

## Effects and Timing of Tranexamic Acid on Transfusion Requirements in Patients Undergoing Cardiac Surgery with Cardiopulmonary Bypass

To the Editor:

Sigaut *et al.*<sup>1</sup> published a double-blind, randomized, controlled trial comparing low-dose and high-dose tranexamic acid (TA) bolus injections followed by continuous infusion in patients undergoing cardiac surgery with cardiopulmonary bypass.

The primary study endpoint was the incidence of overall blood products transfusions during surgery and up to 7 days postsurgery, which was not different between the two groups, a part from a lower transfusion of platelets concentrates during surgery in the high-dose TA group. The high-dose TA group showed also lower amounts of blood losses during day 1 and reduced administration of fresh-frozen plasma and platelets concentrates during the first postoperative week. Moreover, in the high-dose TA group, the rate of bleeding-related reexploration was less than half. Interestingly, although not statistically different, the 7-day and 28-day mortality rates were lower in the high-dose compared with low-dose TA group.

These results are very interesting and may partially support the use of high-dose TA. However, concerns may be raised against the protocol and design of the study. The primary outcome of transfusion at day 7 seems rather inappropriate for several reasons.

First, the half-life of TA (in order of a couple of hours)\* and the need to maintain appropriate levels to ensure antifibrinolytic efficacy ( $>10 \mu\text{g/ml}$ )<sup>2</sup> are not consistent with a 7-day evaluation.

Second, during the first week, many other factors influence the risk of bleeding and transfusion requirements, for instance, postoperative strategies for antiplatelets therapy after coronary artery bypass grafting, for anticoagulation after valve surgery, or in patients developing atrial fibrillation. The authors did not clarify about the presence of standardized protocols for postoperative antiplatelet and anticoagulant therapy, and the incidence of postoperative atrial fibrillation was not reported.

Last, acute kidney injury is a well-known complication after cardiac surgery, with different incidence according to the criteria used and up to 5% of patients requiring postoperative renal replacement therapy.<sup>3</sup> The anticoagulation associated with renal replacement therapy is another factor that may increase the risk of bleedings and incidence of transfusions. Importantly, in this study, the baseline creatinine was higher in the high-dose group. The peak postoperative

creatinine was not different between the groups, but the incidence of postoperative renal replacement therapy is not reported what hampers the interpretation of the results.

It may be speculated that significantly less blood loss and lower incidence of bleeding-related repeat surgery during the first 24-h postsurgery in the high-dose group was related to TA effects, considering the half-life of the drug, whereas the 7-day outcome could have been influenced at least by these three factors: strategies for antiplatelets/anticoagulation, development of atrial fibrillation, and need of renal replacement therapy and the related anticoagulation.

Further data analysis in this regard in both groups may be very useful to clarify the difference between the two groups.

### Competing Interests

The authors declare no competing interests.

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### In Reply:

We thank Dr. Sanfilippo *et al.* for their interest in our recent study published in *ANESTHESIOLOGY*<sup>1</sup> about the comparison of two doses of tranexamic acid in adults undergoing cardiac surgery.

They criticize the choice of the primary outcome in our study, which was the number of patients who received at least 1 unit of blood product during the first postoperative week (including the intraoperative period).<sup>1</sup> They would have preferred a shorter period of observation for the primary outcome because of the half-life of tranexamic acid which was discontinued at the end of surgery. We disagree with their point of view. First, transfusion at day 7 includes the first day, when the majority of the transfusions occurred: 62% of the transfused patients were transfused only on the first day, 77% of the packed erythrocytes and 71% of the fresh-frozen plasma were given during day 1. Furthermore, transfusion during the first day, including the intraoperative period is reported

\* Available at: <http://labeling.pfizer.com/ShowLabeling.aspx?id=556>. Available July 11, 2014.

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in table 6 and transfusion was similar between groups. Second, major surgical bleeding may have been responsible for delayed transfusion after the first 24 h. Third, several major articles about antifibrinolytic therapy used a 1-week (or even more) endpoint.<sup>2-4</sup> Indeed, the goal of antifibrinolytic therapy is to decrease transfusion with its related complications, some being life threatening, and cost. Transfusion risk depends on the number of units or donors to which the patient is exposed during his whole hospitalization, not just during day 1. Thus, in our opinion, focusing on the first day is looking through the wrong end of the telescope. If one dose of tranexamic acid does not make a difference compared with another after the intraoperative period, then it is not superior.

