Deprescribing practices for anticonvulsants after benign seizures secondary to high-dose tranexamic acid in a single, large UK cardiothoracic centre

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ABSTRACT

Objective High-dose tranexamic acid (TXA) can cause seizures in patients who have undergone pulmonary endarterectomy (PTE). Seizures secondary to TXA will resolve once the drug is excreted from the body, and the patients do not have to be on long-term anticonvulsants. The aim of the study is to find out if medication review in the hospital has led to deprescribing of anticonvulsants for TXA-associated seizures on discharge from the critical care unit (CCU) and hospital.

Methods This is a single-centre retrospective study conducted at a tertiary cardiothoracic hospital between 2012 and 2017. The inclusion criteria consisted of all adult patients who have undergone PTE surgery. Patients who were started on anticonvulsants preoperatively or postoperatively for seizures secondary to organic causes were excluded.

Results A total of 933 patients underwent PTE from January 2012 to August 2017. 25 patients had TXA-related seizures postoperatively and were started on anticonvulsant therapy, giving an incidence of 2.7%. 15 patients were discharged from the CCU without anticonvulsants. A further three patients had their anticonvulsants deprescribed in the ward before being discharged from the hospital.

Conclusion Deprescribing of anticonvulsants after benign seizures secondary to high-dose TXA is facilitated by verbal and written handover, which can be improved in our hospital. A detailed handover summary, as well as a discharge letter with clearly defined instructions for drug review, is needed to make deprescribing a more robust process.

INTRODUCTION

Chronic thromboembolic pulmonary hypertension is a disease caused by chronic and recurrent pulmonary thromboembolism that do not undergo complete resolution, resulting in obstruction of the pulmonary arteries. Patients can present with severe breathlessness and heart failure symptoms, which significantly impact their quality of life. Pulmonary endarterectomy (PTE) is indicated for this group of patients, and it involves the removal of obstructive tissue and clots from the pulmonary arteries during a period of deep hypothermic circulatory arrest (DHCA) after the patient is on cardiopulmonary bypass (CPB).

Perioperative bleeding and hence the need for blood transfusion is common following cardiac surgery and is associated with poor outcomes.^{1,2} Antifibrinolytic agents are used routinely in cardiac surgeries to decrease bleeding. After major concerns

with the safety of aprotinin and its subsequent withdrawal from the market in 2008,^{3,4} tranexamic acid (TXA) has been used more frequently. It prevents fibrinolysis by competitive inhibition of the activation of plasminogen to plasmin. There are few side effects with its use, but one of the more serious complications is seizures at high doses, such as those administered in the Blood conservation using Antifibrinolytics in a Randomised Trial (BART) trial (80–100 mg/kg total dose).^{5,6}

The TXA protocol for patients undergoing PTE in our hospital includes an intravenous induction dose of 1 g TXA followed by an infusion of TXA at 7 mg/kg/hour for the duration of the surgery. These patients typically received a higher total dose compared with elective cardiac surgical patients, who received a standard dose of 30 mg/kg after heparin administration.

The elimination half-life of TXA following intravenous administration is approximately 2 hours. However, it is likely that its clearance is reduced at a temperature of 20°C during DHCA even though the pharmacokinetics of TXA is not studied at low temperature. Furthermore, during CPB, liver perfusion is often reduced, affecting its metabolic function. Seizure activity is also suppressed by intravenous propofol infusion used during surgery and for sedation postoperatively. Propofol infusions are usually discontinued 8–24 hours postoperatively, and hence these patients are therefore at a higher risk of postoperative seizures.

Postoperative seizures are associated with longer hospital length of stay and higher morbidity and mortality.⁵ Anticonvulsants are therefore started to control seizures especially when they are persistent. If the seizures are secondary to TXA, they will resolve once the drug is excreted from the body and the patients do not have to be on long-term anticonvulsants. They may be continued on discharge from the critical care unit (CCU) to the wards, but plans should be in place for review and subsequent discontinuation when no longer indicated due to high risk of drug interactions and organ dysfunction.

Deprescribing is a process of discontinuation of drugs to prevent polypharmacy and improve patient outcomes. The social implications of being on anticonvulsants are manifold. Job restrictions and driving bans are some of the more serious consequences. If anticonvulsants for benign seizure activity are not discontinued, epilepsy has to be declared to driving standards authorities and may lead to loss of licence. In the UK, patients on anticonvulsants need to be free from seizures for more

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than 6 months before they can have their licence reinstated. Therefore, patients might be reluctant to stop the drugs once they have got their licence back.

In our local institution, a handover including drug review is mandatory on discharge from CCU. In addition, after the introduction of ward-based electronic documentation system in 2017, this handover process is also electronically documented. CCU-based electronic patient records and mandatory discharge summary from CCU have been in use since 2006. If the patient still requires anticonvulsants on discharge from the hospital, a discharge letter with drug review is provided.

