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Protocol in managing oral surgical patients taking dabigatran

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ABSTRACT

New anticoagulants are being introduced into the market. These drugs are orally administered, have predictable pharmacokinetics and dose response, do not require monitoring and have an acceptable safety profile when used appropriately, and so avoid many of the disadvantages and possible complications of warfarin and heparin. Dabigatran is the most widely used, and has been approved by the Therapeutic Goods Administration. The use of dabigatran will likely increase in the coming years, and so it is important for dentists to be aware of its mechanism of action, the possible complications, and how to reverse the bleeding if it occurs. This review discusses dabigatran and reports on our experience of five cases, and provides practical clinical advice on how to manage patients on dabigatran who require dental treatment, particularly extractions.

Keywords: Anticoagulants, bleeding, dabigatran, extractions, oral surgery.

Abbreviations and acronyms: aPTT = activated partial thromboplastin time; DVT = deep venous thrombosis; FFP = fresh frozen plasma; INR = International Normalized Ratio; LMWH = low molecular weight heparin; PT = prothrombin time; TGA = Therapeutic Goods Administration; TT = thrombin clotting time; UFH = unfractionated heparin.

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INTRODUCTION

Anticoagulants are among the most commonly used medications in our community. They are predominantly prescribed to patients at risk of venous thromboembolism (history of previous thromboembolism, immobilized hospital patients, patients after major surgery, pregnancy, etc.), or those at risk of embolic strokes (patients with atrial fibrillation, prosthetic heart valves). The most common anticoagulant encountered in outpatient oral surgical and dental practice is warfarin. The use of warfarin is associated with many difficulties including its delayed onset of action, individualized dosing regimens, many drug and food interactions, and the need for regular monitoring and adjustment. The other main anticoagulants are the heparins, which are mainly used in the hospital environment. They are also not ideal anticoagulants, mainly because unfractionated heparin (UFH), needs to be administered parenterally or subcutaneously, it has long-term side effects such as osteoporosis and thrombocytopenia, and must be carefully monitored to ensure therapeutic dosing. Also, low molecular weight heparin (LMWH) – such as enoxaparin – needs to be administered subcutaneously, which makes it useful in the hospital setting but limits its application in the outpatient setting.

To find alternatives to heparin and warfarin, significant research has gone into the development of new classes of anticoagulants. Several novel agents have undergone large scale clinical trials to compare their efficacy and safety profiles to current anticoagulants. These novel agents operate on targeted inhibition of specific proteins or proteases of the coagulation cascade such as thrombin and activated factor Xa. A detailed discussion of these is beyond the scope of this article, but references to some key studies have been provided.[1–3] The thrombin inhibitors have been the main focus of research, and one of the agents dabigatran (Pradaxa®) has Therapeutic Goods Administration (TGA) approval since November 2008 for post-orthopaedic surgery thromboprophylaxis.[4] It has also been approved by the TGA for prevention of thromboembolism associated with atrial fibrillation

since April 2011.[5] As this drug has made its way into our hospitals and the community and are being prescribed by general practitioners, it is important for all medical and dental practitioners to be aware of these drugs, how they work, how to administer them, and most importantly how to deal with complications arising from them.

Thrombin inhibitors

The antithrombotic activity of the heparins is mediated by their ability to potentiate the activity of antithrombin III. Normally the inactivation of thrombin by antithrombin III is a slow process, but after conformational change induced by heparin, antithrombin irreversibly binds to and inhibits the active site of thrombin. The antithrombin activity is potentiated 1000 times its normal activity.[6] This binding of the heparin-antithrombin complex to thrombin requires access to multiple binding sites on the thrombin complex. The binding is impaired when the thrombin is already bound to fibrin, limiting the capacity for the inhibition of fibrin-bound thrombin, which is still capable of further thrombus growth.[7] Since direct thrombin inhibitors are independent of antithrombin, they are able to inhibit soluble circulating thrombin and thrombin which are bound to fibrin.