Sanfilippo *et al.* asked for some details about postoperative procedures, such as antiplatelet therapy and anticoagulation. In fact, we forgot to mention in the article that postoperative care was adapted to the medical and surgical problems of each patient and did not differ from those usually practiced. It was indeed important for us to evaluate tranexamic acid in a “real-life situation,” once again to be sure to bring out a strong difference.

Finally, Sanfilippo *et al.* asked for the incidence of postoperative renal replacement therapy. Unfortunately, we did not collect these data. We would like to add that hemorrhagic events (pleural and pericardial effusions) after the first 24 h (day 2 to day 28) were rare: 12 in the low-dose group (4.3%) and 8 in the high-dose group (2.8%). The low incidence of such events attenuates the possibility that all these potential flaws may have biased our study.

### Competing Interests

The authors declare no competing interests.

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## Lipid Emulsion Increases the Fast Na<sup>+</sup> Current and Reverses the Bupivacaine-induced Block: A New Aspect of Lipid Resuscitation?

### To the Editor:

We read with great interest the article by Wagner *et al.*,<sup>1</sup> in which the authors evaluated the effects of lipid emulsion with bupivacaine on cardiac action potential and fast Na<sup>+</sup> current ( $I_{Na}$ ) in native rat cardiomyocytes. Because lipid emulsion is becoming a standard rescue treatment for intractable fatal arrhythmias resulting from local anesthetic systemic toxicity, it is of great significance to assess the effects of lipid emulsion on cardiac electrophysiology. Of special interest was the result showing a “direct lipid effect” in the presence and absence of local anesthetics on sodium channels, separating a “lipid sink” by ultracentrifugation. In the presence of local anesthetics, a direct lipid effect was clearly shown by subtracting the effect of centrifuged from uncentrifuged lipid solutions. However, we had some concerns in interpreting these results. In our recent study, we also evaluated the lipid sink effect using lipid emulsions and their centrifuged solutions in voltage-gated proton channels.<sup>2</sup> Use of these solutions in proton channels was unimportant because lipid emulsions did not affect proton currents. However, we thought some care should be taken when using these solutions in voltage-gated sodium channels.

Our first concern is in regard to a small amount of sodium ions contained in lipid emulsions. Wagner *et al.* used Lipovenös® MCT 20% (medium-chain triglycerides) (Fresenius Kabi AG, Bad Homburg, Germany), which contains sodium hydrate and sodium oleate, that is, up to 5 mM sodium ions in total.\* These concentrations are low but can slightly increase the driving force of sodium currents. In addition, as the authors described in detail, sodium currents in cardiomyocytes can easily lead to voltage errors. Therefore, the low concentration of sodium in lipid emulsions may increase the  $I_{Na}$ . Indeed, Wagner *et al.*<sup>1</sup> showed that 10% Lipovenös®-containing solutions without local anesthetics increased the  $I_{Na}$  by approximately 20% compared with the control solutions. Lipovenös® MCT 20% consists of 50% long-chain triglycerides and 50% MCTs. Some long-chain triglycerides (linolenic acid, linoleic acid, and oleic acid) and caprylic acid in MCT have been shown to reduce  $I_{Na}$ , whereas other monounsaturated or saturated fatty acids did not.<sup>3,4</sup> Indeed, recent report by Nadrowitz *et al.*<sup>5</sup> indicated that 15% Lipofundin® (B. Braun Melsungen AG, Melsungen, Germany) (50/50 long-chain triglyceride/MCT) significantly reduced  $I_{Na}$  by  $42 \pm 4\%$  in human embryonic kidney cells expressing human Nav 1.5. In contrast, Wagner *et al.* first showed the increase of  $I_{Na}$  by lipid emulsion in native rat cardiomyocytes, which could be the

\* Available at: [http://www.fresenius-kabi.de/files/Fachinfo\\_Lipovenoes\\_MCT20.pdf](http://www.fresenius-kabi.de/files/Fachinfo_Lipovenoes_MCT20.pdf). Accessed April 20, 2014.