An update on the management of anticoagulated patients programmed for dental extractions and surgery

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Abstract

Oral anticoagulants (OACs) antagonizing vitamin K - fundamentally sodium warfarin and acenocoumarol - are widely used for preventing arterial thromboembolism in patients with atrial fibrillation and/or heart valve prostheses, and for the treatment and prevention of deep venous thrombosis and pulmonary embolism.

The handling of these drugs requires correct monitorization and dose adjustment to obtain the desired therapeutic effect while minimizing the adverse effects associated both with excessive anticoagulation (which leads to bleeding) and with insufficient antithrombotic action (which can produce thrombosis). This is particularly important when patients must be subjected to surgical procedures such as tooth extractions. In this context, a number of management recommendations are available.

The present study offers an update on the recommendations for the management of anticoagulated patients programmed for tooth extractions. In recent years, most studies do not recommend reducing or interrupting anticoagulation, or replacing it with heparin, prior to tooth extraction - provided therapeutic international normalized ration (INR) levels are maintained, with emphasis on the application of local measures such as antifibrinolytic agents, for the control of hemostasia.

Key words: *Oral anticoagulants, extraction, tranexamic acid, warfarin, acenocoumarol, surgery.*

Introduction

The term oral anticoagulant (OAC) refers to oral vitamin K antagonists, including mainly sodium warfarin (the most widely used agent in Anglo-Saxon countries) and acenocoumarol (widely used in Spain). These drugs are widely prescribed for preventing arterial thromboembolism in patients with atrial fibrillation and/or heart valve prostheses, and for the treatment and prevention of deep venous thrombosis and pulmonary embolism (1).

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When such patients require surgery (e.g., tooth extractions), increased bleeding risk is postulated if the OAC dose is not lowered. However, reducing the drug levels in turn can increase the risk of thromboembolism. Thus, a series of management guidelines are needed in such situations.

The present study offers an update on OACs and on the recommendations for the management of anticoagulated patients programmed for tooth extractions, based on the results of clinical studies and expert opinions.

Oral anticoagulants

Anticoagulant drugs inhibit the plasma phase of blood clotting by either liver synthesis of coagulation factors (oral anticoagulants, OACs) or blocking the action of already formed factors (heparins). Thus, the term OAC refers to oral antagonists of vitamin K.

OACs can be derived from coumarin (4-hydroxycoumarin, sodium warfarin, phenprocoumon, acenocoumarol, dicoumarol) or indandiones (indan-1,3-dione, anisindione, phenindione). The coumarin derivatives are the most widely used OACs, and in this context sodium warfarin (Coumadin®) is the most commonly used agent in Anglo-Saxon countries, while acenocoumarol (Sintrom®) is the most widely used drug Spain. The indandiones are presently little used, due to their adverse effects - particularly hypersensitivity (1-3).

OACs inhibit the enzyme vitamin K reductase, which converts vitamin K epoxide to its active form. The vitamin K-dependent blood coagulation factors (factor II, VII, IX, X and proteins C, S and Z) present a group of carboxyglutamic acid residues (GLA residues) that allow binding of the factor (via ionic calcium bonds) to the carboxyl and hydroxyl radicals of the membrane phospholipids of platelets and other cells - resulting in physiological blood coagulation. Supplementary carboxylation of glutamic acid requires the participation of vitamin K in its active form (hydroquinone) - the latter being degraded to epoxide during the process. By means of reductases, the liver cells regenerate this epoxide into the active form of the vitamin, thereby allowing another cycle of formation of active coagulation factors. This continuous recycling process explains why only small daily amounts of vitamin K are needed. OACs that are structurally similar to vitamin K competitively interfere with its regeneration process. In the absence of active vitamin K, proteins lacking GLA residues are synthesized, and such factors are unable to participate in blood coagulation (4,5).

The anticoagulant effect in turn depends on the half-life of the inhibited factors. In this sense, the half-lives of factors VII, IX, X and II are 6, 24, 40 and 60 hours, respectively. Blood coagulation factor VII is the first to be affected, prolonging prothrombin time (PT). Factors IX, X and II are posteriorly affected: factor IX prolongs activated partial thromboplastin time (aPTT), while factors X and II prolong both PT and aPTT (6).

These are well tolerated drugs, with rapid absorption via the oral route. The peak plasma concentrations are reached one hour after administration, though the reduction in coagulation factors takes place 48-72 hours after dosing. The half-life of warfarin is 48-72 hours, versus 8-10 hours in the case of acenocoumarol. Thus, the effects of warfarin are longer lasting in terms of both the induction and disappearance of therapeutic action.

Some patients are particularly sensitive to OACs, and the activity of these drugs moreover can be affected by a range of factors including individual patient response, diet, or the simultaneous administration of other commonly used drugs such as antibiotics, analgesics, or even herbal remedies. As a result, regular monitorization is required, and such control must be more frequent when changes occur in any of the aforementioned aspects (3,5).

