Emergency management of patients being treated with oral anticoagulants

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ABSTRACT

Vitamin K antagonists (VKA) are among the most widely prescribed drugs in the industrialized world. In fact, for decades, VKA have been the only orally available anticoagulant for the primary and secondary prevention of venous and arterial thrombotic events. Their efficacy has been widely demonstrated in a series of studies carried out in the 1990s. Since the incidences of atrial fibrillation and venous thromboembolism increase exponentially with age, the number of anticoagulated patients is destined to increase. This paper examines anticoagulation therapy management with particular attention to the use of VKA.

Introduction

Vitamin K antagonists (VKA) are among the most widely prescribed drugs in the industrialized world. The reasons for this success are that, for decades, VKA have been the only orally available anticoagulant for the primary and secondary prevention of venous and arterial thrombotic events and that their efficacy has been widely demonstrated in a series of studies carried out in the 1990s.[1] Since the incidences of atrial fibrillation and venous thromboembolism increase exponentially with age, the number of anticoagulated patients is destined to increase; it has been estimated that there are currently more than 600,000 patients receiving oral anticoagulant therapy (OAT) in Italy alone.[2] The efficacy of VKA is, however, counterbalanced by the notable difficulties in managing these drugs caused by their rather narrow therapeutic ranges, interactions with a myriad of other drugs, and strong dependence on diet and lifestyle.[3] It has been estimated that only 60% of patients on VKA have coagulation parameters within the therapeutic range at any given time.[4] Therefore, an International Normalized Ratio (INR) above the upper limit, with a consequently increased risk of bleeding, is a common occurrence.

Bleeding is the most serious potential complication of OAT and is the most important cause of underuse of VKA. In a study carried out in patients followed by OAT Surveillance Centers in Italy,[5] the annual prevalence of hemorrhagic complications was 7.6 per 100 patients (0.25 fatal, 1.1 major, 6.2 minor). The incidence can double in patients not followed by specialized centers.[6] The Control of Anticoagulation Subcommittee recommends that bleeds are to be considered major if fatal and/or cause symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular, pericardial or intramuscular bleeding with compartment syndrome, and/or causes a fall in the hemoglobin level of 20 g/L or more, or leads to a transfusion of two or more units of whole blood or red cells. All other bleeds can be considered minor.[7]

In the last few years, the pharmaceutical industry has produced new oral anticoagulants with anti-factor Xa and IIa activity.[8,9] It is possible that these, thanks to their more predictable dose response, may replace dicoumarols as the most widely used anticoagulants worldwide.[10] However, the higher cost of these drugs and, above all, the lack of an effective antidote, still leave VKA in advantage. It is, however, essential to understand the pharmacology of these drugs and be familiar with the available treatment options in order to be able to neutralize their effects. The vitamin K-dependent factors (factors II, VII, IX, and X) are synthesized in the liver as inactive precursors and they must undergo γ-carboxylation of the glutamic acid residues on the N-terminal part of the molecule in order to be activated. Carboxylation, indispensable for binding Ca^{2+} and, therefore, for the activation of these serine-proteases, not only requires the enzyme γ-glutamyl carboxylase,

