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Anesthetic Considerations in Patients Receiving Colony-stimulating Factors (G-CSF and GM-CSF)

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In an effort to achieve the maximum therapeutic benefit, chemotherapeutic agents are administered to the point of severe hematopoietic toxicity. This aggressive therapy leads to marrow aplasia with thrombocytopenia, anemia, and neutropenia. In an effort to decrease the period of neutropenia and thereby lessen the risk of infection, recent investigation has centered on the administration of granulocyte-macrophage and granulocyte colony-stimulating factors (GM-CSF and G-CSF, respectively) to increase granulocyte production.^{1,2} Although these new interventions effectively increase granulocyte production, adverse cardiovascular and pulmonary effects have occurred.^{2,3}

Currently, use of these agents is limited; however, early success suggests that their administration to patients with

neutropenia of various causes will continue to increase. In addition, these agents have recently been released for general medical use and are no longer restricted to specialized centers and protocols. Patients with neutropenia frequently require intraoperative and intensive care management for various diagnostic and therapeutic modalities.

Currently there is no information about these factors in the anesthesia literature. This report presents the anesthetic treatment of a patient receiving GM-CSF, reviews the current information available concerning colony-stimulating factors, discusses their adverse physiologic effects, and comments on the anesthetic implications of patients receiving these agents.

CASE REPORT

A girl aged 4 yr and 3 months and weighing 15.4 kg presented for treatment of juvenile chronic myelogenous leukemia. After preconditioning with cytosine arabinoside and total body irradiation, a matched unrelated bone marrow transplant was performed. Posttransplant graft function showed persistent neutropenia, anemia, and thrombocytopenia. Seventy days posttransplant, the absolute neutrophil count was 400-500 neutrophils per mm³. At this point, therapy with GM-CSF (20 µg · kg⁻¹ · day⁻¹) was started.

Because of persistent fever, further testing was performed and included computed tomography of the head, which showed opacification of the maxillary sinuses compatible with sinusitis. Follow-up chest x-rays revealed a diffuse interstitial pattern compatible with pulmonary edema, a small right-sided pleural effusion, and a left lower-lobe infiltrate. Based on these findings, the patient was scheduled for bron-

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choscopy and antral windows with biopsy of sinus mucosa. At preoperative examination, the girl appeared to be cushingoid and in no obvious distress. The respiratory rate was 28 breaths per min and the hemoglobin oxygen saturation (by pulse oximetry) 92% while she was breathing room air. The remainder of the examination was unremarkable except for alopecia and a diffuse, dry, scaling rash compatible with chronic graft-versus-host disease. Echocardiogram demonstrated a shortening fraction $([LVEDV - LVESV]/LVEDV)$, where LVEDV = left ventricular end-diastolic volume and LVESV = left ventricular end-systolic volume) of 0.32 and a small pericardial effusion (less than 0.5 cm).

On the morning of the procedure, the patient received 2 units of platelets for a platelet count of 18,000 platelets per mm^3 . Anesthesia was induced with propofol (3 mg/kg) and maintained with isoflurane (inspired concentration 0.5–1.5%) and nitrous oxide (50–70%) in oxygen. Atracurium was used for muscle relaxation. Bronchoscopy and lavage were accomplished without difficulty, after which antral windows and sinus biopsy were performed. Intraoperative blood loss was 10–20 ml. The trachea was extubated without difficulty.

The patient's postoperative course was uncomplicated; however, she continues to have unsatisfactory graft function, with an absolute neutrophil count of 1,680 neutrophils per mm^3 after a 14-day course of GM-CSF.

DISCUSSION

The hematopoietic growth factors, or colony-stimulating factors, regulate the development and differentiation of bone marrow stem cells into erythrocytes, granulocytes, and megakaryocytes.^{4,5} These growth factors are a heterogeneous group of glycoproteins which, through recombinant deoxyribonucleic acid (DNA) cloning technology, now can be produced in sufficient quantities to permit clinical trials in patients with loss of bone marrow function. Of these growth factors, six are currently available for clinical trials; these include GM-CSF, G-CSF, macrophage colony-stimulating factor (M-CSF), and interleukins 1, 2, and 3 (IL-1, IL-2, and IL-3).