OAC action is monitored on the basis of the effect of such drugs on prothrombin time (PT), i.e., the time required for the clotting of citrate-treated plasma, after adding calcium and thromboplastin. Thromboplastin is extracted from different tissues with different levels of sensitivity - a fact that complicates the comparison of PT test results. The PT results are usually reported as the ratio patient time / control time. The simple ratio is extremely variable, depending on the sensitivity of the reagent used - thus making it impossible to establish universally applicable therapeutic margins. For this reason, in 1978 the World Health Organization (WHO) recommended PT standardization, and in 1983 it introduced the INR (international normalized ratio), which is calculated by raising the simple ratio to the international sensitivity index (ISI) of the thromboplastin used. Thus, INR = (patient time / control time) ISI. This is the formula used to standardize PT, allowing comparison regardless of the thromboplastin used by the different laboratories, and ensuring increased reliability in monitoring OAC treatment. At the same time, the different international societies established recommendations regarding the therapeutic anticoagulation levels to be maintained according to the existing patient pathology - the corresponding INR value ranging from 2 to 3.5 (Table 1)(4,7). Thus, there is a strong correlation between

Table 1. Therapeutic anticoagulation levels (2,3).

Clinical pathology	INR
- Prophylaxis – venous thromboembolism (high risk surgery)	2.0-3.0
- Prophylaxis – venous thromboembolism (hip surgery)	2.0-3.0
- Treatment of deep venous thrombosis or pulmonary embolism	2.0-3.0
- Prevention of systemic embolism in patients with atrial fibrillation, heart valve disease, bioprostheses, or acute myocardial infarction	2.0-3.0
- Valve prostheses, recurrent systemic embolism, recurrent myocardial infarction	2.5-3.5

INR = international normalized ratio

INR and bleeding risk - the latter increasing when INR >4. However, there are also other factors to be taken into account that may facilitate bleeding, such as the existing background disease (e.g., liver pathology, bone marrow alterations, anemia, malabsorption, kidney disease) and the administration of different drugs. There are both effect enhancing drugs - which generally act by displacing the coumarinic agent from the plasma albumin transporter to which it is bound - and effect reducing or inhibiting drugs that block the intestinal absorption of the coumarin drug or accelerate its metabolism. Following the introduction of a new drug, it is advisable to perform more frequent laboratory controls (4,5,8). The prophylactic antibiotic dose which some patients require before tooth extraction does not appear to affect the capacity to secure adequate hemostasia. In contrast, longer antibiotic treatment exerts a greater effect, since it alters vitamin K absorption secondary to action upon the gastrointestinal flora, with an increase in bleeding risk (3).

The experts always recommend monitoring INR on the same day as tooth extraction (1-6).

Management of orally anticoagulated patients requiring surgery

Due in part to the lack of randomized studies, a number of recommendations have been made for the management of anticoagulated patients programmed for surgery, in view of the need to lower the OAC regimen in order to prevent bleeding complications, while at the same time avoiding thromboembolic phenomena secondary to this reduction in INR to subtherapeutic values.

The recommendations vary according to the bleeding risk of the surgical intervention and the indication of anticoagulation therapy (i.e., the thromboembolic risk of the patient). Thus, for example, treatment to prevent venous thromboembolism is not the same as treatment for dealing with an acute thrombotic episode.

Although consensus is lacking, the expert groups do establish a series of recommendations:

- For patients at low risk of bleeding after the operation, anticoagulation can be maintained at the lower limit of the therapeutic range (INR = 2.0).
- For patients at high bleeding risk, anticoagulation should be maintained at subtherapeutic levels (INR = 1.5). Accordingly, acenocoumarol should be suspended 3-4 days before surgery (4-5 days in the case of warfarin). On day -3, low molecular weight heparin (LMWH) should be provided at therapeutic, medium or prophylactic doses, depending on whether the thrombotic risk of the patient is high, moderate or low, respectively. This is to be maintained until 12 hours before surgery, followed 12 hours after surgery be reintroduction of the original treatment, provided there is no bleeding (1,4-6).

