Anesthesiologists are experts at drug dosing, and we likely have more experience doing so than any other specialty in medicine. With anesthetic drugs such as fentanyl or propofol, we often dose by titrating to effect, which is sometimes more an art than a science. So what about drugs that are not titrated? Why do we give 2 g of cefazolin to virtually all adult patients, whether they are 40 or 120 kg? In fact, we give many such nontitratable drugs, tranexamic acid being one of them, for which the optimal dosing regimens have yet to be determined. Perhaps one dose does not fit all.

Although tranexamic acid was first discovered more than 50 yr ago, its clinical utility to reduce blood loss and transfusion requirements has only been popularized in the past decade. A synthetic lysine analog that competitively inhibits the conversion of plasminogen to plasmin,1 tranexamic acid reduces the proteolytic action of plasmin on fibrin clots, resulting in inhibition of fibrinolysis. The mechanism of action is to stabilize existing clots rather than promoting new clot formation. Although the Food and Drug Administration–approved indications are limited to reducing bleeding in hemophiliacs having tooth extraction and in women with menorrhagia, the off-label use to reduce blood loss and transfusion requirements—were also similar between groups. The secondary outcomes—blood loss from surgical drains, percentage of patients transfused, and postoperative thrombotic events—were compared to a single bolus dose.

Overall, the study was well designed and conducted and adds to the growing body of evidence supporting the efficacy and safety, as well as optimal dosing regimens for tranexamic acid. There are, however, some limitations that should be recognized. The doses were not weight-based, and according to recent pharmacokinetic studies,7 the postoperative infusion may have been subtherapeutic. In addition, a placebo

1. Tranexamic Acid

What Is Known and Unknown, and Where Do We Go From Here?

Susan M. Goobie, M.D., F.R.C.P.C., Steven M. Frank, M.D.

ANESTHESIOLOGISTS are experts at drug dosing, and we likely have more experience doing so than any other specialty in medicine. With anesthetic drugs such as fentanyl or propofol, we often dose by titrating to effect, which is sometimes more an art than a science. So what about drugs that are not titrated? Why do we give 2 g of cefazolin to virtually all adult patients, whether they are 40 or 120 kg? In fact, we give many such nontitratable drugs, tranexamic acid being one of them, for which the optimal dosing regimens have yet to be determined. Perhaps one dose does not fit all.

Although tranexamic acid was first discovered more than 50 yr ago, its clinical utility to reduce blood loss and transfusion requirements has only been popularized in the past decade. A synthetic lysine analog that competitively inhibits the conversion of plasminogen to plasmin,1 tranexamic acid reduces the proteolytic action of plasmin on fibrin clots, resulting in inhibition of fibrinolysis. The mechanism of action is to stabilize existing clots rather than promoting new clot formation. Although the Food and Drug Administration–approved indications are limited to reducing bleeding in hemophiliacs having tooth extraction and in women with menorrhagia, the off-label use to reduce blood loss and transfusion requirements has increased dramatically. In fact, the evidence supporting tranexamic acid is so extensive that in 2011 the World Health Organization included tranexamic acid on their list of 350 essential medicines.2 There is ongoing debate, however, around optimal perioperative tranexamic acid dosing, which varies widely, by up to tenfold, in recent studies.3–5

In this issue of Anesthesiology, Zufferey et al.6 report a double-blind prospective randomized trial on tranexamic acid dosing regimens in total hip orthroplasty. The authors enrolled about 80 patients in each of two groups: one group receiving a single 1-g bolus of tranexamic acid preincision and the other receiving the same bolus, followed by 1 g infused during 8 h. The primary outcome, calculated blood loss based on hemoglobin change over a 5-day period, was no different between groups. The secondary outcomes—blood loss from surgical drains, percentage of patients transfused, and postoperative thrombotic events—were also similar between groups. The authors conclude that supplementary tranexamic acid as a perioperative infusion did not add benefit to a single preincision bolus dose and that blood loss, transfusion rates, and thrombotic event rates were all very low. The authors also include a small meta-analysis (six studies, 611 patients), showing that additional tranexamic acid did not further reduce blood loss in hip replacement surgery, when compared to a single bolus dose.

Overall, the study was well designed and conducted and adds to the growing body of evidence supporting the efficacy and safety, as well as optimal dosing regimens for tranexamic acid. There are, however, some limitations that should be recognized. The doses were not weight-based, and according to recent pharmacokinetic studies,7 the postoperative infusion may have been subtherapeutic. In addition, a placebo...
group was not used; therefore, we cannot comment on efficacy or safety compared to no treatment.

