Understanding Potential Drug Side Effects

Can We Translate Molecular Mechanisms to Clinical Applications?

Andreas Koster, M.D., Jerrold H. Levy, M.D., F.A.H.A., F.C.C.M.

CLINICAL pharmacology is one important basis of modern anesthesiology. In this month's edition of Anesthesiology, Lecker *et al.*[1] report the results of an investigation of high concentrations of tranexamic acid (TXA) on *N*-methyl-D-aspartate (NMDA) and glutamate receptors in cultured murine hippocampal neurons. The investigation was prompted by reports of seizures in patients receiving TXA during cardiac surgery. It is an excellent example of "reverse translation": taking clinical problems to the laboratory to understand their etiology and mechanism.

"[This study] is an excellent example of 'reverse translation': taking clinical problems to the laboratory to understand their etiology and mechanism."

The role of antifibrinolytic therapy for bleeding continues to expand in medical practice. The antifibrinolytic agent most extensively used in 2016 is the lysine analog TXA, a drug developed in the 1950s by Okamoto Utakoin in Japan when searching for a therapy to treat postpartum hemorrhage. From the late 1960s until today TXA has been used in a growing number of surgical and nonsurgical settings to reduce bleeding including menorrhagia, cardiac surgery, orthopedic surgery, and in trauma. The results of the Clinical Randomization of an Antifibrinolytic in Significant Hemorrhage 2 (CRASH-2) trial in trauma patients had a major impact on its growing use in clinical practice.[2] TXA also is used for prophylaxis in patients with hereditary angioedema and may have important antiinflammatory effects as a protease inhibitor.[3] Despite this extensive use, reported side effects are infrequent.[4] In 2009 TXA acid was entered into the World Health Organization list of essential medicines.

In 2010, reports began to emerge suggesting increased nonischemic clinical seizures after cardiac surgery and cardiopulmonary bypass (CPB) with the use of high-dose TXA infusions.[5] Additional analyses from larger retrospective evaluations also reported an increase in convulsive seizures after CPB even when TXA was used at lower doses.[5] Despite these reports, it is important to realize that case reports are anecdotal. Retrospective analyses of clinical databases and even the gold standard of clinical studies, a double-blind, randomized, placebo-controlled prospective trial, can only suggest a potential association or statistical probability between drug administration and adverse effects. After cardiac surgery, seizures have multiple causes that range from emboli to the cerebral circulation, producing cerebral anoxia to other potential drug-induced effects. However, a cause–effect relationship of adverse events is best proven by elucidation of the molecular/pathophysiologic mechanisms of the potential adverse effect.

Multiple mechanisms may be responsible for TXA producing seizures. Current reports suggest TXA increases neuronal excitation by antagonizing inhibitory γ-aminobutyric acid neurotransmission and inhibits neural glycine receptors.[6,7] When one examines the chemical structures of TXA, γ-aminobutyric acid, and glycine and their similarities, additional mechanisms may be involved; however, epsilon aminocaproic acid, another lysine analog antifibrinolytic agent, has not been reported to produce seizures.[5]

Lecker *et al.*[1] report that high concentrations of TXA inhibit NMDA receptors. The NMDA receptor is an ion channel receptor present in neural cells that is activated after glutamic acid or glycine binding to control neurotransmission in what is called synaptic plasticity. Thus, inhibiting these receptors will allow for neuronal excitation and thus

Image: Adobe Stock.

Corresponding article on page 89.

Accepted for publication January 26, 2017. From the Institute of Anesthesiology, Heart and Diabetes Center North Rhine-Westphalia, Bad Oeynhausen, Ruhr-University Bochum, Germany (A.K.); and Department of Anesthesiology, Cardiac Anesthesiology and Critical Care, Duke University School of Medicine, Durham, North Carolina (J.H.L.).

 Anesthesiology 2017; 127:6-8

<zdoi;10.1097/ALN.0000000000001748>

seizures. However, despite this interesting finding, the TXA concentrations that are effective to inhibit NMDA receptors are much higher than concentrations found in the cerebral spinal fluid and 5- to 500-fold higher than plasma concentrations measured after a high-dose TXA protocol in cardiac surgery.[5,7]As the authors note, such concentrations are currently not systemically achieved *via* intravenous administration but only topically *via* local application.

