The Heart Surgery Forum #2010-1014
13 (4), 2010 [Epub August 2010]
doi: 10.1532/HSF98.20101014

Online address: http://cardenjennings.metapress.com

Tranexamic Acid in Cardiac Surgery and Postoperative Seizures: A Case Report Series

David Bell, MBBS,[1] Silvana Marasco, FRACS,[1,2] Aubrey Almeida, FRACS,[2] Michael Rowland, FRACS[3]

[1]Department of Surgery, Monash University, Melbourne; [2]Cardiothoracic Surgery, Epworth Hospital, Melbourne; [3]Cardiothoracic Surgery, Cabrini Hospital, Melbourne, Australia

ABSTRACT

With the recent withdrawal of the antifibrinolytic aprotinin from the market, tranexamic acid (TxA) has become more widely used. This change has led to increasing concern about the side-effect profile of TxA, particularly the incidence of postoperative seizures. In this case series, we describe 7 patients over an 18-month period who had open-chamber cardiac surgery and developed seizures in the postoperative period. This incidence is increased compared with that of a cohort of patients in the previous 36 months who did not receive TxA (0.66% versus 0%; $P < .05$). The exact mechanism of TxA-induced seizures is thought to be via inhibition of γ-aminobutyric acid receptors in neurons. Data from the neurosurgical literature show a well-established link between this antifibrinolytic and seizures. There is now increasing awareness of this association in cardiac surgery, particularly when high TxA doses are used.

INTRODUCTION

Aprotinin has been used with great success to reduce postoperative bleeding and transfusion rates in patients undergoing cardiac surgery. When the recent BART study (Blood Conservation Using Antifibrinolytics in a Randomized Trial) found aprotinin to be associated with a significantly higher 30-day mortality rate, however, most centers abandoned aprotinin use, and tranexamic acid (TxA) has become the antifibrinolytic of choice [Fergusson 2008]. This change has led to an increased scrutiny of the side-effect profile of TxA. In particular, there has been a concern about an association with postoperative seizure activity [Martin 2008].

TxA is a synthetic lysine analogue formed by the hydrogenation of the benzene ring of *p*-aminomethylbenzoic acid. It reversibly blocks lysine-binding sites on plasmin and plasminogen, preventing their adhesion to and breakdown of fibrin. This action works to stabilize clot formation and reduce bleeding. TxA is a water-soluble compound that easily crosses the blood-brain barrier. Before the popularity of its use in cardiac surgery, TxA was used to lower the risk of rebleeding after subarachnoid hemorrhage. However, although TxA proved successful in reducing the risk of rebleeding, it was shown to increase the risk of cerebral vasospasm, ischemia, and hydrocephalus and is therefore no longer used in this application [Adams 1987].

In addition to its increasing the risk of ischemia and cerebral vasospasm, various case reports and animal studies have revealed that TxA has an epileptogenic effect when applied to the cerebral cortex. Case reports of inadvertent intrathecal administration of TxA have described generalized tonic clonic seizures [Mohseni 2009].

The exact mechanism of TxA-induced seizures is thought to be via inhibition of γ-aminobutyric acid (GABA) receptors in neurons. Receptor-binding studies on rat brain membranes found that TxA competitively binds to the cells expressing GABA at GABA type A receptors [Furtmüller 2002]. This action inhibits their interaction with GABA receptor agonists in a dose-dependent fashion, leading to a net excitatory effect on the neurons and thus increasing the risk of seizure activity. Experiments confirm that this inhibition is a competitive rather than an allosteric relationship, because the addition of high concentrations of GABA reverses the effect [Furtmüller 2002].

The aim of this case report series was to review our own experience with this antifibrinolytic drug and to assess the likely factors associated with postoperative seizures in these patients.

CASE REPORT

We identified 7 patients who sustained seizures in the early postoperative period after cardiac surgery. These patients form the basis of this case report. The seizures occurred over an 18-month period at 2 private hospitals in Melbourne, Australia, between March 2008 and August 2009. Access to limited deidentified prospectively collected data on cardiac surgery patients at both hospitals was granted for the purposes of this case report review.

Received January 19, 2010; accepted March 16, 2010.

Correspondence: Dr. Silvana Marasco, MBBS (Hons), MS, MBioeth, FRACS, Cardiothoracic Surgeon, The Alfred Hospital, Commercial Rd, Prahran, Victoria, Australia 3181; 61-3-9076-2558; fax: 61-3-9076-2317 (e-mail: s.marasco@alfred.org.au).

Patient Data*

Patient No.	Age	Sex	Procedure	Preexisting Neurologic History	Neurologic Event	Management	Outcome
1	84	M	MVR and CABG	None	Generalized seizure followed by left-sided weakness	Phenytoin	Neurologic deficit completely resolved within 2 days
2	87	M	Redo AVR	None	Generalized seizure	IV diazepam	Complete resolution
3	73	M	AVR	TIA	Generalized seizure	IV clonazepam	Complete resolution
4	83	F	MVR	Focal epilepsy of unknown etiology; current medication, carbamazepine	Generalized seizure	Phenytoin	Cardiogenic shock, prolonged inotropic support, death
5	76	F	AVR and aortic endarterectomy	Schizoid personality disorder	Generalized seizure	IV diazepam	Complete resolution
6	76	F	MV repair	None	Generalized seizures	IV clonazepam	Complete resolution
7	72	M	Redo MVR	None	Generalized seizures	IV clonazepam	Complete resolution

*MVR indicates mitral valve replacement; CABG, coronary artery bypass grafting; AVR, aortic valve replacement; IV, intravenous; TIA, transient ischemic attack; MV repair, mitral valve repair.

