*6 CE Credits

AANA Journal Course

3

AANA Journal Course: Update for nurse anesthetists–Low molecular weight heparin: Pharmacology and regional anesthetic implications

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Low molecular weight heparins were first introduced in the United States in May 1993 as an alternative to currently available anticoagulant therapy. Like standard heparin, these anticoagulants inhibit activation of a number of coagulation enzymes, but low molecular weight heparins have their primary inhibitory effect on factor Xa. A decrease in plasma protein binding by low molecular weight heparin results in greater bioavailability and a more predictable therapeutic response than that of standard heparin. Although drug action is not measurable by commonly available laboratory tests of coagulation, greater predictability of drug response led to acceptance of these agents for perioperative thromboprophylaxis.

The introduction of low molecular weight heparin into the perioperative surgical management of patients also has influenced perioperative anesthetic care. Postmarketing reports of the formation of spinal epidural hematoma when these agents were used concurrently with regional anesthesia prompted the US Food and Drug Administration to issue an advisory to anesthesia providers.

This Journal *course includes the pharmacology of the class of drugs known as low molecular weight heparins, the incidence and risk factors for the development of spinal or epidural hematoma, and current recommendations for the use of these anticoagulants in conjunction with spinal or epidural anesthesia. Guidelines for the postoperative use of indwelling spinal or epidural catheters in patients who receive this drug therapy in the course of their perioperative care are presented.*

Key words: Anticoagulants, low molecular weight heparin, regional anesthesia, spinal or epidural hematoma.

*The American Association of Nurse Anesthetists is accredited as a provider of continuing education in nursing by the American Nurses Credentialing Center Commission on Accreditation. The *AANA Journal* course will consist of 6 successive articles, each with objectives for the reader and sources for additional reading. At the conclusion of the 6-part series, a final examination will be printed in the *AANA Journal*. Successful completion will yield the participant 6 CE credits (6 contact hours), code number: 22789, expiration date: July 31, 2001.

Objectives

Upon completion of this course, the reader should be able to:

1. **Contrast the pharmacokinetics and pharmacodynamics of low molecular weight heparin with those for standard unfractionated heparin.**
2. **Delineate the incidence of spinal and epidural hematoma and the risks for patients treated with low molecular weight heparin.**
3. **Define the risk factors for the development of spinal or epidural hematoma.**
4. **Recognize the signs and symptoms, treatment recommendations, and the differential diagnosis of spinal and epidural hematoma.**
5. **Outline the regional anesthetic considerations for patients receiving low molecular weight heparin.**

Table 1. **Low molecular weight heparin**

Advantages	Disadvantages
1. Less frequent dosing	1. Incomplete reversal by protamine
2. More predictable bioavailability	2. Higher cost than unfractionated heparin
3. Decreased cost of laboratory monitoring	3. Lack of commercially available anti-Xa monitoring test
4. Decreased thrombocytopenia	

Table 2. **Indications for and uses of low molecular weight heparin**

1. Prophylaxis of pulmonary embolism secondary to postoperative deep venous thrombosis in patients undergoing elective hip or knee replacement surgery
2. In combination with aspirin therapy for the treatment of unstable coronary artery disease
3. Prophylactic management following ischemic stroke
4. Prophylaxis of pulmonary embolism following major gynecologic surgery

Introduction

Low molecular weight heparins (LMWHs) are a relatively new class of anticoagulants. These agents are fragments created as a result of the depolymerization of unfractionated heparin. This molecular fragmentation produces a class of drugs with both pharmacokinetic and pharmacodynamic alterations in comparison with unfractionated heparin. The LMWH drugs have reduced affinity for binding to plasma proteins. This reduction in protein binding yields superior bioavailability, greater predictability of drug response, and a longer elimination half-life. As a result, LMWH may be administered less frequently and does not require laboratory monitoring of coagulation.[1] While certain disadvantages exist with the use of this class of drugs, these and other proposed advantages of LMWH (Table 1) compared with unfractionated heparin contributed to the preferential use of these agents for the prevention of pulmonary embolism and treatment of venous thromboembolism.[2] Table 2 lists the common indications and uses of LMWH. While unfractionated heparin may be administered intravenously or subcutaneously, LMWHs are administered by the subcutaneous route only.[3]