The univalent direct thrombin inhibitors such as ximelagatran and dabigatran reversibly bind only to the active site on the thrombin molecule, inhibiting both free and clot bound thrombin.[8,9] Direct thrombin inhibitors also have an antiplatelet effect by reducing the thrombin mediated activation of platelets.[10] One of the early direct thrombin inhibitors ximelagatran (Exantra®) demonstrated a good safety profile and reasonable efficacy compared with enoxaparin for thromboprophylaxis in major orthopaedic surgery,[11] but with long-term use the drug appeared to be hepatotoxic with prolonged elevation of liver function tests.[12]

Dabigatran etexilate

The direct thrombin inhibitor dabigatran etexilate has recently been investigated in large multicentre trials for orthopaedic thromboprophylaxis and demonstrated sound safety and efficacy. Dabigatran etexilate is a low molecular weight prodrug of dabigatran, a potent molecule that specifically and reversibly inhibits free and clot-bound thrombin. When taken orally, it has a bioavailability of 6.5%, terminal half-life of 12 to 17 hours, with its peak plasma volume 2–3 hours after administration.[13] Eighty per cent of circulating dabigatran is cleared renally, with the remainder conjugated and excreted via the bile. Patients with a moderate or severe decline in renal function exhibit reduced clearance and elevated plasma concentration. Hence the dose needs to be adjusted in patients with creatinine clearance of <50 ml/min, and the drug is contraindicated in patients with creatinine clearance of <30 ml/min.[14] Dabigatran is not metabolized by cytochrome p450, and it displays low protein binding (approximately 35%), and so the risk of drug interaction is low.[15]

The major advantages of dabigatran are that it is orally administered, and it has predictable pharmacokinetics and dose response. For the prescribing medical practitioner, this allows a fixed dose regimen in most patients without the need for routine monitoring of anticoagulant effect.[16]

Most of the initial clinical studies performed have been non-inferiority trials comparing dabigatran with enoxaparin for thromboprophylaxis after orthopaedic surgery, or dabigatran and warfarin for atrial fibrillation. The studies comparing dabigatran with enoxaparin demonstrated non-inferiority of dabigatran with enoxaparin, and similar rates of bleeding.[17,18] In the RE-LY study comparing dabigatran with warfarin in patients with atrial fibrillation, at the dabigatran dose of 110 mg twice daily, there was similar efficacy in preventing thromboembolism and stroke as compared with warfarin (to target INR 2-3), but statistically significant reduced rates of major bleeding, which is very promising.[19] Table 1 compares the properties of dabigatran and warfarin.

As dabigatran acts on thrombin mediated conversion of fibrinogen to fibrin, it has an effect on all of the routine coagulation assays. However, the different tests seem to behave differently with increasing concentrations of dabigatran.[20] Prothrombin time (PT) and in turn the International Normalized Ratio (INR) are not normally affected by dabigatran, but at very high doses may be elevated up to an INR of 2.0.[16] There appears to be a relationship between increasing dabigatran levels and prolongation of the activated partial thromboplastin time (aPTT). At peak concentration, the aPTT is approximately two-fold that of control, and 12 hours later (trough level), the aPTT is approximately 1.5-fold that of control. As a general rule, a normal aPTT suggests minimal drug is present, whereas a significantly prolonged aPTT at trough, or at peak time suggests that there is excess drug[16] (Table 2). Other more accurate tests can also be ordered such as thrombin clotting time (TT) and serum dabigatran levels,[16] but for practice outside of the hospital setting, the aPTT should be sufficient to determine if the dose effect of dabigatran will cause significant bleeding or not.

Cases

We report the outcome of five patients on dabigatran who underwent tooth extractions. Cases 1–3 were for

Table 1. Comparison between warfarin and dabigatran

Property	Warfarin	Dabigatran
Administration	Oral	Oral
Dosing	Individualized – highly variable	Fixed dose dependent on renal function
Onset of Action	36–72 hours	2–4 hours
Duration of Action	48–96 hours	24 hours
Elimination half-life	20–60 hours	14–17 hours
Interactions	Yes – many drugs and foods	Possible interaction with drugs that impair renal function
Clearance/ Metabolism	Metabolized by hepatic route	Renally cleared
Bleeding risk	Significant	Significant – not worse than warfarin or enoxaparin in RCTs
Monitoring	INR checked fortnightly	Not needed
Bridging anticoagulation	Needed due to initial procoagulant effect	Not needed
Reversibility	Vit K, fresh frozen plasma, prothrombin complex concentrates	Partially reversed with haemodialysis (60% after 2 hours)

