule derived from L-arginine, is available as an anticoagulant for prophylaxis or treatment of thrombosis in HIT^{5,6} and in patients with or at risk for HIT undergoing percutaneous coronary interventions.⁷

A randomized, double-blind study demonstrated the safety of argatroban in patients who experienced an acute ischemic stroke.⁸ In this study, argatroban was used within 12 hours of presenting with National Institutes of Health Stroke Scale scores of 5–22, constituting moderate-to-severe ischemic stroke. In the three treatment groups—58 patients given argatroban 1 µg/kg/minute with a goal of 1.75 times baseline aPTT, 59 patients given argatroban 3 µg/kg/minute with a goal of 2.25 times aPTT, and 54 patients given placebo—the rates of intracranial hemorrhage and other major bleeding were low, and differences between the groups were not statistically significant.

The effect of argatroban on stroke in patients with HIT was evaluated in a retrospective study that reviewed records of patients who had been treated with argatroban or control therapy

(typically heparin discontinuation and/or warfarin therapy, without direct thrombin inhibition).⁹ Argatroban was administered at 2 µg/kg/minute or less if hepatic impairment was present, with goal aPTT 1.5–3 times baseline. Stroke occurred within 37 days of HIT diagnosis in 15 (2.0%) of the 767 patients who had received argatroban, compared with 9 (4.7%) of the 193 control patients. Of the 436 patients who had HIT with thrombosis at diagnosis, stroke developed in 7 (1.8%) of the 390 patients in this category who received argatroban and in 2 (4.4%) of the 46 controls. This suggests an approximately 50% reduction in new stroke when HIT is treated with argatroban compared with warfarin anticoagulation or no thrombin inhibition. There was no significant difference in intracranial or major bleeding between the treatment and control groups. Stroke in patients with HIT was most frequent in women, patients with more severe thrombocytopenia, and patients whose HIT had presented within the past 2 weeks.

We chose argatroban as the preferred anticoagulant for our patient in light of safety and efficacy data from patients with HIT and stroke. Indeed, target levels of argatroban anticoagulation were readily achieved and maintained, without thrombotic or bleeding complications.

Lepirudin. Another direct thrombin inhibitor is lepirudin, a recombinant protein derived from leech hirudin. Lepirudin prevents further thromboembolic complications in patients with HIT and associated thromboembolic disease. It is given as a 0.4-mg/kg bolus dose and a 0.15-mg/kg/hour continuous infusion (dosages reduced in renal impairment), adjusted to obtain aPTT values of 1.5–2.5 times baseline aPTT. In controlled studies, lepirudin has been shown to improve the outcomes of patients with HIT, including reducing new thrombosis, with an associated major bleeding rate of 13–19%.^{10, 11} A known complication of lepirudin is the development of antibodies, which occurs in 40% of patients and can alter the drug's pharmacokinetics. Anaphylaxis, including anaphylactic death, has been reported.¹²

Bivalirudin. Bivalirudin, another intravenously administered direct thrombin inhibitor, is a 20-amino acid polypeptide with sequence homology to hirudin. Many studies have investigated the use of bivalirudin in patients with acute coronary syndromes, and it is

approved in the United States for use as an anticoagulant in patients with unstable angina who undergo percutaneous transluminal coronary angioplasty. A case report describes intravenous and intraarterial use of bivalirudin in a patient who experienced an acute ischemic stroke.¹³ Bivalirudin is not approved for use in patients with HIT, and reported experience with this agent for treating HIT is anecdotal. Its use for long-term management is impractical, since it is not available for subcutaneous administration.