In December 1997, anesthesia providers received notification from the US Food and Drug Administration (FDA) of potential problems associated with the administration of spinal and epidural anesthesia to patients treated with LMWH. Four anticoagulants were specifically noted within the advisory: dalteparin (Fragmin, Pharmacia & Upjohn, Inc, Peapack, NJ), enoxaparin (Lovenox, Rhône-Poulenc Rorer Pharmaceuticals Inc, Collegeville, Pa), ardeparin (Normoflo, Wyeth Laboratories, Malvern, Pa), and danaparoid (Orgaran, Organon Inc, USA, West Orange, NJ). As of November 1997, the FDA had received 30 reports of spinal or epidural hematoma following subarachnoid or epidural block in patients who were receiving LMWH therapy.[4] By using the Freedom of Information Act, we were able to review the cases of spinal or epidural hematoma reported to the FDA since the November 1997 advisory to anesthesia providers. Between November 1997 and June 1999, an additional 86 cases of extradural hematoma were found in patients who were receiving LMWH, bringing the total number of reported cases of this adverse event to well over 100. It can be assumed that all cases have not been reported.

Enoxaparin, the first LMWH introduced in the United States, was released by the FDA in May 1993.[5]

Before the release of enoxaparin in the United States, the LMWH class of drugs had been used extensively in Europe. Reviews of clinical trials of patients receiving central neural blockade while being treated with LMWHs identified no catheter-related neurologic complications.[6] Anesthetists, while recognizing the risks of regional anesthesia in patients receiving any medications that inhibit coagulation, were nevertheless influenced by these reports of apparent safety.[7] Lack of initial reporting of complications with the use of regional anesthesia in patients treated with enoxaparin also may have been affected by dosing differences. The European dosage recommendations were for 40 mg of enoxaparin once daily; however, the initial recommended dosage in the United States was 30 mg twice daily.[8]

In April 1995, the manufacturer of enoxaparin (Rhône-Poulenc Rorer Pharmaceuticals Inc, Collegeville, Pa), revised the package insert to caution providers about using regional anesthetic techniques for patients receiving enoxaparin and for patients who were receiving combined therapy of enoxaparin and platelet inhibitors. After early reports of hematoma development, manufacturers acknowledged the potential for an information gap since anesthesia providers do not prescribe these medications. In response to this dilemma, the manufacturer of enoxaparin conducted a survey in 1995 of US anesthesiologists who frequently were involved in the care of patients undergoing hip or knee replacement. This questionnaire revealed that the respondents were largely unaware that patients received these agents postoperatively, few recognized these agents by name, and most were unfamiliar with the pharmacokinetics of LMWH.[9] The FDA advisory not only highlighted a need to modify current practice, but also compelled anesthetists to have a thorough understanding of the pharmacology of the LMWH class of drugs.

History and review of the literature

Standard or unfractionated heparin is a naturally occurring anticoagulant that has been used extensively for decades. It occurs as a heterogeneous mixture of sulfated mucopolysaccharides that are isolated from porcine gut or from bovine lung or gut. Commercially available solutions are supplied with their molecular components ranging from 3,000 to 30,000 d.[1] The potency of these heterogeneous mixtures is standardized so that each unit of heparin has the same efficacy.[1] The anticoagulant action of unfractionated heparin is to catalyze the formation of a complex between the naturally occurring antithrombin III and several factors in the coagulation cascade, most notably factors IIa (thrombin) and Xa (Figure). These complexes are unable to act in the coagulation cascade leading to inhibition of clot formation.[11]