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but also a molecule of O_2, one of CO_2, and the reduced form of vitamin K (hydroquinone: KH2) which, in the reaction, is oxidized to vitamin K epoxide. Vitamin K epoxide can be re-used through its reduction first to vitamin K and then to reduced vitamin K by two enzyme systems: the first, vitamin K epoxide reductase, is completely inhibited by dicoumarols, while the second, vitamin K reductase, is only partially inhibited by dicoumarols.[3] The anticoagulant effect of VKA can, therefore, be overcome by even small doses of phytonadione (vitamin K). In Italy, two VKA are available: sodium warfarin (Coumadin) and acenocoumarol (Sintrom). Both are rapidly absorbed through the intestines, with peak blood concentrations being reached after 90 min, and, transported by albumin, accumulate in the liver where they are metabolized. The main difference between the two drugs is their half-lives. Warfarin is a racemic mixture of two isomers: R-warfarin has a half-life of 45 h, while S-warfarin, which is 2.7-3.8 times more potent than R-warfarin, has a half-life of 29 h. Acenocoumarol is also produced as a mixture of two isomers: the half-life of R-acenocoumarol is 9 h, while that of S-acenocoumarol is only 0.5 h. Traditionally, VKA treatment is monitored by measuring the prothrombin time expressed as an INR, which reflects the levels of three clotting factors (II, VII, X) of the four that are vitamin K-dependent. When treatment with VKA is started or suspended, the changes in the prothrombin time/INR reflect the changes in these aforementioned three factors which do, however, have notably different half-lives: 2-9 h for factor VII, 17-44 h for factor X and 60-72 h for factor II. In these situations, the prothrombin time does, therefore, reflect above all the levels of factor VII, while the antithrombotic effect of VKA is correlated with the concentration of factor II.[3]

Anticoagulant therapy is associated with a risk of bleeding for the entire duration of the treatment, independently of the drug used. Although it would be extremely useful to have clinical prediction parameters for estimating bleeding risk in patients on OAT, unfortunately, none of the available clinical prediction criteria has sufficient predictive accuracy and there have been no trials to evaluate the impact of their use on patients' outcomes.[11] The main variables that influence bleeding are the intensity and duration of the anticoagulation.[5,12,13] In the ISCOAT study,[5] the most significant predictor of bleeding in multivariate analysis was an INR of 4.5 or over (the relative risk of bleeding was 5.96 when compared to the risk in patients with an INR below 4.5) and the first 90 days of anticoagulation (relative risk 1.75). A higher risk of bleeding is associated with older age, concomitant diseases (renal or liver failure, uncontrolled hypertension, a history of gastrointestinal or cerebral bleeding), and the use of other medications such as anti-platelet drugs.

There are at least three situations in which the action of VKA must be neutralized: i) in asymptomatic patients with an excessively high INR; ii) patients on anticoagulant treatment who must undergo an urgent invasive procedure; and iii) patients who are bleeding. The management options in these three cases include: i) withholding the anticoagulant; ii) administration of vitamin K; iii) infusion of fresh-frozen plasma (FFP); iv) infusion of prothrombin complex concentrates (PCC); and v) administration of recombinant activated factor VII (rFVIIa). The best choice depends on the clinical circumstances, the time available before the invasive procedure, and the entity and site of the bleeding.

Withholding vitamin K antagonists treatment

In asymptomatic patients with an elevated INR and a low risk of bleeding, it is reasonable to withhold VKA and wait until the INR has reached the therapeutic range or, in patients who need an elective procedure, a normal or near normal INR (*i.e.* <1.5) that will not increase the risk of bleeding.[14] For most patients taking acenocoumarol, the time required to reach an INR below 4.0 is usually no more than one day.[15,16] Nevertheless, it must be noted that in patients receiving warfarin therapy with an INR ranging from 6.0-10.0, after only withholding the drug, the INR takes approximately 2.6 days to decline to a level below 4.0.[17] Moreover, in patients with an INR over 9.0, advanced age, decompensated congestive heart failure or active cancer, the INR takes longer to reach the therapeutic range.[18]

The risk of major hemorrhage increases exponentially with increasing INR: with an INR over 5.0 the 30-day risk is 0.96%, but with an INR over 9.0 the risk is 9.5%.[19] In patients with mechanical heart valves, the risk of adverse events increases from 2 per 100 patient-years at an INR of 2.5-4.9 to 75 per 100 patient-years at an INR of 6.5 or over.[20] For patients who are not bleeding and who are judged not to be at high risk of bleeding, the upper limit of INR at which VKA treatment should be withheld, as the only measure, remains controversial: 6.0 for French guidelines,[21] 9.0 for Australasian guidelines,[22] 8.0 for British guidelines,[23] and 10.0 for the American College of Chest Physicians guidelines.[24] We agree that partial reversal of the INR should be considered in patients at high risk of bleeding, in those who have factors that prolong the time with an INR above the upper limit of the therapeutic target when the VKA is omitted, and in those with an INR over 9.0.[25] This can be done by administering vitamin K.