A total of 1164 patients underwent cardiac surgery at the 2 hospitals over the 18-month period. The breakdown of the types of procedure and the percentages of patients who received intraoperative TxA are as follows: coronary artery bypass grafting (CABG) alone, 573 patients (89%); valve surgery alone, 261 patients (95%); valve and CABG surgery, 182 patients (93%); other cardiac procedure, 148 patients (89%). Seven patients in this cohort were reported to have had seizures in the postoperative period (Table). All of these patients had received TxA (7/1059 = 0.66%). Furthermore, no seizures were reported in the 908 patients who did not receive TxA in the preceding 36 months ($P < .05$).

The standard TxA dose used in these patients was either a 60-mg/kg bolus at induction with an infusion of 5 mg/kg per hour for the duration of surgery or a 30-mg/kg bolus with an infusion of 15 mg/kg per hour. For a 3-hour operation, the total dose was 6 g with either protocol.

All 7 patients had open-chamber valve surgery. No patient who had CABG alone developed postoperative seizures. All of the patients except patients 4 and 7 received pericardial insufflation with carbon dioxide gas during the procedure.

The seizures occurred within 24 hours of surgery in all of the patients, and there was no recurrence of seizure activity after 24 hours. All patients except patient 5 survived. Patient 5 developed cardiogenic shock soon after intravenous phenytoin administration for the seizures and required prolonged inotropic support. The patient died of respiratory failure 6 days postoperatively. Five of the 7 patients had mild renal impairment (creatinine, 123-139 mmol/L). The mean age of the patients (76 years) was not significantly different from that of the overall cohort. The mean (±SD) cardiopulmonary bypass time for this patient group was 91 ± 14 minutes and, again, was not significantly different from that of the entire cohort.

DISCUSSION

To our knowledge, only 3 published studies make note of an association between seizures and TxA in cardiac surgery. To compare the risks of aprotinin and TxA, Martin et al [2008] followed 1188 consecutive adult patients undergoing cardiac surgery. Twenty-seven (4.6%) of 592 patients administered TxA experienced seizures, whereas only 7 (1.2%) of 596 patients administered aprotinin experienced seizures ($P < .001$). A subgroup analysis showed that this difference was particularly marked in the patients who underwent valve surgery or high-risk surgery (defined as redo operations, combined CABG and valve surgery, aortic surgery, and ventricular aneurysm repair).

The same group of authors also reported their results with a pediatric cohort of 199 patients who underwent cardiac surgery and found a nonsignificant trend toward an increased incidence of postoperative seizure incidence in the TxA group (4/114, 3.5%) versus the aprotinin group (0/85, $P = .14$]) [Breuer 2009].

A more recent report described the results for 669 patients who were administered TxA during cardiac surgery, 24 of whom sustained postoperative seizures (24/669 = 3.6%) [Murkin 2010]. Similar to our observations, a large proportion of the patients had renal impairment and underwent open-chamber surgery. The patients in that series had received large TxA doses (61-259 mg/kg) much higher than the doses used in our patients. This difference probably accounts for the much higher incidence of postoperative seizures in their series.

In all 3 studies noted above, open-chamber cardiac surgery seemed to be the main risk factor in the TxA groups. Interestingly, all of the patients in our case series also had open-chamber surgery. We have not seen this complication in any patient who underwent straight CABG during this study period. This result points to a propensity for seizures in those patients who receive TxA and in whom cardiac air and consequently cerebral microbubbles occur.

In conclusion, we have demonstrated an increased incidence of postoperative seizures in patients who have undergone open-chamber cardiac surgery and received TxA. This apparent association needs to be investigated further with prospective studies.

ACKNOWLEDGMENTS

The authors thank J. Goldstein, FRACS, and B. Davis, FRACS, for their input.

REFERENCES

Adams HP Jr. 1987. Antifibrinolytics in aneurysmal subarachnoid hemorrhage. Do they have a role? Maybe. Arch Neurol 44:114-5.

Breuer T, Martin K, Wilhelm M, et al. 2009. The blood sparing effect and the safety of aprotinin compared to tranexamic acid in paediatric cardiac surgery. Eur J Cardiothoracic Surg 35:167-71.

Fergusson DA, Hebert PC, Mazer D, et al. 2008. A comparison of aprotinin and lysine analogues in high-risk cardiac surgery. N Engl J Med 358:2319-31.

Furtmüller R, Schlag MG, Berger M, Hopf R, Huck S, Sieghart W, Redl H. 2002. Tranexamic acid, a widely used antifibrinolytic agent, causes convulsions by a gamma-aminobutyric acid(A) receptor antagonistic effect. J Pharmacol Exp Ther 301:168-73.

Martin K, Wiesner G, Breuer T, Lange R, Tassani P. 2008. The risks of aprotinin and tranexamic acid in cardiac surgery: a one-year follow-up of 1188 consecutive patients. Anesth Analg 107:1783-90.

Mohseni K, Jafari A, Nobahar MR, Arami A. 2009. Polymyoclonus seizure resulting from, accidental injection of TxA in spinal anesthesia. Anesth Analg 108:1984-6.

Murkin JM, Falter F, Granton J, Young B, Burt C, Chu M. 2010. High-dose tranexamic acid is associated with nonischemic clinical seizures in cardiac surgical patients. Anesth Analg 110:350-3.