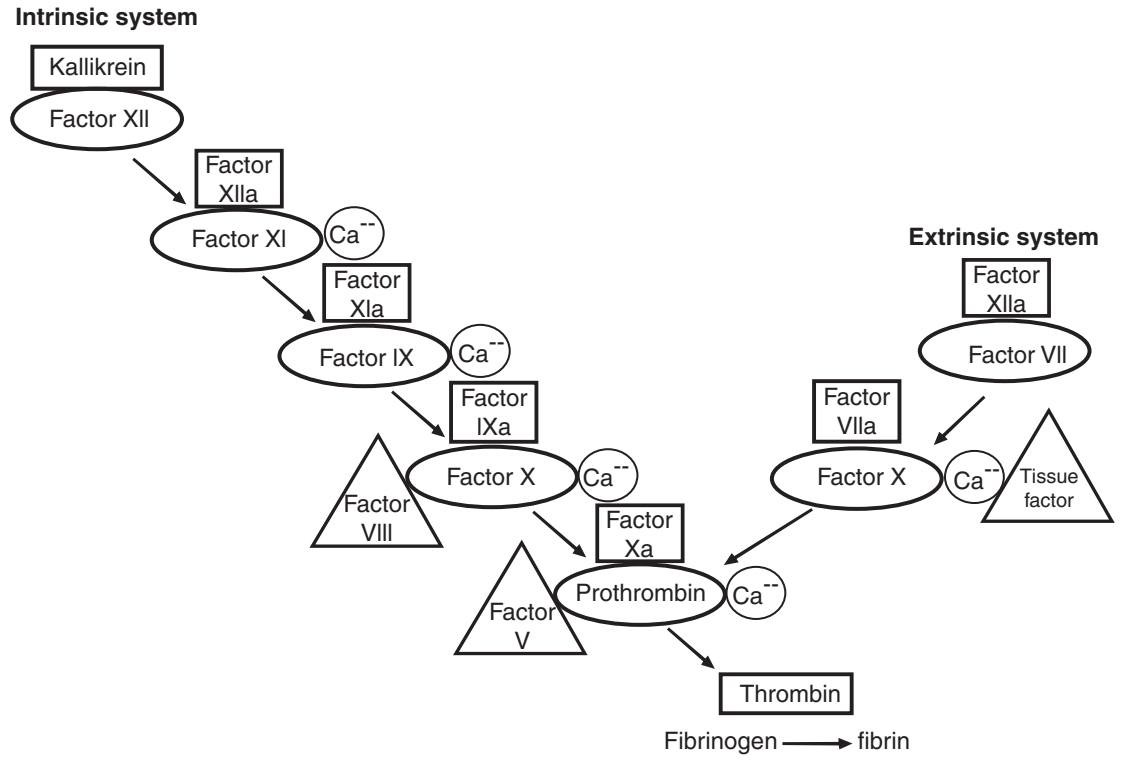
The LMWHs are fragments of heparin produced by one of several enzymatic or chemical processes and are generally in the molecular weight range of 2,000 to 8,000 d.[12] Both LMWH and unfractionated heparin act by the same mechanism to inhibit the coagulation process, but while unfractionated heparin has equal inhibitory action against factors Xa and IIa, LMWH has a preferential inhibitory action against factor Xa.[2] The variable bioavailability and binding to plasma proteins of unfractionated heparin leads to significant intrapatient variability in drug response. In contrast, LMWH binds minimally to these proteins[13] and has a higher, more predictable bioavailability, resulting in a more predictable therapeutic response.[14]

Individual patient anticoagulant response to a given dose of unfractionated heparin varies widely, partially as a consequence of available plasma proteins that serve as drug binding sites. This variation in patient response requires careful monitoring by a number of available laboratory tests of coagulation. Heparin anticoagulation can be monitored by activated coagulation time or activated partial thromboplastin time.[1] On the other hand, since LMWH has minimal protein binding with a dose-dependent response, it has not been deemed necessary to monitor the anticoagulant activity of these drugs.

Neither activated partial thromboplastin time[2] nor activated coagulation time[15] accurately reflects the action of LMWH. The anticoagulant response to LMWH may be monitored by anti-Xa levels, but this test may not reflect all drug activity since LMWH drugs also inhibit factor II. The Heptest (Haemochem Inc, St. Louis, Mo) assay measures inhibition of factors X and II and can be used to monitor LMWH therapy, but neither the Heptest nor anti-Xa levels have been shown to offer advantages over a standard drug dose adjusted for weight.[16] Second, neither of these tests is commonly available in hospitals. Furthermore, with the exception of ardeparin, the LMWH dosing recommendations have not been based on weight.[17]

The pharmacokinetics of unfractionated heparin are poorly understood. While the elimination of unfractionated heparin relies on both renal and hepatic clearance, the effects of renal or hepatic disease on biotransformation and excretion are not clear.[1] The elimination of LMWH is