Table 2. Summary of correlation between coagulation test results and bleeding risk

Test result	Bleeding risk
aPTT and TT normal	No drug effect present
aPTT normal or slightly prolonged and TT abnormal	+ Drug effect present, but likely low level
aPTT and TT abnormal	++ Drug effect present

aPTT = activated partial thromboplastin time; TT = thrombin time.

single tooth extractions and cases 4 and 5 were for multiple tooth extractions. A summary of the cases is provided in Table 3.

Case 1

Seventy-eight year old male referred for extraction of tooth 24. He was taking dabigatran 110 mg daily for thromboprophylaxis due to atrial fibrillation. The dabigatran was continued. Tooth 24 was extracted without complication and the socket was sutured tightly. There was no significant intraoperative or postoperative bleeding.

Case 2

Eighty year old male referred for extraction of tooth 36. He was taking dabigatran for atrial fibrillation. Dabigatran was continued. Tooth 36 was extracted and the socket sutured without significant intraoperative bleeding. The patient reported minor postoperative bleeding for three hours not significant to warrant the patient returning to the hospital. Bleeding was controlled by pressure.

Case 3

Sixty-seven year old male referred for extraction of tooth 17. His medical history included ischaemic heart disease, atrial fibrillation, hypertension and gout. He was taking 110 mg dabigatran daily. Dabigatran was continued and tooth 17 was extracted and the socket sutured and packed with Surgicel™. There was no significant intraoperative or postoperative bleeding encountered.

Case 4

Seventy-two year old female referred for extraction of multiple teeth – 44, 46 and 35. Her medical history included hypertension, type 2 diabetes mellitus and atrial fibrillation. She was taking 110 mg dabigatran daily. The dabigatran was stopped 48 hours preoperatively and the teeth were extracted without complication. There was no significant intraoperative or postoperative bleeding noted.

Case 5

Eighty-four year old male referred for left sided facial swelling secondary to multiple abscessed teeth. His dentition was found to be grossly carious. His medical history included hypertension, type 2 diabetes mellitus

Table 3. Summary of cases

Case	Age	Gender	Reason for dabigatran	Dabigatran management	Procedure	Postop complications
1	78	M	AF	Continued	Extraction 24	None
2	81	M	AF	Continued	Extraction 36	Minor postop bleed
3	67	M	AF	Continued	Extraction 17	None
4	72	F	AF	Ceased 48 hrs preop	Extraction of multiple teeth – 44, 46, 35	None
5	84	M	AF	Continued	Extraction of 18 teeth under GA and drainage of abscess	Severe postop bleeding requiring suturing under anaesthetic and ceasing dabigatran

and atrial fibrillation. His medications included atorvastatin, digoxin and 110 mg dabigatran daily. Preoperative coagulation studies revealed an elevated INR of 1.5 and aPTT of 47 seconds. The dabigatran was not ceased preoperatively. He was taken to theatre and 18 teeth were extracted under a general anaesthetic as well as drainage of the facial abscess. Intraoperatively it was noticed that he had significant bleeding and the wounds were sutured tightly. Postoperatively but while still in hospital, he had significant haemorrhage necessitating a return to theatre for further suturing and haemorrhage control. The dabigatran was then ceased, and the bleeding stopped 24 hours later.

The cases of single tooth extractions were managed without ceasing the dabigatran and there were no episodes of significant postoperative bleeding. Case 4 reports the successful extraction of multiple teeth after ceasing dabigatran for 48 hours, but ceasing the dabigatran for 24 hours would have been equally effective. Case 5 reports significant postoperative bleeding in a patient who underwent a full clearance of his remaining dentition while still taking dabigatran. The bleeding ceased after stopping the dabigatran for 24 hours. The following section describes the current management protocol we recommend for managing patients taking dabigatran.

