

Preface

Adverse Effects of Drugs on Hemostasis and Thrombosis

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Primum non nocerum - Hippocrates

Adverse effects of drugs and procedures have been known since the time of Hippocrates. In recent years, several high-profile adverse drug reactions (ADRs) were discovered after the drug was presumed safe and had passed regulatory scrutiny. As a result, there is an increased vigilance by both regulatory agencies and the public. Among the ADRs, many are associated with risks of thrombosis or bleeding. To some extent, the adverse prothrombotic effects of prohemostatic therapy aimed to correct bleeding or the adverse bleeding risk of agents aimed to prevent thrombosis occurrence, including the new oral anticoagulants dabigatran and rivaroxaban, can be viewed as anticipated risks under certain conditions, and this has perhaps been well illustrated by recent reports in *Seminars in Thrombosis & Hemostasis*.¹⁻³

The current issue of *Seminars in Thrombosis & Hemostasis* will provide the reader with a much broader review of drug-associated risks factors for thrombosis and bleeding, a subject that is otherwise infrequently described in the literature. The first article by Maxwell and Bennett⁴ reviews the importance of venous thromboembolism prophylaxis for cancer patients, with a focus on the ambulatory care setting. They summarize the currently available guidelines, including those by the American College of Chest Physicians, the American Society of Clinical Oncology, and the National Comprehensive Cancer Network. They also point out the increasing importance of prophylaxis in the outpatient setting.

In many cases, bleeding and thrombotic ADRs were not common during drug development, but then occurred unexpectedly at an alarming rate when the drug is given in the postapproval period. This is often seen in the setting when the drug is given in combination with other agents. These

ADRs can also occur when postapproval, these drugs are administered in off-label clinical conditions that have inherent prothrombotic risks. One such example can be seen in the use of thalidomide, a drug that was not associated with thrombosis when administered for erythema nodosum leprosum, but was highly thrombogenic when administered with dexamethasone or doxorubicin for persons with multiple myeloma. The clinical findings and current concepts of the underlying mechanisms are reviewed Zangari et al.⁵

Another unusual and recently recognized example is seen when the illicit drug cocaine is coadministered with the antihelmintic levamisole. Complications including thrombosis, agranulocytosis, and vasculopathy are being increasingly seen among cocaine users in many inner city emergency rooms. The syndrome of cocaine-associated thrombovasculopathy, first described in 2008 in Alberta, Canada, is reviewed by Dy and Wiernik,⁶ who report findings on this unexpected toxicity. They identify cocaine adulterated with levamisole as the cause of this toxicity, and point out that, if unrecognized, patients with this syndrome are very likely to be misdiagnosed as agranulocytosis or vasculitis, and undergo extensive diagnostic evaluation, and ultimately not receive appropriate treatment.

In other instances, drugs can be highly thrombogenic (both with respect to arterial and venous thromboembolism), but may go unnoticed for years. Such is the case with the erythropoiesis stimulating agents, epoetin and darbepoetin, as reviewed by Bennett et al.⁷ They describe the findings in the project Southern Network on Adverse Reactions and provide a comprehensive review of the toxicities of these agents. The association was first recognized in 2007, 18 years after Food and Drug Administration (FDA) approval. With appropriate foresight, they have included

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thrombotic findings in the most recently approved erythropoietic agent peginesatide, a homodimeric erythropoietic receptor agonist.

In contrast, estrogens have long been recognized to be associated with high risk of thrombosis even since the advent of oral contraceptives. In recent years, this risk is also encountered in the use of selective estrogen receptor modulators. The thrombogenic mechanisms associated with these are reviewed by Artero et al.⁸

In a disease with a high risk of thrombosis such as cancer, the use of chemotherapeutic agents with prothrombotic properties require additional vigilance. In addition, both the cancer and the therapeutic agents may also increase bleeding risks. In the article by McMahon and Kwaan,⁹ this double hazard of bleeding and thrombosis is reviewed.

Two subsequent articles review the less recognized hemorrhagic and prothrombotic risks encountered with the use of antimicrobial agents. The first by Loo et al¹⁰ covers antibiotics and thrombocytopenia and the second by Auerbach and Aboulafia¹¹ covers venous thromboembolic complications with antiviral agents used in human immunodeficiency virus patients.

Knowledge about the mechanism and treatment of drug-associated thrombotic microangiopathy is accumulating rapidly. Kreuter and Winters¹² provide an interesting overview of this field, bringing to bear the rapid knowledge that has been gained in the area of thrombotic microangiopathy. In particular, they point out why certain individuals are more susceptible to this complication, and provide therapeutic recommendations based on an understanding of the pathophysiology.

The article by Jacob et al¹³ then describes one of the most fascinating and unexpected drug-associated thrombotic microangiopathies, thienopyridine-associated thrombotic thrombocytopenic purpura (TTP). This research team reported the first large series of ticlopidine-associated TTP in 1998, followed shortly thereafter by 11 cases of clopidogrel-associated TTP, and now for the first time, 14 cases of TTP with the newest thienopyridine-prasugrel. The mechanistic differences between ticlopidine- and clopidogrel-associated TTP are unexpected and outlined in this article for the first time in the published literature. Postulates about the possible mechanism of prasugrel-associated TTP are also raised.

An often underrecognized important thrombogenic role of the rheologic factors is then reviewed by Baskurt and Meiselman.¹⁴ They describe changes in viscosity caused by red blood cell aggregation, platelet aggregation, and endothelial injury, resulting in thrombotic complications. The following article by Scharf¹⁵ deals with bleeding risks when using drugs with adverse effect on platelet function. Paradoxically, antithrombotic agents can cause nonhematologic ADRs. Walenga et al¹⁶ provide an important review of the nonhematologic toxicities of anticoagulant and antiplatelet agents. This topic has rarely been covered to this extent in any of the literature on these drugs, yet has important implications for risk-benefit assessments. Genetic variants are increasingly recognized as important determinants of why some patients have difficulty

achieving or maintaining an appropriate anticoagulated state with warfarin. Fung et al¹⁷ therefore provide great clarity to a subject that heretofore is difficult to fully understand.

The final article by Moore and Bennett¹⁸ fittingly gives important insights into why so little is otherwise known about ADRs. Using empirical data from clinical trials, epidemiologic studies, and databases maintained by the FDA, they report that a staggering 99% of all serious ADRs associated with thrombotic or bleeding complications are not reported. They describe the first empirical study that documents rates of underreporting of serious ADRs. The study has broad implications across all fields of medicine. It is therefore not surprising that hemostatic and thrombotic toxicities of pharmaceuticals take years to uncover.

In conclusion, this issue of *Seminars in Thrombosis & Hemostasis* provides an impressive breadth and depth of articles on the topic of ADRs. We hope that you as readers enjoy the articles as much as we as editors have.

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