Figure. **Schematic diagram of clotting mechanism**



Reprinted with permission from Horlocker and Wedel.[10]

delayed in patients with renal insufficiency and failure.[18-20] Patients with renal disease may experience drug accumulation and exaggerated response to an equivalent dose of these agents.[18] The plasma clearance of unfractionated heparin is dose dependent, while the clearance of LMWH is independent of dose.[5]

The LMWHs were developed in an effort to reduce the complications associated with unfractionated heparin, such as bleeding and thrombocytopenia;[9] however, 2 meta-analyses comparing LMWHs and unfractionated heparin provide data that suggest that the same degree of major bleeding occurs with both compounds.[21,22] The question of whether drug-induced thrombocytopenia occurs with LMWHs is controversial. Limited data[23] suggest that LMWHs produce less thrombocytopenia, while others have reported equal platelet effects from LMWHs and unfractionated heparin.[24,25]

Animal experiments with LMWH indicate a fibrinolytic action comparable to the action of urokinase.[26] This observation is consistent with the clinical finding that LMWHs result in significant lysis of deep venous thrombosis, an action not readily observed with unfractionated heparin.[27] In addition, LMWH decreases platelet adhesion and binding to fibrinogen and endothelial cells.[28] While these actions of LMWH would be of value in the prevention and lysis of deep venous thrombosis, they may contribute to the reported increase in bleeding associated with their use.[24]

The anticoagulant effects of unfractionated heparin are fully reversible by protamine; however, the reduced binding of protamine to LMWH fractions allows for only partial reversal of the action of these agents. Only the anti-IIa activity of LMWH is completely reversed, while the anti-Xa activity is not neutralized fully.[5] Table 3 compares some of the pharmacologic activities of unfractionated heparin and LMWH.

The true incidence of spinal and epidural hematoma as complications of regional anesthesia is difficult to assess due to failures in reporting and recognition,[30,31] but it is thought to be extremely rare. The overall estimated incidence has been calculated as less than 0.5 per 100,000 spinal anesthetics and less than 0.7 per 100,000 epidural anesthet-

Table 3. Pharmacologic features of unfractionated heparin and low molecular weight heparin (LMWH)

Agent	Route of administration[3]	Peak effect[29]	Anti-Xa/anti-IIa activity[5]	Dose-dependent clearance[5]	Time to normal hemostasis[29] (h)
Unfractionated heparin	Subcutaneous, intravenous	Intravenous, min; subcutaneous, 40-50 min	1:1	Yes	4-6 h
LMWH	Subcutaneous	3-5 h	2:1 to 4:1	No	12 h

ics.[32] Horlocker and Heit,[5] in their review article, calculated the incidence of this complication in orthopedic surgical patients who also were receiving enoxaparin to be between 1:1,000 and 1:10,000. Tryba and Wedel,[8] by assuming that all cases of clinically apparent spinal hematomas were reported in orthopedic surgical patients also receiving enoxaparin, determined the probable incidence in that group to be 1:14,000. These calculations indicate a significant increase in risk in this patient population.

Spinal and epidural hematomas develop as a result of bleeding from the epidural venous plexus, arterial vasculature, arterial venous malformations, hemangiomas, or other vascular lesions.[30] Spinal and epidural hematomas have long been recognized complications of regional anesthesia; although, they have been reported in patients who did not receive regional anesthesia and had no apparent risk factors.[33,34] Non–anesthetic-related risk factors that have been identified as contributing to the development of spontaneous spinal epidural hematoma are minor trauma, sudden increased pressure in the spinal canal produced by lifting or straining, anticoagulant therapy, and abnormal spinal vasculature.[33-39] Some authors have cited male sex[34,38] and age older than 50 years[34] as risk factors for hematoma development, but hypertension does not seem to increase the incidence of spinal/epidural hematoma.[34]

Patients receiving anticoagulants are at greater risk for developing epidural hematoma when regional anesthetics are administered.[34] As previously stated, there also are reports in the literature of spinal and epidural hematomas occurring spontaneously in patients taking anticoagulants who did not receive regional anesthetics, making the cause-and-effect relationship between anticoagulant therapy and regional anesthetic administration difficult to establish.[40-42] There also have been reports of spontaneous epidural hematomas in patients receiving daily aspirin therapy.[40,41] Nevertheless, regional anesthesia as a causative factor must be strongly suspected if the hematoma occurs at the level of the needle puncture.[8]