The aim of the study is to find out if medication review in the hospital has led to deprescribing of anticonvulsants for TXA-associated seizures on discharge from the CCU and hospital.

METHODS

This is a retrospective study conducted at a single centre tertiary cardiothoracic hospital between 2012 and 2017. The inclusion criteria consisted of all adult patients who have undergone PTE surgery and were admitted to a cardiothoracic CCU postoperatively. The exclusion criteria consisted of patients who were started on anticonvulsants preoperatively or postoperatively for seizures secondary to organic causes, as well as those where the reason for starting anticonvulsants was not documented. Information regarding the patients who fulfil the inclusion criteria was taken from an electronic patient as well as medication database.

The case summaries and discharge letters were then reviewed and information was collected on an excel spreadsheet. Data collection was performed by one clinician and data checked by a separate clinician. This included basic demographic details including age, sex and body surface area, medical history of epilepsy, psychiatric illness or other neurological diseases, drug history of anticonvulsants, surgical details including date, nature and type of surgery, as well as hospital details including date of admission, discharge and destination. With regard to the seizures, information regarding the type of seizure, type and dose of anticonvulsant started, duration of anticonvulsant therapy, and the cause of the seizures if any was also collected.

Seizures within 24 hours of surgery with no organic causes are attributed to the high-dose TXA used intraoperatively. They are classified into partial, generalised or partial-generalised.

RESULTS

From January 2012 to August 2017, a total of 933 patients underwent PTE. Fifty-eight of them received anticonvulsants during their critical care stay. These anticonvulsants were levetiracetam, phenytoin and sodium valproate. Out of the 58 patients, 25 of them were started on anticonvulsant therapy postoperatively (figure 1). These patients had their first seizure postoperatively, and CT head when performed showed no organic causes. The incidence of postoperative seizures attributed to TXA-specific anticonvulsant therapy was 2.7% for the whole population. There was one mortality from major aspiration during the same hospital admission.

All patients underwent elective PTE surgeries. Three of them had combined procedures with PTE (two had patent foramen ovale closure and one had coronary artery bypass graft). There was one redo PTE.

Phenytoin was started as the first-line treatment for two of the patients. Levetiracetam was started as first-line treatment for the remaining 23 patients. Out of these 23 patients, 8 required an additional anticonvulsant to control the seizures.

Figure 1 Overall flow diagram. GP, general practitioner; PTE, pulmonary endarterectomy; TXA, tranexamic acid.

Ten of the patients were discharged from the CCU with anticonvulsants, that is, 15 patients had their anticonvulsants deprescribed. Seven of them were eventually discharged from the hospital with anticonvulsants ().

Out of the seven patients, five were referred to their general practitioner for review of their anticonvulsant therapy, of whom three were no longer on anticonvulsant therapy at the time of the study. Two were discharged with anticonvulsants to another hospital with no details of follow-up regarding anticonvulsant therapy (figure 1).

Twenty-eight patients were excluded as they were prescribed anticonvulsants preoperatively, or anticonvulsant therapy was started postoperatively due to an organic cause such as an intracranial bleed. Information was unavailable in five of these patients from the online records and excluded from the analysis. Attempts to contact these patients for more information was unsuccessful as two of them died and three patients were uncontactable (figure 1).

DISCUSSION

Postoperative seizures may occur for a number of reasons in patients undergoing PTE. DHCA, which is required in PTE surgery, can result in seizures. Other organic causes include subdural haemorrhage and stroke. One patient in our series had hypoxic encephalopathy secondary to DHCA and developed seizures secondary to the brain injury. Seizures secondary to high-dose TXA are not uncommon in the postoperative period. We reported an incidence of 2.7% in our population, which is comparable with other published studies.⁷ Known risk factors for TXA-associated seizures include female gender, advanced age and poor general health, prolonged aortic cross-clamp times, long CPB times as well as DHCA.⁷

TXA-associated seizures tend to be generalised tonic-clonic, although focal and mixed seizures can also occur. They usually happen within the first 8 hours postoperatively during the period of weaning from sedation in the CCU. They may last for a few minutes and generally do not progress to status epilepticus. Up to 60% of the patients may have one or more episodes in the first 48 hours postoperatively.^{5 8}

Seizures, especially status epilepticus, can be detrimental to the postoperative recovery of the patient. They can lead to major morbidity such as cerebral oedema, aspiration pneumonia, reperfusion injury as well as line dislodgement. It can also cause distress to both the patient and their family and disrupt nursing care.

The management plan after the first seizure is to resedate the patients for 2–4 hours. If seizures recurred, anticonvulsants were then started and the patients would be further investigated with a CT brain to rule out organic causes. The starting dose of anticonvulsant for levetiracetam was 500 mg twice a day. This was increased to 1 g twice a day if seizures were not controlled. Phenytoin and sodium valproate were added on as a second-line agent if further control was required. However, if the seizures stopped after the patient was extubated, anticonvulsants should be discontinued by the intensivists before discharge from the CCU.