It is useful to summarize what is known and unknown regarding perioperative tranexamic acid. We know that tranexamic acid is being called a game changer at national orthopedic and blood management meetings, and transfusion rates for hip and knee arthroplasties are now under 5% in many centers. When summarizing a large number of studies comparing tranexamic acid to placebo, overall blood loss and transfusion requirements are both reduced by ≈30%.1,4,5,8 We also know that the worldwide popularity of tranexamic acid was greatly enhanced after the CRASH-2 Trial in trauma, published in 2011,9 and may be further enhanced by the much anticipated WOMAN Trial in postpartum hemorrhage published in 2017.10 In these trials, a 1-g loading dose was given, followed by an infusion of 1 g during 8 h (in CRASH-2) or the option for a second 1-g bolus for continued bleeding (in WOMAN). In both these large trials (each more than 20,000 patients), mortality was significantly reduced with tranexamic acid, while thrombotic events were not increased. Both studies also revealed the importance of early tranexamic acid administration within 3 h of the injury or the childbirth. Of interest, the dosing regimen for CRASH-2 was identical to the bolus-plus-infusion group in the Zufferey study. Other known facts are that tranexamic acid is tenfold more expensive than ε-amino caproic acid for an equivalent dose; however, whether tranexamic acid has advantages over ε-amino caproic acid is unclear given the lack of head-to-head randomized trials. The cost per case for the tranexamic acid dose advocated by the Zufferey study (1 g) is only $36 given current U.S. pricing.

There is plenty, however, that we do not know. The optimal plasma concentration to inhibit fibrinolysis has been reported between 10 and 20 μg/ml in older in vitro studies, and as high as 150 μg/ml in more recent studies.7 To date, the minimal effective plasma concentration to inhibit fibrinolysis based on the in vitro dose–response relationship has not been determined. Furthermore, the pharmacokinetic profile of tranexamic acid is just now starting to be elucidated. Sophisticated pharmacokinetic modeling studies report that steady-state concentrations of 20 μg/ml are obtained by a 10 mg/kg loading dose, followed by a 5 mg/kg/h infusion,7 an infusion dose about three times greater than used in the Zufferey study, perhaps explaining why their infusion did not add benefit. Another reason may be that for a 1-h surgery, tranexamic acid simply does not need to be redosed or infused given its 2- to 3-h half-life. However, given that orthopedic patients continue to bleed postoperatively, the rationale for assessing the impact of an 8-h infusion after the bolus makes sense. Regarding venous thromboembolism (VTE) risk, we know that tranexamic acid is a clot stabilizer, and multiple sources report the thromboembolic risk to be negligible. We do not, however, know the safety profile in patients at higher VTE risk since most studies are either underpowered or exclude such high-risk patients. We also do not know the true contraindications for using tranexamic acid. Even in the Zufferey study, they changed one contraindication midstudy, from any history of VTE to acute, ongoing VTE. The package insert says any seizure history is a contraindication, but is this really necessary? Seizures have been mostly reported with high-dose regimen in high-risk patients. And what about renal insufficiency? Should a creatinine clearance less than 15 ml/min be a contraindication, or can we simply reduce the dose according to renal function?

In summary, the study in this issue of Anesthesiology supports the efficacy and safety of tranexamic acid in hip arthroplasty and shows that in short-duration orthopedic procedures, a single bolus of tranexamic acid is adequate, with no additional benefit of a continuous infusion. Further studies, however, need to determine the ideal therapeutic plasma level to reduce bleeding and transfusion while avoiding adverse effects. In addition, for longer surgeries, pharmacokinetic studies are needed to identify the optimum bolus dose and infusion rates to achieve the desired steady-state plasma concentrations. Ongoing well designed tranexamic acid trials including the CRASH-3 trial (head injury) and ClinicalTrials.gov NCT01813058 (scoliosis surgery) will provide answers to these questions. Zufferey et al. should be congratulated for adding to our knowledge base for perioperative tranexamic acid use which will benefit our patients by reducing allogeneic transfusions and their associated risks and costs, thus adding value to the care we deliver.

Competing Interests
Dr. Frank has received consulting fees from Haemonetics (Braintree, Massachusetts), Medtronic (Minneapolis, Minnesota), and Zimmer/Biomet (Warsaw, Indiana). Dr. Goobie declares no competing interests.

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ANESTHESIOLOGY REFLECTIONS FROM THE WOOD LIBRARY-MUSEUM

New Orthoform for Old Freud: Insoluble Numbing for Sigmund’s Insoluble Cancer

Sculptor Robert Toth captured Sigmund Freud (1856 to 1939, left) in one of those rare moments when the “Father of Psychoanalysis” was not puffing on one of his 20 cigars daily. That heavy smoking habit led to an oral cancer, which ulcerated the area where all of those cigar butts had rested at the back right of Freud’s mouth. As the cancer recurred and was surgically carved away, a painful nonhealing crater developed. To ease Freud’s suffering, one consultant, Dr. Joseph Weinmann, directed that New Orthoform (right) be dusted liberally onto the gaping hole at the back of Freud’s mouth before a massive oral prosthesis was inserted. That white dusting powder was a highly insoluble hydroxyaminobenzoic ester which had been synthesized by Alfred Einhorn (1856 to 1917) and manufactured by Hoechst, as had its predecessor, Orthoform. By interchanging “Old” Orthoform’s hydroxy and amino groups, New Orthoform had proven to be not only a cheaper local anesthetic to manufacture but also one which could double as a bactericidal desiccant. How ironic that Freud’s academic career had opened with his professional (and personal) use of one local anesthetic, cocaine, and would close with his terminal use of another, New Orthoform! (Copyright © the American Society of Anesthesiologists’ Wood Library-Museum of Anesthesiology.)

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