Management of Warfarin-Induced Necrosis

Warfarin-induced necrosis is a rare and serious adverse effect of warfarin therapy. It is usually associated with local thrombosis that starts within days after a patient begins taking warfarin. Most commonly, it presents with livedo reticularis, rash, gangrene, hypertension, stroke, and renal failure.¹⁴ This complication most frequently occurs in women treated for deep vein thrombosis (DVT) or pulmonary embolism. It typically occurs 1–10 days after the start of warfarin, and it most commonly affects the breast, buttocks, or thigh.¹⁵ Our patient had thigh necrosis approximately 16 days after starting warfarin, and he also had livedo reticularis and distal thromboembolism in the right thumb. Other etiologies of skin necrosis to be considered are cryofibrinogenemia, lupus anticoagulant-associated skin necrosis, pyoderma gangrenosum, acute necrotizing fasciitis, disseminated intravascular coagulopathy, and heparin-induced thrombocytopenia.¹⁵ Venous limb gangrene associated with HIT is defined as distal limb necrosis and DVT and may be secondary to an acquired abnormality of the protein C anticoagulation pathway.¹⁶ The key to treatment is discontinuation of warfarin.

We employed two strategies with our patient. First, warfarin was discontinued. Given the patient's concurrent diagnosis of HIT, argatroban was started. Second, the patient underwent surgical debridement with surgical flap closure of his thigh necrosis.

Management of Stroke and Elevated ACLA Titers

In addition to anticoagulation, immunosuppression, including plasmapheresis, has been used to treat patients with refractory and catastrophic antiphospholipid syndrome. Plasma exchange can remove pathologic IgG, ACLA, cytokine, and complement levels; however, the exact mechanism of its action in patients with

elevated ACLA titers is not yet clear. Fresh frozen plasma contains natural anticoagulants, in particular, antithrombin III and protein C. Although plasma exchange improves outcomes in patients with catastrophic antiphospholipid syndrome, most patients with reported benefits had received fresh frozen plasma, glucocorticoids, and anticoagulants in addition to plasmapheresis. Despite encouraging reports on the efficacy of intravenous immunoglobulin therapy in the obstetric complication of antiphospholipid syndrome, most data are based on case reports and small series of patients.¹⁷

A retrospective study found that methylprednisolone followed by cyclophosphamide, when given to patients with both systemic lupus erythematosus and antiphospholipid syndrome, decreased serum ACLA titers but not lupus anticoagulants; however, the rate of thrombotic events was not analyzed.¹⁸ Rituximab, an anti-CD20 chimeric monoclonal antibody that is effective in patients with B-cell non-Hodgkin's lymphoma, has been found by a limited number of studies to improve outcomes of patients with antiphospholipid syndrome and corticosteroid-resistant hemolytic anemia, thrombocytopenia, as well as catastrophic antiphospholipid syndrome.¹⁹ Further clinical experience and randomized clinical trials, particularly in patients with catastrophic antiphospholipid syndrome, are needed for this promising agent.

Plasmapheresis could not be performed in our patient because of significant anemia requiring transfusions and his need for several surgical interventions. The glucocorticoid dexamethasone was added to his drug therapy, but use of cyclophosphamide, azathioprine, or rituximab was deferred due to the patient's relatively immunocompromised state and open wound, and was reconsidered at a later date.

Long-Term Treatment Issues

Secondary Stroke and Thrombosis Prevention

Antithrombotic Therapy. Because our patient developed warfarin-induced necrosis, warfarin was no longer considered an option for his long-term treatment. Several clinical factors gave our team equipoise in deciding against the use of antiplatelet agents for secondary stroke prevention. First, the patient had thrombocytopenia, and we were loathe to disable platelet function further. Second, the patient had significant anemia requiring transfusion, and we wished to minimize further bleeding risks. Finally, our

patient was thought to be at higher risk of thrombotic events due to his excessively high ACLA titer.