The degree of coagulopathy at which a regional anesthetic is absolutely contraindicated is not established.[43] Certainly the risk-benefit ratio must be considered before performing spinal or epidural anesthesia in any patient taking medication that affects platelet function or the clotting mechanism. It is recommended that central neuraxial blockade be avoided in patients receiving thrombolytic therapy such as streptokinase.[44]

The combination of subcutaneous unfractionated heparin and regional anesthesia has been deemed safe by Schwander and Bachmann[45] in their review of 5,000 cases. Management approaches to the patient receiving heparin vary widely. Some clinicians abandon regional anesthesia and postpone surgery for patients receiving systemic anticoagulants if a bloody tap occurs during attempts at epidural catheter insertion.[5] Although institution of anticoagulant therapy when an epidural catheter already is in place has not been associated with an increased incidence of hematoma formation,[5] some have recommended that epidural catheter removal should be avoided in a patient who is receiving heparin infusion.[43] Flexion or extension of the vertebral column with an epidural catheter in place increases the risk of catheter migration into a blood vessel or the dislodgment of an existing clot,[46] and catheter removal may create trauma to epidural vasculature.[17]

It is imperative that anesthetists effectively identify the patient at greater risk for development of spinal or epidural hematoma, recognize the presenting signs and symptoms of this complication, and take appropriate measures if such an event occurs. Sudden onset of severe back pain may be the first indication of an epidural hematoma.[35,38,39,44] The pain may develop a radicular component that is consistent with the involved spinal nerve roots affected by the pressure of the expanding hematoma.[38] Motor and sensory dysfunction, as well as bladder and rectal dysfunction,

also are cited as presenting symptoms.[34,38] In an examination of the first 30 cases of spinal and epidural hematoma associated with LMWH administration reported to the FDA, an atypical presentation of symptoms was noted. The most common presenting symptom in this patient group was not sudden onset of pain, but rather motor weakness and sensory deficit.[17]

In either case, initial symptoms may be masked in a patient who is receiving concurrent general and regional anesthesia, as is common during major revascularization procedures of the lower extremities. Symptoms would be obscured further by local anesthetic levels above that of the involved nerve roots.[43] For this reason, the anesthetist may choose to use neuroaxial opioids for postoperative pain management for patients at risk for developing spinal or epidural hematoma.[17] The choice of opioid solutions might obviate the need for local anesthetic solutions and, thereby, avoid the masking effects of these agents.

The 2 conditions most likely to mimic acute spinal or epidural hematoma are epidural abscess and a herniated intervertebral disk. Spinal or epidural hematoma may be differentiated from epidural abscess by its more sudden onset;[47] although, in the patients in whom a neurologic deficit developed in association with LMWH, the median time to onset of symptoms was 3 days.[17] Hematomas affecting selected nerve roots of the cauda equina have a greater potential for misdiagnosis as a herniated disk.[34] In either event, a review of the patient's history might lead to a more precise diagnosis.

Once suspected, the diagnosis and treatment of epidural hematoma is urgent.[38,43] Early signs of neurologic deficit, if not recognized and treated in a timely fashion, may ultimately progress to paraplegia or quadriplegia depending on the level of involvement.[38] If spinal cord compression persists unrecognized beyond 6 to 12 hours, permanent neurologic deficit and paralysis seem more likely.[35,43,48] Hematoma formation may be detected by computed tomography or magnetic resonance imaging (MRI) scanning,[34] but MRI scanning has been found superior as a tool of early detection.[34,37,38,49] MRI scanning can provide a determination of the extent of the hematoma as well as the degree of cord compression.[34] Furthermore, MRI can help differentiate epidural hematoma from an epidural abscess.[34]

Some[34,50] have reported excellent results from conservative management of spinal and epidural hematoma in patients who had no apparent neurologic deficit. If nonsurgical treatment is elected, serial MRI scanning is the monitoring modality of choice.[34] Nevertheless, the appropriate response to detection of hematoma with associated neurologic deficit is for the patient to undergo emergency surgical laminectomy and spinal cord decompression.[37,43,48]

The degree of neurologic compromise resulting from an epidural hematoma is variable.[51] As noted, duration of cord compression with resultant spinal cord ischemia has been linked to the severity of outcome. Three major factors have been cited in determining the degree of postoperative neurologic deficit:[38,52]

1. The force of spinal cord compression,
2. The severity of neurologic deficit preoperatively, and
3. The time from onset of symptoms to eventual surgical decompression.