From a molecular perspective, the chemical structure of TXA is very similar to the amino acid glycine, which in the brain and spinal cord acts as an inhibitory neurotransmitter. In a previous study, Lecker *et al.*[7] reported that TXA, in concentrations found in the cerebrospinal fluid after a standard high-dose protocol in cardiac surgery, inhibits cerebral glycine receptors as a potential mechanism to cause seizures. However, in cardiac surgery the increase in seizures potentially associated with TXA has been observed predominantly in older patients after procedures with CPB.[5] In open-heart surgery, air enters the heart and circulation, and despite efforts to prevent systemic embolism, microbubbles may enter the systemic circulation, produce local microvascular injury, and damage the blood–brain barrier (BBB). Other potential sources of emboli include atheromatous material or calcified plaques from the aorta, thrombotic material from the left side of the heart, particulate matter after valve surgery, and potential right-to-left communication with a patent foramen ovale. Local sites of vascular injury may cause local disturbances of the BBB, increase TXA concentrations at the site of injury of the brain, and potentially promote seizures. This effect may be aggravated in older patients, who already often present with age-related dysfunction of the BBB.[8] Additionally, using newer sensitive laboratory methods, large variations in TXA plasma levels and the interindividual ratio between plasma concentrations and concentrations found in the cerebral spinal fluid have been reported.[7,9] Therefore, additional mechanisms may be responsible for producing seizures in addition to circulating levels of TXA. This is particularly important because the risk of seizures seems insignificant in women receiving approximately 4 g/d TXA for menstrual bleeding, in trauma patients in the large CRASH-2 trial who received 2 g TXA, and in noncardiac surgical patients.[2]

Glycine is also an obligatory co-agonist of the NMDA subtype of ionotropic glutamate receptors that control numerous calcium-dependent processes. These receptors are not only distributed widely in the central nervous system but also in renal, myocardial, and other tissues. The NMDA receptors are currently under intensive investigation as targets for treatment of psychiatric disorders such as depression, schizophrenia, and Alzheimer disease.[10] The NMDA receptors outside the central nervous system also are discussed as potential targets for new pharmacologic targets.[11]

One of the interesting aspects of TXA use is the increasing application of this agent topically. A recent Cochrane review addressed the topical application of TXA in a large variety of clinical settings such as cardiac surgery, knee arthroplasty, and spinal surgery.[12] The authors concluded that topically administered TXA may reduce bleeding and transfusions but expressed concern that safety data, particularly with regard to thromboembolic complications, are missing.[12] High topical concentrations of TXA may lead to lower plasma levels that depend on the dose used, the application site, and local readsorption and may achieve plasma levels that are considerably lower than concentrations measured after a high-dose intravenous protocol in cardiac surgery but are effective at inhibiting systemic hyperfibrinolysis.[1,5]

Important for the elucidation of the causes of adverse drug reactions is the understanding of drug actions on nontarget receptors, proteases, or other pharmacologic processes as well as on-target effects. As in this case, TXA, a hemostatic agent, potentially facilitates seizures. In understanding key functions of NMDA receptors in controlling neurotransmission, their distribution in the different organ systems, and the effects of TXA as noted by Lecker *et al.*,[1,7] molecular mechanisms are important to explain better and potentially earlier-recognized potential side effects. However, there are likely additional mechanisms behind both TXA and seizures after cardiac surgery. Multiple factors may be important in producing seizures that involve multiple receptors, disruption of the BBB, and other potential concomitant events that contribute to the clinical side effects. We look forward to further investigation of the mechanisms of TXA-induced seizures in patients.

Competing Interests

The authors are not supported by, nor maintain any financial interest in, any commercial activity that may be associated with the topic of this article.

