Anticoagulation in clinical practice: Part I – oral anticoagulation

Ana Teresa Timóteo,* Maria João Pais**

Abstract

The authors review, in the first part of the anticoagulation subject the use of anticoagulants in clinical practice, namely oral anticoagulation in this paper. In general, anticoagulation is essential when trying to prevent thromboembolic events in risk situations. In particular, oral anticoagulants, owing to their easy administration and monitoring allowing long-term anticoagulation. As in the use of any drug, it is important to know the correct administration, necessary monitoring and adverse effects, of these drugs. These issues are reviewed briefly in this paper. Nowadays, oral anticoagulants are widely used, however there are still new indications emerging where their use is appropriate.

Key words: anticoagulation, oral anticoagulation, warfarin, international normalised ratio, vitamin K.

Introduction

Hemostasis phenomena are a crucial physiological mechanism to a correct and efficient solution of all haemorrhagic events in the body. The secondary haemostasis process is subsequent to a primary process where platelets have a crucial role, in the process that is not totally independent from each other. Sometimes, such defensive phenomena becomes pathological, whether due to hyper clotting (e.g. anti-thrombin III, C protein, S protein, antiphospholipid lipid antibody presence), whether triggering the clotting cascade (*Fig. 1*) (e.g. coronary thrombosis triggered by atherosclerotic plaques).[1] For such reason it is important to develop drugs with anticlotting activity. At present, there are available in our market oral anticoagulants as warfarin (Varfine®) and acenocoumarol (Sintrom®). For practical reasons detailed ahead, warfarin is the most used, therefore a great deal of this text relates to warfarin. There are also anticlotting drugs to be given by parenteral route, namely non-fractioned heparin and low molecular weight heparin, which will be dealt in detail in the second part of this subject.

Mechanism of action

Among all proteins involved in clotting, it should be highlighted factor II (prothrombin), VII, IX,X, C protein (CP) and S protein (SP), which needs a g – carboxylation process during their biosynthesis, enabling, in the presence of calcium ions, the fixation at membrane phospholipids level and building indispensable complexes to generate thrombin. For such g – carboxylation it is necessary, as cofactor, a reduced K vitamin, which is obtained through an interconversion cycle (*Fig. 2*). K vitamin antagonists or oral anticlotting drugs (OAC), and the best known are coumarin derivatives (warfarin and acenocoumarol) and indanedione derivatives, acting while inhibiting K vitamin epoxide reductase and possibly also K vitamin reductase. The reduction on the Gla number of residues leads to a proportional reduction of the clotting activity. The first to be affected are factor (F) VII and CP, with half-lives ranging from 4 – 6 hours. After that are F IX and FX and lastly F II (3 – 5 days).[2]

Pharmacokinetics

The most used drug is warfarin, in oral form, as the parenteral form is not used in the clinical practice. Warfarin has a plasmatic peak at three hours and a bioavailability ranging from 75 to 90%. It is strongly linked to serum proteins (99%, from which 97.5% to albumin) with the remaining fraction being intracellular. Hypoalbuminemia can lead to an increase on the intracellular concentration. The metabolization is hepatic following an entero–hepatic cycle. A major kidney failure can lead to an accumulation of metabolites and consequently, to a drug overdose. Oral