Vitamin K

Vitamin K1 (phytonadione, phytomenadione: a form of vitamin K derived from plants) is synthetically

produced for the treatment of VKA-associated coagulopathy. The administration of vitamin K does not reverse the inhibition of vitamin K oxide reductase, but is a source of reduced vitamin K that allows the carboxylation of the precursor coagulation proteins. The impact of administration of vitamin K on bleeding events and thromboembolism was recently addressed in non-bleeding patients by Crowther *et al*.[26] (INR between 4.5 and 10.0; 1.25 mg oral vitamin K) and Denas *et al*.[27] (INR between 5.0 and 10.0; 2.0 mg oral vitamin K). The data from these studies demonstrated that vitamin K is safe and not associated with an increased frequency of hemorrhagic or thromboembolic events. It is, therefore, reasonable to administer 1.0-2.5 mg oral vitamin K to patients with an INR of 5.0-9.0 if they are at high risk of bleeding. For non-urgent correction of over-anticoagulation of patients with an INR over 9.0, the administration of 2.0-5.0 mg of vitamin K is effective without over-reversing anticoagulation.[28] Since vitamin K is fat soluble, oral administration is ineffective in the case of obstructive jaundice. Intravenous vitamin K is preferred if a more rapid effect is required, *i.e.* in patients with non-major bleeding. The intravenous route of administration has a much faster effect; the INR starts to decrease within 2 h and normalizes within 12-16 h.[29-31] However, a recent meta-analysis concluded that at 24 h the effects of vitamin K given orally or intravenously are equivalent.[32] There is a small risk of allergic reactions which must absolutely not preclude this route of administration, above all in patients who are bleeding or who require urgent surgery. In order to minimize the risk of anaphylactic reactions, the vitamin K must be dissolved in at least 50 mL of fluid and administered slowly over at least 20 min.[3] An intravenous dose of 0.5-1.0 mg reliably reduces the INR within the therapeutic range in the majority of patients. Higher doses (1.0-3.0 mg) may have to be used for INR values over 10[25] or for patients with minor bleeding,[23] even if the evidence in the literature is scarce. Intramuscular injection should be avoided because of the risk of hematomas, especially in patients who are strongly anticoagulated. The subcutaneous route of administration should also be avoided, because of its unpredictable effect and because it leaves an area of induration at the site of the injection.[32] It should, however, be emphasized that the action of vitamin K is too slow to be effective when emergency surgery must be performed or when the patient has life-threatening bleeding. In these cases, concomitant treatment must be used.[1,22]

Fresh-frozen plasma

Fresh-frozen plasma is an excellent source of replacement of vitamin K-dependent factors and is currently the most widely used source in the USA.[33,34] It does, however, have some important limitations.[35] First, in emergency circumstances, the delay before achieving correction of the coagulopathy is unacceptable because of the need to carry out ABO-cross-matching before the transfusion (although in emergency situations, AB FFP can be used without prior blood typing), thaw the plasma (at least 20-30 min), and infuse it safely to reduce the risk of volume overload. Secondly, in most patients, a large volume of plasma is needed to reverse a high INR (approximately 2 L),[13] particularly if the target INR is below 1.5.[36] The volume is important, given the likelihood of transfusion-associated volume overload.[37] It has, however, been demonstrated that, with an INR over 5.0, the volume required would be so great that it would not be possible to correct the coagulopathy completely anyway.[38] Thirdly, there is a risk, albeit a low one, of transfusion-related acute lung injury and anaphylactic reactions. Finally, hemodilution can lead to a significant drop in the hemoglobin concentration, alter the rheological properties of the blood and, paradoxically, increase bleeding.[39] FFP should, therefore, only be used if PCC is not available.[23] Furthermore, it should be emphasized that the duration of action of FFP is limited because of the short half-life of some factors, in particular factor VII, and for this reason, vitamin K must be administered at the same time to stimulate the synthesis of the endogenous factors and support the correction of the coagulopathy when the effect of the FFP is lost.[3]