The largest clinical experience is with the myeloid colony-stimulating factors (G-CSF and GM-CSF). Trials have included patients with marrow function loss due to several causes, including aplastic anemia, idiopathic neutropenia, congenital agranulocytosis, and chemotherapy-induced neutropenia, as well as loss of function after bone marrow transplantation.^{3,6–11} In addition to reducing morbidity from neutropenia after chemotherapy, these agents also may allow increased therapeutic intensity and thereby improve the long-term outcome of patients with malignancy.^{8,12}

Despite these practical applications, adverse effects can occur after the administration of colony-stimulating factors. Although generally mild with G-CSF, significant adverse effects have been described with GM-CSF. Mild toxicities include bone pain and flulike symptoms, including fever, rash, anorexia, and myalgia.³ Of particular concern to the anesthesiologist are the effects on fluid balance and the occurrence of pleural and pericardial effusions, as seen in our patient and reported in other clin-

ical trials.^{2,8,9,13–15} Although our patient's pericardial effusion was asymptomatic, preoperative echocardiography is recommended and treatment indicated in symptomatic patients.

In addition to pericardial and pleural effusions, a generalized capillary leak syndrome, similar that described with IL-2 administration, may occur and lead to interstitial pulmonary edema.¹⁶ Although these effects generally are mild, acute deterioration in respiratory status has been described during GM-CSF administration.¹⁷ The etiology of the capillary leak syndrome remains controversial. Proposed mechanisms include increased release of tumor necrosis factor from macrophages or activation of neutrophil-endothelium interactions that lead to the release of vasoactive mediators.^{14,18}

The frequency with which these adverse effects occur depend on the particular recombinant product (mammalian, yeast, or bacterial [*Escherichia coli*]) and dosage that is used. Toxicities vary because the method of production affects both the specific activity and the glycosylation pattern of the protein. For the mammalian- and bacterial-produced product, pleural and pericardial effusions occur more commonly with doses exceeding $16 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$.^{13,19}

The combination of pleural effusions with interstitial edema may compromise respiratory function and thereby decrease functional residual capacity and increase the likelihood of perioperative hypoxemia. The likelihood of hypoxemia is further increased by an increased oxygen consumption in children and in those with fever or sepsis.

Treatment of the pulmonary and peripheral edema with diuretic agents may further compromise preoperative status and lead to intravascular volume depletion and electrolyte imbalance. The preoperative chest x-ray in our patient revealed a small pleural effusion with an interstitial infiltrate. Although she was asymptomatic, hemoglobin oxygen saturation (by pulse oximetry) was 92–93%.

In addition to the more chronic effects on pulmonary and fluid status, Lieschke *et al.* have described an acute first-dose effect after intravenous bolus administration.¹⁴ Manifestations include hypoxemia with normal chest x-rays, hypotension, tachycardia, and syncope. Additionally, a small number of patients (3 of 48) had decreased peak expiratory flow rates, suggesting bronchoconstriction, but no symptomatic complaints were noted. These adverse effects were presumed to be the result of an unidentified vasoactive mediator because there was no change in serum levels of complement, histamine, or tumor necrosis factor.

Other complications arising with the administration of GM-CSF include thrombosis around central venous catheters. Again, the reasons for this remain unknown, although possibilities include mediator release from granulocytes or alterations in granulocyte-endothelium interactions. Although generally of little clinical significance,

one death due to pulmonary embolism has occurred in a patient receiving GM-CSF.¹⁵

In summary, recent clinical trials have shown the efficacy of the colony-stimulating factors in the treatment of neutropenia of diverse etiologies. Although initially limited to patients with neutropenia associated with chemotherapy or acquired immunodeficiency syndrome, the initial success has led to early clinical trials in various other "at-risk" groups, including patients with thermal injuries, those undergoing emergency laparotomy, and those with overwhelming sepsis. Due to the clinical status of many of these patients, anesthesiologists will be called on to provide perioperative care for patients receiving these factors. Preoperative identification and treatment of the adverse physiologic effects of colony-stimulating factors, including capillary leak syndrome with pericardial and pleural effusions, will help in the provision of safe anesthetic care.

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