*Resident to the Cardiology Supplementary Internship

**Head of Internal Medicine Service

Santa Cruz Hospital, Carnaxide

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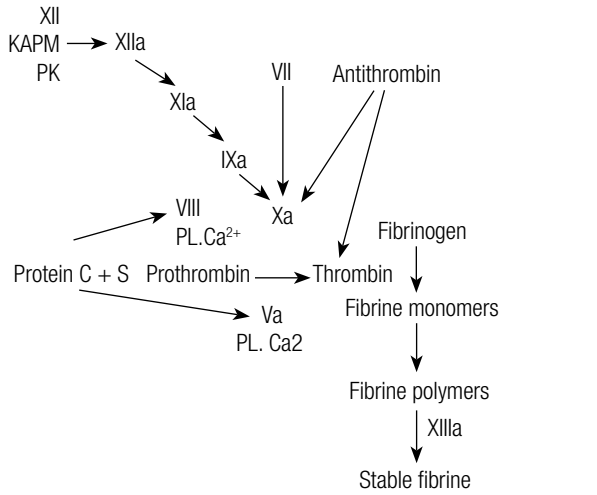
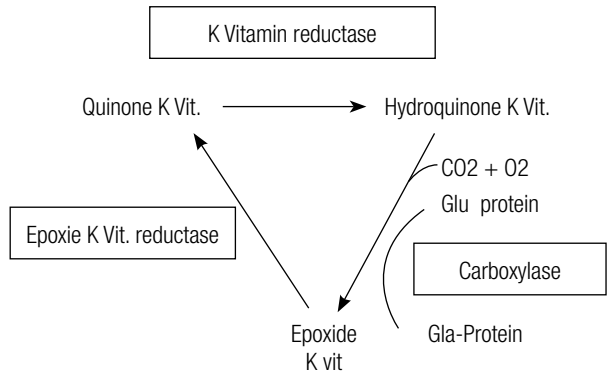


KAPM – High molecular weight kininogen; PK – Prekalicraine; PL – Phospholipids

Clotting cascade and main natural anticlotting mechanisms.

FIG. 1



K vitamin interconversion cycle to the γ-carboxylation process

FIG. 2

anticlotting drugs plasmatic half-life is variable, and it is recommended to use molecules with a long half-life, as warfarin (35 – 45 hours) and acenocoumarol (8– 9 hours), enabling the first to only a daily intake.[2]

Interactions

There are numerous drug interactions which can propitiate or reduce the anticlotting effect and should be present when an anticlotting patient receives another drug (*Table I and II*).[1,2,3,4] Drugs presented in the tables mentioned are considered as one and two level of evidence, i.e., those with a higher probability of interfering with warfarin. For other drugs, such level is less evident or even doubtful.[5] Warfarin exists in the form of two isomers, being the S five times more potent than the R, and this way the interaction on the S isomer is more significant in clinical terms.[3] The simultaneous administration of drugs interfering with platelets, as the acetyl salicylic acid, non-steroid anti-inflammatory drugs and penicillin (in high doses) increase the haemorrhagic risk.[3,4] When there is a high intake of K vitamin, the dicoumarinic effect is reduced. On the other hand, when there is a reduced intake (as in a diet poor in K vitamin, patients treated with antibiotics or intravenous fluids without K vitamin supplements and in conditions of lipid malabsorption), in liver diseases (due to a decrease in the factors synthesis) and in hyper metabolic conditions (fever and hyperthyroidism increases the clotting factors catabolism) with an increase on anticlotting effect.[6,7]

In some patients subject to anticlotting therapy, it is difficult to reach the desired anticlotting level, even using double or triple dosage regime. In such patients, the most common cause is a bad compliance to the treatment by the patient, making around 90% of such resistances, or sometimes the result of drug interaction. In this last group it should be highlighted that K-1 vitamin, which can be reduced through an enzymatic system resistant to warfarin, the period of up to 10 days, mainly when given in high dosages; it can also correspond to a laboratory error (which nowadays are scarce) or perhaps a diet rich in K vitamin (vegetables, particularly spinaches, cabbage and broccoli). Excluding such situations, we are left with hereditary resistance (dominant and autosomal) with a genetic anomaly causing a change on the receptor affinity for warfarin, although this is a very rare situation.[2]

Monitoring

In order to monitor the therapy, the most used test is prothrombin time which can be obtained by adding calcium and thromboplastin to a citrate plasma. Thromboplastin is a phospholipid protein extracted from tissues containing the tissue factor and phospholipids necessary to promote F X activation by F VII. Such test reflects the depression on F II, VII and X. Thromboplastin changes markedly the response to warfarin anticlotting effects, therefore it becomes

TABLE I

Drug interactions (potentiation)

ANTICLOTTING EFFECT POTENTIATION
Decrease of metabolic clearance
Phenylbutazone – S
Sulphinpyrazone - S
Metronidazole – S
Co-trimoxazole – S
Cimetidine – R
Omeprazole – R
Amiodarone – S + R
Allopurinol
Competition with albumin link
Diflunisal
Fibrates
Phenylbutazone
Without changes of plasmatic levels
2nd and 3rd generation cephalosporins
Clofibrate
Estroprogestatives
Tyroxine
Heparin
Sulphamydes
Wide spectrum antibiotics
Non clarified mechanism
Erithromycin
Anabolisant steroids
Ketoconazole
Fluconazole
Isoniazide
Piroxycam
Tamoxyphen
Vitamin E (high doses)
Quinidine
Propaphenone
Phenitoin
Warfarin isomers are designated by letters S and R.