Prothrombin complex concentrates

The most efficient way of replacing missing coagulation factors is to administer them in the form of a concentrate. PCC are highly purified concentrates, produced by ion exchange chromatography starting from a large pool of plasma.[40,41] PCC can be classified into three types, based on the technique used for their preparation:[25,42] i) 4-factors PCC (4PCC), which contain six vitamin K-dependent factors (II, VII, IX, X and proteins C and S), are the most effective in neutralizing the action of VKA; ii) 3-factors PCC (3PCC) have therapeutically useful levels of only factors II, IX and X and although they have been available for decades to treat hemophilia B, given that factor VII, severely depleted in VKA-treated patients, is not present in 3PCC, these concentrates would not appear able to correct the hemostatic defect adequately in patients taking VKA. Supplementation with a small amount of plasma increases the likelihood of lowering the INR satisfactorily;[43] iii) the third type is formed of activated products, such as factor VIII inhibitor bypassing agents (FEIBA), whose use is only foreseen for the treatment of cases of congenital or acquired hemophilia (this latter being caused by inhibitors to factor VIII or factor IX).

The concentration of the vitamin K-dependent factors is 25-fold higher in PCC than in plasma;[13] 1000 units of coagulation factor, equivalent to the amount found in 1 L of plasma, can be administered in 40 mL of fluid. Furthermore, the full therapeutic effects of PCC are achieved within a few minutes of administration and thus these concentrates are the first choice treatment for major hemorrhage in patients on VKA. The activity of PCC is expressed in international units (IU) and refers to the concentration of factor IX, although similar concentrations of factors II and X should be present. In a recent review of the literature, Leissinger *et al.*, while stating that most of the studies are retrospective or, if prospective, not randomized, concluded that PCC are a rapid and specific means of restoring normal hemostasis in anticoagulated subjects.[44] The Australasian guidelines recommend the use of 3PCC plus the adjunctive administration of FFP as a source of factor VII (4PCC is not available in Australia or New Zealand) for any clinically significant bleeding for which warfarin-induced coagulopathy is considered a contributing factor.[22] French guidelines recommend 4PCC for the management of severe bleeding in patients on VKA.[21] The British Committee for Standards in Haematology recommends 4PCC for emergency anticoagulation reversal in patients with major bleeding.[23] The American College of Chest Physicians guidelines suggest 4PCC as the first choice for warfarin reversal.[24]

There are currently two 3PCC available in Italy: Uman complex D.I. (Kedrion, Castelvecchio Pascoli, Italy) and Prothomplex TIM 3 (Baxter, Vienna, Austria).[45] Both contain 25-30 IU/mL of factors II, IX and X; both also contain a small amount of heparin. Recently, a new 4CCP, previously called Beriplex P/N, was registered in Italy with the name of Confidex® (CLS Behring, Marburg, Germany).[41] This PCC not only contains the four vitamin K-dependent coagulation factors, but also the physiological inhibitors of coagulation (protein C, protein S and antithrombin) and small amounts of heparin. In circumstances in which both 4PCC and 3PCC are available, it is obvious that the better choice is the 4PCC. If, however, 4PCC are not available, the 3PCC should be used together with small amounts of FFP as the source of factor VII.[22,25,43]

There is some controversy in the literature about the optimal dose of PCC to use. Although there is a lack of prospective, randomized studies, it is clear that the dose required depends on the clinical situation and, in particular, on the degree of bleeding, the clinical status of the patient, and the target INR. For life-threatening hemorrhages, it is important to reverse the INR rapidly to 1.0. For major, but non-life-threatening bleeding in a patient with a high risk of thromboembolic complications, a reversal to INR 1.5 or below is preferable; this target represents a value of at least 60% factor IX which is known from the treatment of patients with hemophilia B to be a protective level of factor IX. The optimal dose of PCC reported in the literature ranges from 8.8 to 50.0 IU/kg.[22,23,38,46-48] The efficacy of the correction is improved by using a dose that is adapted on the basis of the initial INR, the patient's weight and the target INR.[49] A recent study demonstrated the hemostatic efficacy of three different doses of 4PCC chosen on the basis of the initial INR and then multiplied by the patient's weight:[50] one dose of 25, 35, or 50 IU/kg body weight of 4PCC was administered to patients with a baseline INR of 2-3.9, 4-6 or over 6, respectively. At 30 min after administration of the 4PCC, the INR had decreased to 1.3 or below in 93% of the 43 patients.