Correspondence

Address correspondence to Dr. Koster: akoster@hdz-nrw.de

References

1. Lecker I, Wang DS, Kaneshwaran K, Mazer CD, Orser BA. High concentrations of tranexamic acid inhibit inotropic glutamate receptors. Anesthesiology 2017; 127:89–97
2. Shakur H, Roberts I, Bautista R, Caballero J, Coats T, Dewan Y, El-Sayed H, Gogichaishvili T, Gupta S, Herrera J, Hunt B, Iribhogbe P, Izurieta M, Khamis H, Komolafe E, Marrero MA, Mejía-Mantilla J, Miranda J, Morales C, Olaomi O, Olldashi F, Perel P, Peto R, Ramana PV, Ravi RR, Yutthakasemsunt S; CRASH-2 trial collaborators: Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): A randomised, placebo-controlled trial. Lancet 2010; 376:23–32
3. Levy JH: Antifibrinolytic therapy: New data and new concepts. Lancet 2010; 376:3–4
4. Henry DA, Carless PA, Moxey AJ, O´Connell D, Stokes BJ, McClelland B, Laupacis A, Fergusson D: Anti-fibrinolytic use for minimizing perioperative allogenic blood transfusion. Cochrane Database Syst Rev 2007; CD00011886
5. Koster A, Faraoni D, Levy JH: Antifibrinolytic therapy for cardiac surgery: An update. Anesthesiology 2015; 123:214–21
6. Kratzer S, Irl H, Mattusch C, Bürge M, Kurz J, Kochs E, Eder M, Rammes G, Haseneder R: Tranexamic acid impairs γ-aminobutyric acid receptor type A-mediated synaptic

transmission in the murine amygdala: A potential mechanism for drug-induced seizures? ANESTHESIOLOGY 2014; 120:639–49

7. Lecker I, Wang DS, Romaschin AD, Peterson M, Mazer CD, Orser BA: Tranexamic acid concentrations associated with human seizures inhibit glycine receptors. J Clin Invest 2012; 122:4654–66
8. Marques F, Sousa JC, Sousa N, Palha JA: Blood–brain-barriers in aging and in Alzheimer's disease. Mol Neurodegener 2013; 8:38
9. Abou-Diwan C, Sniecinski RM, Szlam F, Ritchie JC, Rhea JM, Tanaka KA, Molinaro RJ: Plasma and cerebral spinal fluid tranexamic acid quantitation in cardiopulmonary bypass patients. J Chromatogr B Analyt Technol Biomed Life Sci 2011; 879:553–6
10. Ohig Y, Futamoro T, Hashimoto KG. Glutamate signaling in synaptogenesis and NMDA receptors as potential therapeutic targets for psychiatric disorders. Curr Mol Med 2015; 15: 206–21
11. Bozic M, Valdivielso JM: The potential of targeting NMDA receptors outside the CNS. Expert Opin Ther Targets 2015; 19:399–413
12. Ker K, Beecher D, Roberts I. Topical application of tranexamic acid for the reduction of bleeding. Cochrane Database of Systematic Reviews. 2013; CD010562

ANESTHESIOLOGY REFLECTIONS FROM THE WOOD LIBRARY-MUSEUM

Stamping Out Pain with Brandy Anesthesia: McDowell's Cystolithotomy of Polk

A 32-cent commemorative U.S. postage stamp was released (*right*) in 1995 on the 200th anniversary of the birth of Tennessee politician James K. Polk (1795 to 1849). As a sickly 12-yr-old, Polk had drunk the brandy prescribed him as his only anesthetic for bladder stone removal. This cystolithotomy likely required that the boy be secured for surgery by leather straps and strong assistants—brandy was an impotent anesthetic. And impotence likely precluded future children for the young patient after his scarring from the rapid perineal dissection of his famous surgeon, Ephraim McDowell (1771 to 1830). A 4-cent commemorative U.S. postage stamp was released (*left*) in 1959 to commemorate McDowell on the 150th anniversary of ovarian surgery, which he pioneered. Ironically, Polk's surgeon, McDowell, hailed as the "Father of Abdominal Surgery," would die from appendicitis and never live to see Polk reject brandy and all alcohol in adulthood as the teetotaling eleventh president of the United States. (Copyright © the American Society of Anesthesiologists' Wood Library-Museum of Anesthesiology.)

George S. Bause, M.D., M.P.H., Honorary Curator and Laureate of the History of Anesthesia, Wood Library-Museum of Anesthesiology, Schaumburg, Illinois, and Clinical Associate Professor, Case Western Reserve University, Cleveland, Ohio. UJYC@aol.com.