TABLE II

Drug interactions (antagonism)

ANTICLOTTING EFFECT ANTAGONISM
Decrease on absorption
Cholestyramine
Sucralfate
Increase on metabolic clearance
Barbiturates
Rifampicin
Carbamazepine
Griseofulvin
Hydantin
Chronic alcoholism
Non clarified mechanism
Nafcillin
Other mechanisms
K vitamin

difficult comparing results, depending on the used thromboplastin. A need emerged to create the ISI (International Sensitivity Index) enabling each manufacturer to compare his reactive products to the reference thromboplastin (1.0 ISI). The most used are those ranging from 1.0 to 2.0. Such index has enabled to obtain the calibration standard, called the International Normalised Ratio (INR), adopted by the WHO in 1982, used to standardise PT results, comparing it with the control PT obtained by the average results of 20 normal individuals. It is recommended the use of higher response reacting drugs, i.e., those with an ISI closer to 1.0, particularly when a low warfarin dose is used.[2,3,4]

Administration rules

The beginning of an anticlotting effect is delayed by a period ranging from 2 to 7 days, corresponding to the time necessary to the clotting factors depending on normal K vitamin be replaced by the changed ones. If a quick effect is desired, heparin should be overlapped initially (of quick effect) during at least four days, suspending heparin when the desired INR is achieved for a minimum of two days. Oral anticlotting can be started with induction doses (for instance, starting with a 10 mg dose, and reducing the dose gradually) or maintenance (usually 5 mg in the first few days). If the treatment is urgent, it should be started with 10 mg, followed by 5 mg in the following days, reaching an INR of 2.0 stable by the end of four or five days. Using maintenance dosage, a stable INR is reached within 5 to 7 days. There should be a daily monitoring until an INR therapy level is reached, and then three times a week for 1 to 2 weeks, and afterwards monitoring can be less frequent depending on the PT stability (if stable, it can be monitored with intervals from 4 to 6 weeks). If there is a need to adjust the dosage, the described monitoring cycle should be restarted until stability is reached again.[3,4]

Acting before a high INR value changes according

TABLE III

INR values recommended for invasive procedures in anticoagulated patients

Procedure	INR
Needle biopsy of massive organ Upper digestive endoscopy Polypectomia Laparoscopy with biopsy CPRE Thoracoscopy Therapeutic thoracocentesis Arthroscopy Pacemaker placement	≤ 1,5
Carotid arteriography Muscle biopsy Laparoscopy without biopsy Osteomedullary biopsy Diagnostic thoracocentesis Lumbar puncture Electromyogram	≤ 2,0
Sternum puncture Paracentesis Angioplasty Femoral arteriography Dental extraction	≤ 2,5

to the value found. Therefore, when the INR is situated between 5.0 – 8.0, it is enough to withdrawal the anti-clotting administration, so far as there is no evidence of haemorrhage. If the INR is higher than 8.0, without associated haemorrhage and without the need of a quick reversal on the anticlotting effect, apart of suspending the drug, K-1 vitamin should be given in the usual dosage of subcutaneous (SC) of 2.5 mg. When there is haemorrhage, or a need for a quick reversal, a part of the steps already mentioned, K vitamin dosage can be higher and fresh plasma (containing normal clotting factors missing) or the concentrate of prothrombin complex (such therapy is usually reserved to patients who cannot cope with fluid increases, as in such concentrate some of the factors are activated and might trigger the clotting cascade).[4,8]