Antithrombotic therapy for recurrent stroke prevention in patients with antiphospholipid syndrome is guided by the recent Antiphospholipid Antibodies and Stroke Study,²⁰ a publication of the Warfarin-Aspirin Recurrent Stroke Study (WARSS)²¹ subgroup. This analysis demonstrated that the effects of aspirin 325 mg/day were equivalent to those of warfarin (target INR 1.4–2.8) in patients with stroke and antiphospholipid syndrome and that antiphospholipid syndrome does not increase a patient's risk for future strokes. A randomized, double-blind trial found that high-intensity warfarin (target INR 3.1–4) was not superior to moderate-intensity warfarin (target INR 2–3) in patients with antiphospholipid syndrome and past thrombosis.²² In that study, all patients had evidence of ACLA titers, lupus anticoagulants, or both and were followed for almost 3 years. In the moderate-intensity group, two patients had strokes and four had major bleeding, whereas in the high-intensity group, six patients had strokes and three had major bleeding.

A special note should be made concerning monitoring of warfarin therapy in patients with antiphospholipid syndrome. The INR can be effectively used to monitor warfarin anticoagulation in most, but not all, patients with ACLA titers.^{23–25} Antiphospholipid antibodies interact with clotting factors differently, and controversy exists as to their effect on INR values. However, if the INR is found to vary or is deviated from an expected value, other methods, such as the chromogenic factor X assay, which does not require a phospholipid substrate, should be considered. Levothyroxine, antidepressants, and acetaminophen are commonly prescribed to patients who have experienced strokes, and these agents can inhibit warfarin metabolism. Therefore, INR must be closely monitored if these drugs are started or their dosages are changed. Given our patient's history of warfarin-induced skin necrosis and his relative contraindications for antiplatelet therapy, we looked to other possible antithrombotic options.

Ximelagatran. For acute management we used the direct thrombin inhibitor, argatroban; however, argatroban could not be considered for long-term therapy since it is available only as an intravenous preparation. Lepirudin is available for short-term subcutaneous use, but few data

exist on that route of administration. Moreover, lepirudin's high cost made it impractical for long-term use by our patient.

Ximelagatran, an oral direct thrombin inhibitor, has been studied in patients with DVT. In one study, 612 patients were treated with ximelagatran 24 mg twice/day, and 611 patients received placebo.²⁶ In the group given ximelagatran, 12 (19.6%) patients developed another DVT, 6 (1.0%) died, 134 (21.9%) experienced bleeding, 6 (1.0%) experienced intracerebral hemorrhage, and 39 (6.4%) had increased alkaline phosphatase levels. In the placebo group, 71 (11.6%) patients developed another DVT, 7 (1.1%) died, 111 (18.2%) had bleeding, 5 (0.8%) experienced intracerebral hemorrhage, and 7 (1.2%) had increased alkaline phosphatase levels. Thus, ximelagatran decreased the rate of secondary DVT compared with placebo, with the only significant difference in adverse effects between groups being a transient increase in alkaline phosphatase levels.

Although ximelagatran was expected to be approved by the FDA, it was unavailable even for compassionate use in our patient. Ultimately ximelagatran was not approved in the United States, owing to concerns of hepatic toxicity, and its marketing and development were terminated in 2006.

Fondaparinux. We turned to the indirect, selective factor Xa inhibitor, fondaparinux, as another possible option for long-term antithrombosis management. Fondaparinux is available in the United States for prophylaxis of venous thrombosis. It may be used for patients undergoing hip fracture surgery, knee or hip replacement, or abdominal surgery. More recently it has been approved for treatment of DVT or pulmonary embolism in patients receiving concurrent warfarin.

In one study, 2213 patients with pulmonary embolism were treated with either daily subcutaneous fondaparinux or intravenous heparin.²⁷ Recurrent venous thromboembolism occurred in 42 (3.8%) of 1103 patients given fondaparinux compared with 56 (5.0%) of 1110 patients treated with heparin. The rate of major bleeding was similar for the treatment modalities (1.3% and 1.1%, respectively). Fondaparinux has the major advantage, compared with heparin, of being administered on an outpatient basis, thus reducing overall cost and improving quality of life.