Depending on the existing thromboembolic risk, the American Heart Association / American College of Cardiology Foundation Guide to Warfarin Therapy recommends different heparin management regimens:

- Patients with moderate thromboembolic risk: Administration of prophylactic LMWH doses of 3000 U via the subcutaneous route (every 12 hours) prior to surgery until the INR values have been normalized, with the reintroduction of treatment 12 hours after surgery together with the OACs combined during 4-5 days, until the therapeutic anticoagulation levels of the patient have been reached. In the event of important bleeding risk after the operation, heparin or LMWH dosing is to be postponed 24 hours or more.
- Patients with high thromboembolic risk: In these cases heparin dosing must be therapeutic rather than prophylactic: 100 U LMWH every 12 hours via the subcutaneous route. Administration is to be interrupted 24 hours before surgery. If the maintenance of patient anticoagulation is a critical consideration, then heparin can be administered in hospital at a dose of 1300 U/hour via intravenous infusion, with suspension 5 hours before surgery. Heparin or LMWH can be resumed 12 hours after the intervention at prophylactic doses alone or in combination with OACs, until the INR value has been restored.
- Patients with low thromboembolic risk: OAC can be suspended and resumed after the operation, with subcutaneous LMWH supplements every 12 hours, if necessary.

In general, heparins are not reintroduced before 12 hours postsurgery, and dosing is postponed for longer periods in the case of evidence of bleeding (4).

Orally anticoagulated patients and extractions

However, the recommendations in the case of minor surgery - including tooth extraction - appear to be more unanimous. In effect, most sources recommend that OAC should not be interrupted, working within a therapeutic INR range of 2-3 or 2.5-3.5, depending on the pathology involved (Table 1)(1,4,9,10), in view of the low bleeding risk that does not justify increasing the risk of thromboembolism associated with OAC reduction or suspension. Recent randomized studies such as the work published by Sacco in 2007 (11) compare the complications between two groups of patients subjected to oral surgery: one with OAC reduction to subtherapeutic INR levels (INR = 1.8), and the other without OAC reduction and presenting therapeutic INR values, with postoperative local hemostatic measures. The conclusion is that there are no differences between the two groups warranting a reduction in OAC coverage.

Not all authors coincide with this view, however, and there are protocols that advise interruption or reduction of OAC in the days prior to the intervention, in order to secure subtherapeutic INR levels (INR <2) in a short period of time before the operation. This measure is suggested to be safe in patients requiring dental extraction, preventing the development of bleeding episodes (12-14).

The different studies not only relate post-extraction blee-

ding to the absolute INR values, but also to the general patient condition, the surgical technique employed, and the patient preparation and instructions provided (10,15). In this sense, bleeding reduction in these patients is facilitated by a lessening of tissue inflammation and irritation (oral hygiene, tartar removal, chlorhexidine rinses) before extraction, a careful surgical technique with thorough socket curettage to remove the inflammatory and granulation tissue, followed by wound compression, suturing and compression with dressings impregnated with tranexamic acid or epsilon-aminocaproic acid (11,15).

The placement of fibrin adhesives, oxidized cellulose and gelatin sponges in the tooth socket has also been suggested, to help clot formation before suturing (3,10,11).

Studies have been made of the use of antifibrinolytic agents (3,11), which favor local hemostasia by inhibiting fibrinolysis - such as tranexamic acid in the form of socket irrigating solutions and rinses in the days following tooth extraction. In 2003, Carter et al. (16) conducted a randomized study in patients under oral anticoagulation and subjected to extractions without modifying the OAC regimen, and applying two types of hemostatic agents (4.8% tranexamic acid and autologous fibrin adhesive). The authors concluded that both approaches are effective and safe in controlling post-extraction bleeding. In this context, increased efficacy was obtained with socket irrigation using 10 ml of tranexamic acid immediately after extraction, with the placement of absorbable oxidized cellulose impregnated with tranexamic acid in the socket, and reabsorbable suturing with tranexamic acid rinses (10 ml four times a day during 7 days). Autologous fibrin adhesive applied to the socket walls in turn was recommended when the patient has difficulties performing rinses correctly. Posterior studies reported the same efficacy in controlling hemostasia by applying rinses for only two days (17). Tranexamic acid has no marketing license in the United Kingdom, and fibrin adhesives (Tissucol®) are not recommended by all authors, due to the risk of disease transmission - though such systems are subjected to viral inactivation processes - and their high cost (8).

Post-extraction bleeding is generally controlled by local measures such as socket curettage, suturing, and local compression, thanks to easy access to the bleeding zone. When such measures prove insufficient, and the anticoagulation effect must be suppressed, this can be done by administering vitamin K. In this sense, intravenous administration elicits faster effects than the oral route - the recommended dose being 5-10 mg. The use of concentrates of prothrombin complex or fresh frozen plasma is reserved for cases of important bleeding. Based on the evidence that the benefit of preventing thromboembolism outweighs the risk of bleeding, the recommendations of the published clinical studies and the expert opinions are to keep the OAC dose unchanged, working with therapeutic INR levels, and adopting local hemostatic measures - with the use of antifibrinolytic agents such as tranexamic acid, in dental extractions. More invasive oral surgery with an increased bleeding risk may constitute an exception to these guidelines, requiring due evaluation in coordination with the hematologist (3,5).

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