Intravenous K vitamin is recommended usually in cases of peripheral circulatory insufficiency (in which the subcutaneous route absorption is very irregular) and the haemorrhage is very severe (as the reversal must be quick), although in such situation, fresh plasma is more often used. When such route is used, K vitamin should be diluted and given slowly, in 20 – 30 min, to avoid anaphylactic reactions. Do not forget that after K vitamin administration there is a period up to 10 days, without response to warfarin where sometimes is necessary to associate heparin.[3,4]

In chronically anticlotting treated patients, several strategies exists regarding elective surgery.[3] The most common one consists of interrupting oral anticlotting drugs 4 – 5 days before surgery, using instead subcutaneous heparin (average of 17.500U every 12 hours) replacing by the continuous intravenous route when admitted into hospital (the infusion is withdrawn three hours before the procedure). However the subcutaneous route can be kept, stopping it 12 – 14 hours before surgery. 5000 units are administered into pre--surgical and after surgery periods heparin or warfarin in low dosage can be restarted. Another alternative (less used) goes to the progressive reduction of INR to 1.5, a value that some authors have shown to be safe for orthopaedic and gynaecological surgery, for a period of 4 – 5 days, and before the surgery (48 and 24 hours) to give small doses of K vitamin. Warfarin is restarted in the post-surgical period, with heparin supplement, if needed. For dental extractions, tranexamic acid should be used (in our country replaced by aminocaproic acid) with around 20 min compression, by a soaked gauze in it and subsequently gargling every six hours for over two days.

In a patient treated with anticlotting, it is also important to take into account either invasive procedures he/she can be subject to and which are the recommended INR values (*Table III*).[9]

Indication and contraindication

The indications for oral anticlotting therapy are expressed in *Table IV,* as well as the recommended INR values for each situation, according to the guidelines issued by the American College of Chest Physicians, based on numerous random studies.[10] In general, oral anticlotting therapy is recommended for vein thrombosis and pulmonary embolism prophylactic approach in high risk surgery, in the treatment of deep venous thrombosis and pulmonary embolism, preventing systemic embolism in patients with atrial fibrillation, cardiac valvular disease, cardiac biologic valvular prosthesis and in the myocardial acute infarction (in particular situations). It is also recommended for patients with a mechanical cardiac valvular

TABLE IV

Indications and recommended INR

Indications	INR
DVT primary prevention DVT and PE treatment Prevention of systemic embolism in case of: Atrial fibrillation Biologic valvular prosthesis Valvular cardiopathy Myocardial acute infarction	2,0 – 3,0
Mechanic valvular prosthesis	2,5 – 4,0

DVT – Deep vein thrombosis; PE – Pulmonary embolism

TABLE V

Embolic risk factors in patients with non valvular atrial fibrillation

- Age > 60 years old
- Myocardial infarction
- Left ventricular dysfunction
- Increase of left atrium
- Mitral calcification
- History of arterial hypertension
- Previous history of thromboembolism
- Diabetes mellitus

prosthesis, here with a higher INR value, although the last conference for consensus recommended a lower value than usual in clinical practice. In the case of recurring systemic embolism, INR should be between 3.0 and 4.5.

For the prevention of deep vein thrombosis in surgery,[11] it is recommended a 2.0 – 3.0 INR with therapy starting on the first day of the post-surgical period.[3,4] In oral anticlotting therapy, the haemorrhagic risk is higher than heparin use, therefore its prescription is reserved to high risk patients (previous plain thrombosis or major orthopaedic procedures), being kept for a minimum of 8 – 10 days. An indication for oral anticlotting therapy is the prevention of subclavian vein thrombosis in cancer patients with a catheter in such location, as well as breasts neoplasm, stage IV, in chemotherapy using lower doses of warfarin (1 mg/day) in order to achieve n INR of 1.5.[12,13] It is also recommended in patients with anti-phospholipid syndrome and recurring thrombosis.[2]

In the treatments of deep vein thrombosis,[3,4] heparin is usually used during 5 – 10 days, overlapping with warfarin until reaching a 2.0 – 3.0 INR and afterwards keeping only warfarin for a period of three – six months (three months if risk factors do not persist and indefinitely if they persist). Therapy should be extended up to 6 months if the deep vein thrombosis has proximal location or if it is complicated by pulmonary embolism.[2]

