Commentary

Measuring the anticoagulant effect of low molecular weight heparins in the critically ill

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Abstract

Antithrombotic prophylaxis in critically ill patients frequently fails. Venous thromboembolism is associated with adverse clinical outcomes, including a prolonged intensive care unit stay and death. A potential mechanism by which critically ill patients may be predisposed to antithrombotic failure is the inability to achieve 'prophylactic' anticoagulant drug levels as a result of impaired absorption. For example, previous studies have shown that patients on inotropes have reduced serum levels of low molecular weight heparin, presumably on the basis of reduced absorption from the subcutaneous injection site. In the previous issue of the journal, Rommers and colleagues examined whether subcutaneous edema reduces absorption of a low molecular weight heparin; although small, and thus underpowered, the authors failed to find any relationship between the level of low molecular weight heparin and the presence of edema. These findings provide reassurance that subcutaneously administered medications may be used in critically ill patients with edema.

It is now widely accepted that patients in the intensive care unit (ICU) are at a high risk of deep vein thrombosis and pulmonary embolism. Patients who develop these thromboembolic complications have a higher risk of both ICU and hospital-acquired morbidity and mortality, including the need for and the duration of mechanical ventilation, the ICU and hospital lengths of stay, and, perhaps, death [1]. It is therefore important that all patients in the ICU receive effective thromboprophylaxis [2]. In those patients with an absolute contraindication to anticoagulants, such prophylaxis should take the form of intermittent pneumatic compression devices and, perhaps, screening ultrasonography.

In the absence of a contraindication, all patients in the ICU should receive some form of pharmacologic thromboprophylaxis. In most cases this will consist of either unfractionated heparin or low molecular weight heparin (LMWH). Unfractionated heparin at a dose of 5000 U subcutaneous twice or three times daily is the preferred anticoagulant in North America, while LMWH at prophylactic doses is used most frequently in Europe.

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Despite the routine provision of anticoagulant prophylaxis, failures do occur. For example, in a prospective study of 261 patients performed by our group, 25 patients (9.6%) developed ultrasonographically detected deep vein thrombosis despite routine and protocol-directed provision of thromboprophylaxis [1]. This observation suggests that additional research is required to refine prophylaxis for these very-high-risk patients.

Failure of pharmacologic prophylaxis may be due to an overwhelming prothrombotic stimulus or due to inadequate anticoagulant effect. Critically ill patients may harbor ICUspecific characteristics that predispose to failure of thromboprophylaxis. Dorffler-Melly and colleagues demonstrated that critically ill patients receiving inotropic support have significantly lower peak LMWH levels than similar patients not exposed to ionotropes [3]. They hypothesize that impaired tissue perfusion as a result of vasoconstriction reduces absorption of LMWH. This reduced anticoagulant effect may in turn predispose to thrombosis.

Many patients in the ICU have extensive subcutaneous edema. Such edema is due to aggressive fluid resuscitation, reduced colloid oncotic pressure, renal insufficiency and tissue trauma associated with injury or surgery. It is reasonable to hypothesize that subcutaneous edema may impair absorption of LMWH, thus predisposing to lower peak heparin levels and an increased risk of thrombosis.

In the previous issue of the journal, Rommers and colleagues [4] reported results of a pilot study that examined the impact

of subcutaneous edema on the pharmacokinetics of LMWH. In this small (total recruitment 14 patients), nonrandomized pilot study, the authors performed careful pharmacokinetic analysis of the anti-factor Xa heparin levels found after subcutaneous administration of 2500 U dalteparin in a group of critically ill patients. In their study, patients with edema were defined by at least a 10% increase in body weight and the appearance of generalized edema. The pharmacokinetics were compared by examining the peak anti-factor Xa heparin level and the area under the anti-factor Xa heparin level-time curve. The authors conclude that there was no difference in the observed anticoagulant effect; however, the peak levels were lower than those expected - an observation consistent with previous publications.

Although small, and thus underpowered, the study of Rommel and colleagues does provide some reassurance that the degree of tissue edema found in critically ill patients does not significantly impact the anticoagulant effect of dalteparin. Methodologically rigorous conclusions would require a much larger study, with more explicit control of variables such as renal function, use of inotropes and baseline-dependent and time-dependent variables (age, gender and admission diagnosis) included in a rigorous multivariable analysis. In the absence of such data, however, the results of this study should reassure us that subcutaneously administered medications will be absorbed into the circulation of critically ill patients. These observations are important for the design of future studies of both thromboprophylaxis and other interventions that may require medication to be given by this route.

Competing interests

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