There are still some fears concerning the use of PCC. One is the risk of transmitting diseases: one dose of PCC is derived from tens of thousands of donors and, historically, has been an efficient means of transmitting infections. However, the current viral inactivation methods introduced by the companies that produce plasma products have dramatically decreased this risk to the point that an ampoule of PCC now carries a significantly lower infective risk than a unit of FFP.[51] A second fear is the risk of thrombosis: an association between the use of PCC and fatal thrombosis was first described in the 1990s.[52] The last generation PCC, produced according to the indications of the European Quality Standards,[53] are considerably less thrombogenic. The strategies used to decrease the thrombogenicity of these products include the addition of small amounts of heparin to prevent *in vitro* activation of the clotting factors, addition of natural anticoagulants (antithrombin, protein C and protein S), precise proportions of the concentrations of the single factors, more precise indications on the dose to use based on the patient's initial INR and weight, and the recommendation that the infusion must be slow (no more than 2-3 mL/min),[54] even if some authors have recently demonstrated that infusion even two or three times faster than this are in any case safe.[55]

Contraindications to the use of PCC are hypersensitivity to any of its constituents, *e.g.* heparin (as noted above, PCC contain heparin) for patients with a positive history of heparin-induced thrombocytopenia or disseminated intravascular coagulation, because this worsens the risk of thrombosis associated with the condition. Relative contraindications are a recent myocardial infarct or thromboembolic event. In these cases, the balance between the thrombotic risk and the bleeding risk must be evaluated carefully. Chronic liver disease, being associated with a deficiency of antithrombin, is another relative contraindication, which can be overcome by the contemporaneous administration of this physiological inhibitor.[35]

The effects of PCC on coagulation last 6-8 h (ex-

cept in the case of massive blood loss). The effects of the concomitant administration of vitamin K start after 4-6 h. For this reason, many guidelines[21-24] recommend the simultaneous administration of PCC and vitamin K (at high doses) for urgent neutralization of the effects of VKA. Furthermore, the overlap of the effects of the PCC and the vitamin K is sufficient to guarantee normal hemostasis in the majority of cases, without having to administer further PCC.

One particularly serious event is cerebral hemorrhage. VKA therapy is associated with an increased risk of intracerebral hemorrhage (ICH) and the incidence of ICH is increasing because of the growing use of VKA therapy and the older age of treated patients. Approximately 5-12% of ICH are related to VKA therapy.[56,57] With every increase of 1.0 in the INR, the risk of developing ICH approximately doubles.[58] The rate of ICH in VKA-treated patients is approximately 2-9 cases per 100,000/year, an incidence that is 7-10 fold higher than that in the untreated population.[59] The prognosis is poor with a mortality rate between 30 and 55%[60,61] probably mediated by enlargement of the hematoma 6-12 h after the onset of the bleeding, which is common in VKA-related ICH, but rare in spontaneous ICH.[62] Anticoagulation reversal is considered a time-critical intervention[63] and patients on OAT in whom ICH is strongly suspected should have their INR reversed before any investigation. Despite the long history of use of VKA, there is a lack of evidence from randomized clinical trials addressing the efficacy of treatment regimens in ICH patients on OAT. Nevertheless, there are many consensus-based guidelines that suggest the preferred treatment for a rapid reversal of coagulopathy.[1,22,23,64,65] FFP combined with vitamin K is the traditionally used regimen to reverse the INR but has two major drawbacks: a big volume of infusion is needed and the process is time-consuming. Administration of vitamin K alone (5-10 mg i.v.) is not appropriate when rapid reversal is indicated, but is necessary to maintain prolonged reversal of the INR. Randomized data do not yet support the clinical efficacy of rFVIIa in patients with ICH.[66,67] PCC + intravenous vitamin K is considered the first therapeutic choice by many authors[1,23,64,65,68] whereas others[22,69] include FFP in their recommendations; the rationale for this is that the only three types of PCC available in their country are 3PCC.