Deprescribing is a process of reducing, withdrawing or stopping medicines to avoid polypharmacy as well as adverse effects by a constant review of reasons and effectiveness of the medical therapy. This should be patient-centred and supervised by a doctor or pharmacist. The clinical benefits of deprescribing, such as reduced mortality and morbidity, are hard to measure due to the large variability and the small number of patients. However, improved quality of life and reduced medication costs are also important benefits to consider.⁹

There are many ways of approach, but it usually involves a comprehensive review of medical history and drug history, identification of potential drugs that can be stopped, followed by a plan of withdrawal and a review after withdrawal.¹⁰ In addition to this generic approach, there are also multiple online resources targeting specific medications such as proton pump inhibitors, benzodiazepines and antihyperglycaemics. Deprescribing checklists such as Beers, Screening Tool of Older people's Potentially inappropriate Prescription (STOPP) and Screening Tool to Alert doctors to Right Treatment (START) criteria are also helpful especially in the elderly population.^{11 12} However, our study involves a very specific medication in a targeted population in the hospital setting.

There are few studies in the literature on deprescribing of medication in critical care, but many positive studies were on pharmacist-led initiatives in the hospital. Cheong *et al*¹³ showed that majority of pharmacists' interventions are accepted by physicians. Whitman *et al*¹⁴ demonstrated its feasibility and cost-effectiveness in deprescribing in a geriatric oncology clinic. Martin *et al*¹⁵ also showed in a randomised controlled trial how pharmacist-led educational intervention can lead to discontinuation of inappropriate medications.

Electronic handover forms with medication review as one of the components were only implemented in our department from 2017. Prior to 2017, electronic discharge summaries and verbal handovers were used. However, our department has a dedicated critical care pharmacist who plays a key role in medication review. He or she is involved in the preoperative clerking of all PTE patients and also reviews their discharge medication.

In our study, majority of the patients (72%) had their anticonvulsants deprescribed after these processes. However, there

are areas for improvement, especially better documentation which was not present especially in the earlier years. It is not entirely clear if the rest of the patients were still on anticonvulsants because it is indicated or because deprescribing did not take place. The process was more robust on discharge from the hospital as all the patients had written instructions for medication review in the discharge letter. As this study is the first of its kind in this population, we therefore did not have prior studies to compare our results with.

There are several limitations to our study. First of all, being a retrospective study, there are missing information and inconsistencies in some of the records. Multiple attempts have been made to verify and ensure that the information is accurate. Second, this was conducted in a single centre in a very specific population. The results, therefore, may not be generalisable to other institutions. Lastly, it is possible that the incidence of TXA-associated seizure is higher than reported as we only managed to capture patients who were on anticonvulsants. There may be a number of patients who had seizures that self-aborted after resedation, hence no anticonvulsants were started. However, as the aim of the study was targeted at deprescribing, we were most interested in those who needed anticonvulsants because of recurrent seizures.

Once the patients are discharged from the hospital, the task of deprescribing lies in their general practitioners. Barriers to deprescribing include attitudes and behaviours of patients and physicians, lack of education and working practices. The fear of the return of the initial problem, perceived benefit of continuation and the reluctance of primary care to interfere with medication prescribed by tertiary centres are some examples of attitudes that may hinder deprescribing. Lack of education on the rationale for starting the medication or lack of information to support discontinuation can also prevent effective deprescribing.^{16 17}

As clinicians in tertiary centres, this can be facilitated in a number of ways. A comprehensive handover or discharge summary to the ward or primary care physicians with clear instructions is often the most effective way to educate the team regarding the purpose of the new medication as well as when to deprescribe. General education of primary care physicians and patients regarding new medications will also empower them during medication review.

CONCLUSION

Deprescribing of anticonvulsants after benign seizures secondary to high-dose TXA is facilitated by verbal and written handovers,

What this paper adds

What is already known on this subject

- ▶ Perioperative use of high-dose tranexamic acid infusions can be associated with seizures.
- ▶ Seizure activity is benign.
- ▶ After seizure activity has stopped, anticonvulsant medication can be discontinued.

What this study adds

- ▶ Regular review of inpatient medication is important and deprescribing unnecessary treatment is paramount.
- ▶ If anticonvulsants for benign seizure activity are not discontinued, epilepsy has to be declared to driving standards authorities and may lead to loss of licence and interfere with the lifestyle of patients.

which can be improved in our hospital. Critical care pharmacists play a vital role in deprescribing medications in CCU. A detailed handover summary, as well as a specific discharge letter with clearly defined instructions for drug review, is needed to make deprescribing a more robust process.

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