Fondaparinux is not approved for use in

patients with HIT. However, in vitro cross-reactivity with HIT antibody is significantly less with fondaparinux than with unfractionated heparin (0–5.9% vs 79.8% overall for a variety of tests).²⁸ Case reports have described the successful use of fondaparinux in patients with HIT and thrombosis, although the experience is very limited.^{29–31} Because of the limitations of other antithrombotic agents, as described above, and the available data at the time of decision-making, subcutaneous fondaparinux 7.5 mg/day was judged the best available option for our patient. Fondaparinux was available only in 2.5-mg prefilled syringes at that time, so it was administered in divided doses, 5 mg each morning and 2.5 mg each evening.

Immunomodulatory Therapy

Hydroxychloroquine, which has an anticoagulant effect, is used widely in patients with systemic lupus erythematosus and has been associated with decreased risk of thrombosis in patients with systemic lupus erythematosus and antiphospholipid syndrome.^{32, 33} A case report describes its use for postoperative prophylaxis of DVT after hip arthroplasty.³⁴ Hydroxychloroquine may have multiple mechanisms of action, including inhibition of platelet activation, decreased thrombus size, and inhibition of T- and B-cell receptor-induced calcium signaling.³⁵

A study involving autologous hematopoietic stem cell transplantation found that this procedure can be performed safely in patients with antiphospholipid syndrome and appears to be effective for eliminating ACLA and preventing thrombotic complications in patients with systemic lupus erythematosus.³⁶ In this study, 18 of 22 patients who were refractory to chronic anticoagulation discontinued anticoagulation a median of 4 months after transplantation; 78% of them remained free from thrombotic events and in complete systemic lupus erythematosus remission for up to 78 months (median 15 mo) after transplantation.

Less traditional methods of immunomodulatory treatment include statins, angiotensin-converting enzyme inhibitors, dilazep, and toleragens.³⁷ In addition to lowering cholesterol levels, statins appear to have direct beneficial effects on vascular endothelium, exerting both antiinflammatory and antithrombotic actions. Several angiotensin-converting enzyme inhibitors as well as dilazep, an adenosine uptake inhibitor and antiplatelet agent similar to dipyridamole, may inhibit monocyte tissue factor expression, an

important therapeutic approach for prevention of thrombosis in patients with antiphospholipid syndrome.³⁵

An investigational therapy for antiphospholipid syndrome is based on the premise that pathogenic antibodies may be reduced by depletion of circulating autoantibodies and induction of immune tolerance at the B-cell level. Preliminary results from a phase I–II clinical trial with LJP 1082, a B-cell toleragen, indicate that it was well tolerated.³⁸ This agent may warrant further development for reduction of thrombotic events in patients with antiphospholipid syndrome. Prostacyclin, prostaglandins, anti-cytokines, and complement inhibitors are also potential future therapeutics for antiphospholipid syndrome.

We selected dexamethasone as our patient's first immunosuppressive agent. After he was stable while receiving fondaparinux as an outpatient, we replaced dexamethasone with the long-term immunosuppressant azathioprine. Azathioprine was successfully started and maintained; however, we may eventually replace it with rituximab.

Conclusion

Our patient experienced a stroke associated with antiphospholipid syndrome, skin and muscle necrosis during warfarin therapy, and HIT with thrombosis. He received argatroban for acute treatment during hospitalization and fondaparinux for long-term outpatient care. These agents were safe and effective in this very high-risk patient. The patient was successfully immunosuppressed, first with dexamethasone and later with azathioprine. Although the safety of argatroban in patients with ischemic stroke has been evaluated in a randomized controlled study, no data exist to support the use of argatroban (or any other direct thrombin inhibitor) in patients with antiphospholipid syndrome. Similarly, fondaparinux has not been investigated in this patient population. Evaluation of these agents in patients with antiphospholipid syndrome should continue to be an area of active research.

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