Recombinant activated factor VII

The use of rVIIa is indicated for the control of bleeding in hemophilic patients with inhibitors of factor VIII and factor IX, in patients with Glanzmann's thromboasthenia with antibodies against glycoprotein IIb/IIIa, and in bleeding episodes in patients with FVII deficiency. However, rVIIa has been used in a wide range of clinical situations, including neutralization of dicoumarols, such that it has been recommended for this purpose in the recent American College of Chest Physicians guidelines.[1] One of the main doubts about the use of rVIIa is that, although it corrects the INR, it does not correct the underlying coagulation disorder and the vitamin K-dependent factors must be replaced in any case. Furthermore, the average life of rVIIa is much shorter (60-180 min)[70] than the time it takes for vitamin K to act, which means that repeated doses are probably necessary.[54] The possible complications with high doses, such as thrombosis (particularly arterial) and the high costs are other considerations that limit its use. The recommended dose is unknown: the doses suggested in the literature range from 10 to 120 µg/kg for patients with ICH on OAT,[71] and a recent review of all the literature available on the use of rVIIa to neutralize oral anticoagulants concluded by recommending that rVIIa should not be used for this purpose.[72]

Conclusions

In conclusion the following recommendations can be made.

1. INR outside of the therapeutic range but below 5.0. No or minimal bleeding.
   - Decrease the dose of dicoumarol or miss one dose. Check the INR more frequently and re-start OAT at a lower dose when the INR has reached the therapeutic range.
2. INR between 5.0 and 9.0. No or minimal bleeding.
   - Withhold one or two doses of the OAT. Check the INR more frequently and re-start OAT at a lower dose when the INR has reached the therapeutic range.
   - If the risk of bleeding is high, administer vitamin K (1.0-2.5 mg, o.s. or 0.5-1.0 mg i.v.). Measure the INR within 24 h and re-start the OAT at a lower dose when the INR has reached the therapeutic range.
3. INR over 9.0. No or minimal bleeding.
   - If the risk of bleeding is low, withhold the OAT, administer 2.5-5.0 mg of vitamin K o.s. or 1.0-3.0 mg i.v. Measure the INR within 24 h. Re-start the OAT at a lower dose when the INR decreases to below 5.0.
   - If the risk of bleeding is high, withhold the OAT, administer 1.0-3.0 mg of vitamin K i.v. Measure the INR within 12 h. Re-start the OAT at a lower dose when the INR decreases to below 5.0.
4. Clinically significant bleeding and/or need for urgent surgery with INR below 4.0.
   - Withhold OAT. Administer 5-10 mg of vitamin K by slow i.v. infusion. Administer 25 IU/kg of 4PCC.*

5. Clinically significant bleeding and/or need for urgent surgery with INR 4.0-6.0.
   - Withhold OAT. Administer 5-10 mg of vitamin K by slow i.v. infusion. Administer 35 IU/kg of 4PCC.*
6. Clinically significant bleeding and/or need for urgent surgery with INR over 6.0.
   - Withhold OAT. Administer 5-10 mg of vitamin K by slow i.v. infusion. Administer 50 IU/kg of 4PCC.*
7. Intracerebral hemorrhage.
   - Withhold OAT. Administer 5-10 mg of vitamin K by slow i.v. infusion. Administer 35 IU/kg of 4PCC.*
   - When an INR value is available, if the value at presentation is over 6.0, administer another 15 IU/kg of 4PCC.*

* If only 3PCC is available, add 150-300 mL of FFP.

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