Management protocol

When considering the management of these patients, it is essential to always keep in mind that stopping the dabigatran leads to an increased risk of stroke or venous thrombosis in these patients. Intraoral bleeding can often be managed and is rarely catastrophic, but a stroke can be permanently debilitating.

Elective treatment

General dental procedures

For simple procedures with a minor bleeding risk such as scaling, restoration with use of a matrix band, endodontic treatment, or single tooth extractions, the dabigatran will likely not need to be stopped like warfarin.[21] For single uncomplicated tooth extractions, local haemostatic measures such as mechanical pressure, suturing and topical haemostatic agents (such as Gelfoam™ or Surgicel™) should be adequate to control the bleeding.

Multiple extractions

For patients undergoing multiple extractions, due to the increased bleeding risk, patients should be assessed by their own physician before the procedure is undertaken. Referral to an oral and maxillofacial surgeon should be strongly considered for patients with history of renal failure, patients needing invasive surgical procedures likely to have a high risk of bleeding, or those patients who are also on other anticoagulants or antiplatelet agents (such as clopidogrel or aspirin). The surgeon will liase with the patient's physician to consider temporary cessation of the dabigatran 24 hours (two half-lives) before the procedure is recommended. The aPTT or TT should be checked preoperatively to ensure the drug effect is reduced. If aPTT is still prolonged, then a further 24 hours may be required to reduce the risk of bleeding.

Cessation of dabigatran or any anticoagulant should only be made in consultation with the patient's general practitioner/cardiologist, who will weigh up the risk of bleeding from the proposed procedure with the risk of thrombosis/stroke in each individual patient. For patients who are on dabigatran for atrial fibrillation without a history of a previous stroke, stopping the dabigatran for 24 hours is considered relatively safe. For patients with a history of recent deep venous thrombosis (DVT), pulmonary embolism, or embolic strokes, it may be dangerous to cease the dabigatran. The treating physician may decide to use alternative anticoagulation such as heparin preoperatively as these have established protocols for oral surgical management. The timing of cessation of the dabigatran also depends on the patients renal function.[16,22] Dabigatran has a short half-life (14–17 hours) and so in otherwise healthy patients with normal renal function, stopping the dabigatran 24 hours (two half-lives) before the operation is adequate time to reduce the risk of bleeding to normal. If the patient has a history of renal impairment, they are likely to need the dabigatran stopped 2–5 days before the operation depending on their renal function.[16] Checking coagulation tests such as aPTT preoperatively will help determine if the dabigatran has been stopped for long enough. Patients with severe renal impairment should not be prescribed dabigatran but sometimes this is overlooked and these patients often have severely deranged coagulation markers and can bleed spontaneously.[23] It is important to keep in mind that dabigatran will mainly be indicated in elderly patients, and in these patients renal function may deteriorate without notice. Persistently abnormal coagulation studies in patients who have ceased dabigatran for more than 24 hours should prompt practitioners to assess renal function for possible progressive renal impairment.

If the dabigatran is ceased, it can be restarted when the risk of postoperative bleeding is minimal, usually 24–48 hours after surgery. When restarting the dabigatran, the anticoagulant effect reaches its optimum level within two hours of administration.

Emergency surgery

Oral and maxillofacial surgical emergencies that need prompt surgical intervention such as acute odontogenic infections with risk of airway compromise or haemorrhaging facial fractures will require immediate referral to the nearest tertiary referral centre. Currently, there is no effective reversal agent for dabigatran.

In the situation where emergency surgery is needed in a patient taking dabigatran, then haemodialysis should be considered. Dabigatran can be cleared with dialysis because of its limited plasma protein binding. The mean percentage of the drug removed was 62% at two hours and 68% at four hours as shown in an open label study on patients with end stage renal failure after taking 50 mg of dabigatran.[16] A recent case report described the safe use of haemodialysis for reversal of dabigatran in a patient requiring orthotropic heart transplantation.[24]

In the case of a patient presenting with bleeding while on dabigatran, the dabigatran should be ceased, mechanical pressure should be applied, and intravascular volume should be maintained with intravenous fluid replacement and blood products such as fresh frozen plasma. This maintains adequate renal perfusion enhancing removal of the drug from the circulation. If all else fails, haemodialysis must be considered.