In addition, younger patients[34] and those in whom hematoma development is confined to the cauda equina are thought to have a better prognosis for long-term recovery than patients in whom hematomas develop at L1 or higher.[37]

Based on the findings of this literature review, the following approach to anesthetic care of patients receiving LMWH is recommended:

1. Identify patients who are likely to receive anticoagulant drug therapy in association with their planned surgical procedure. Note the time and drug used for preoperative prophylaxis of deep venous thrombosis. Also, consult with the surgeon to ascertain plans for postoperative use of anticoagulant medications.
2. Recognize that if LMWH therapy has been instituted preoperatively, standard laboratory monitoring tests will not accurately reflect the patient's coagulation status.
3. Other medications affecting platelets or the clotting cascade will increase the risk of epidural hematoma formation if combined with LMWH therapy and should be a consideration in the risk-benefit analysis for administration of regional anesthesia.

If it is determined that regional anesthesia is indicated for the planned procedure, the following recommendations apply:

1. The patient should be informed of the potential added risks, and the discussion should be documented carefully on the anesthesia record.
2. The use of a midline approach to spinal or epidural administration will decrease the likelihood of a bloody tap.
3. Monitoring of the patient's neurologic status should continue for at least 5 days after catheter removal or until the patient is discharged

from the hospital. Patients discharged sooner than 5 days should be instructed to seek immediate attention if they experience pain and/or motor and sensory changes.

4. If a patient has received LMWH preoperatively, regional anesthesia administration should be delayed for at least 12 hours after the last dose of LMWH.

5. If a bloody tap occurs during regional anesthesia administration, surgery need not be postponed, but the initiation of LMWH therapy should be delayed for 24 hours postoperatively.[53]

6. If it is decided to discontinue indwelling spinal or epidural catheters before initiation of LMWH therapy, the catheter should be removed at least 2 hours before the first drug dose.[53]

7. Catheter removal should be delayed for 10 to12 hours after the last dose of LMWH. The subsequent dose after catheter removal should be delayed for 2 hours. Alternative methods of thromboprophylaxis should be considered if catheters are expected to be left in place for more than 24 hours.[53]

8. Postoperative pain management techniques should allow the assessment of neurologic function. The use of an opioid solution devoid of local anesthetic may be most effective for accomplishing this goal.

9. Obtain an immediate MRI and neurologic consultation if signs and symptoms of spinal or epidural hematoma develop.

The LMWH compounds are different in many ways from unfractionated heparin, and practice patterns used with standard heparin cannot be extrapolated for use with LMWH. In comparison with unfractionated heparin, the LMWHs have a more predictable bioavailability, longer half-life, and dose-dependent fibrinolytic activity, and the LMWHs also inhibit the binding of platelets to fibrinogen and vascular endothelial cells. Patient-related factors, such as renal disease and age, may affect therapeutic response to LMWH. Furthermore, combinations of LMWH with other agents that inhibit coagulation, such as nonsteroidal anti-inflammatory drugs, will increase the risk of adverse bleeding.[5]

It cannot be overemphasized that there is no currently available simple perioperative coagulation test for determination of clotting status with LMWH therapy. Therefore, the clinician must rely on a knowledge of the pharmacology of these agents as guidance for anesthetic choice. Also, the surgeon's plans for postoperative prophylaxis for deep venous thrombosis must be determined before institution of a continuous regional anesthetic technique.

In summary, the use of regional anesthesia in patients treated with LMWH during the perioperative period should be individualized based on the perceived risks and benefits associated with the surgical procedure and the findings of the history and physical examination. If a regional technique is elected, close communication with the surgeon about plans for perioperative use of LMWH is imperative. A knowledge of the pharmacology of LMWH is necessary to make informed and prudent decisions for anesthesia care for patients receiving this drug therapy.

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ACKNOWLEDGMENTS

We thank Don Clark Hall, EdS; Karen S. Brown, RPh; and Curtis Baysinger, MD, for their critical review and analysis of the manuscript, and Cindy Cutter, staff assistant, for contributions in manuscript preparation.