Several agents have been considered for reversal of dabigatran but they are lacking any adequate studies in human subjects. The use of blood products like fresh frozen plasma (FFP) will not reverse the anticoagulant effect of dabigatran. This is because the circulating dabigatran will inhibit any newly transfused thrombin. Recombinant factor VIIa (rFVIIa) is a potent procoagulant and general haemostatic agent that can initiate haemostasis at sites of bleeding by directly activating thrombin on the surface of platelets in the absence of tissue factor.[25] In a rat-tail model, addition of rFVIIa significantly reduced bleeding time and aPTT associated with a high dose of dabigatran in a dose-dependent manner.[16] However, no adequate studies on human subjects have been performed to firmly establish the usefulness of rFVIIa in bleeding patients on dabigatran. In the case of an emergency, rFVIIa or other agents can be considered in consultation with the haematology team. See Table 4 for a summary of the management protocol for patients on dabigatran seeking oral surgical management.

The guidelines proposed in this paper are based on the fact that an effective reversal agent is still not available. With further surgical experience on patients taking the drug, and the advent of a simple, effective reversal agent, these guidelines will likely change. At this stage, the protocol proposed here is similar to the protocol for the treatment of patients on warfarin with additional precautions for patients undergoing multiple extractions in the same appointment due to the higher bleeding risk. Future clinical research is required to determine if these guidelines are effective, or if stopping dabigatran preoperatively for all patients is required to reduce bleeding complications.

SUMMARY

Dabigatran is a direct thrombin inhibitor that is likely to become more widely prescribed due to its ease of use. Due to its more predictable pharmacokinetics, and standard dose regimens, stopping and recommencing the dabigatran is easier and causes less risk than warfarin. These decisions should still only be made in conjunction with the patient's general medical practitioner. The protocol recommends not stopping the dabigatran for standard procedures such as

Table 4. Summary of management of oral surgical patients taking dabigatran

	Guidelines
Dental procedures and uncomplicated simple tooth extractions	- Not necessary to discontinue use of dabigatran in patients with normal renal function - Local haemostatic measures need to be applied – mechanical pressure, suturing and local haemostats
Extraction of multiple teeth or elective oral/maxillofacial surgical procedures or patients taking other anticoagulants or antiplatelet agents	- Consider referral to an oral and maxillofacial surgeon - In consultation with the patient's physician, will consider discontinuing dabigatran or changing to another anticoagulant preoperatively - If normal renal function will discontinue dabigatran 24 hours before procedure - Consider checking aPTT preop - If abnormal renal function, consider discontinuing for 48 hours or longer depending on degree of renal impairment[16] - Local haemostatic measures should be used - Can recommence dabigatran 24–48 hours after operation
Emergency oral/maxillofacial surgical procedures or patients presenting with severe haemorrhage	- Refer immediately to a tertiary referral centre - Cease dabigatran, mechanical pressure, maintain intravascular volume with fluid resuscitation and blood products such as FFP - Contact haematology for consideration of rFactor VIIa administration or other agents - Consider haemodialysis

scaling, restorative treatment, endodontic treatment or single uncomplicated tooth extractions as the bleeding can often be managed with mechanical pressure and other local haemostatic measures. The general dentist should consider referral to an oral and maxillofacial surgeon for patients with a history of renal impairment, patients requiring multiple extractions, or more complex oral surgical procedures, or patients who are on additional antiplatelet agents or anticoagulants, as there is a higher bleeding risk. The protocol recommends stopping the dabigatran 24–48 hours prior to the operation, and checking of the aPTT preop to ensure that the bleeding risk is minimal. The dabigatran may need to be ceased earlier if the patient has a history of renal impairment. Guidelines for management of patients on dabigatran in the perioperative setting as well as in cases of emergency bleeding have been developed.[22,26,27] Clinicians managing patients on dabigatran must be aware of such guidelines.

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