In myocardial acute infarction patients, anticlotting therapy is recommended for the 2.0 – 3.0 INR to prevent cerebral vascular accidents and vein thromboembolism.[3,4] Treatment should be kept for three months for the prevention of embolic CVA in patients with a previous Q infarction with a higher risk of intracardiac thrombi, mainly if associated to atrial fibrillation or heart failure.[4]

In patients with cardiac valvular prosthesis, the risk of systemic embolism (mainly cerebral) is increased. Such risk is higher for mechanic valves, according to the kind of valve, the mitral position, 50 years of age or older and association with atrial fibrillation.[4,14] in patients with biologic valves, the risk is higher for the first three months.[4] From such different aspects emerge the following recommendations: a) in the case of mechanical prosthesis, INR should be of 2.5 – 3.5 (if thromboembolic phenomena occur, it should be increased to 3.5 – 4.5 and even if they keep on occurring acetylsalicylic acid should be added in small dosage); b) in biologic valve prosthesis in aortic position, anticlotting therapy in the first three months with 2.0 – 3.0 INR should be added with acetyl salicylic acid is associated to atrial fibrillation; c) in biologic valves in mitral position, without complications, anticlotting therapy is recommended for the first three months, extending sometimes indefinitely if associated with atrial fibrillation, intracardiac thrombi (detected by ultrasound) or systemic embolism.[4]

Valvular atrial fibrillation has been for a number of years a well defined indication for oral anticlotting therapy, with 2.0 – 3.0 INR. Regarding non-valvular atrial fibrillation, it has been seen that the incidence of embolic CVA is around 5% per year, when associated with certain risk factors (*Table V*), being lower than 2% when such factors are not present (the so-called isolated atrial fibrillation).[4] From the studies carried out in such patients, there was a risk reduction of around 60%s, supporting the use of anticlotting thera-

TABLE VI

Oral anticlotting use contraindications

Absolute contraindications
Hemorraghic cerebral vascular accident
Thromboembolic cerebral vascular accident
Recent neurosurgery or cranial trauma
Uncontrolled severe arterial hypertension
Esophageal varices
Non healed peptic ulcer
Pregnancy 1st and 3rd quarters
Hepatic synthesis severe changes
Severe kidney failure
Hemorraghic syndrome
Relative contraindications
Recent surgery
Elderly
Biliary pathology
Bowel infection with destruction of the intestinal flora
Moderate kidney and liver failure

py also in patients with the referred risk factors.[15,16,17]

Recent studies come to the conclusion that in patients younger than 75 years of age, without the clinical risk factor (associated cardiac disease, history of arterial hypertension or previous CVA) and without ultrasound risk factors (left ventricle general dysfunction or an increase of the left atrium) have a lower risk of CVA (around 1% per year), reason why such patients it is licit to use acetyl salicylic acid instead of anticlotting drugs.[4,18] In the remaining patients if there is a contraindication for the use of anticlotting drugs, acetyl salicylic acid is used as alternative, although with less evident results. During the electric cardioversion (whether in the pre- or post-procedure) anticlotting therapy is also recommended due to the embolism risk.[17]

Other indications for oral anticlotting therapy are the mitral valve prolapse (when associated with atrial fibrillation or embolic complications), young patients with patent foramen ovale and paradoxical embolism, as well as patients with dilated cardiomyopathy, mainly when associated with hypokinetic ventricles, with a high intracavitary thrombotic risk.[4]

Some studies have shown that oral anticlotting therapy have an antitumor action, influencing whether the growth, whether metastases spreading, when applied to small-cell lung cancer, osteosarcoma, breast and kidney neoplasms, and lymphoma. One of the explaining hypotheses would be the eventual production, by tumour cells, of proteins dependent on K vitamin, with all studies carried out until now being hardly clarifying.[2,19,20,21]

The contraindications referred previously are mentioned on *Table VI*.[2] Absolute contraindications include haemorrhagic cerebral vascular accidents, thromboembolic cerebral vascular accident for the first week, recent neurosurgery or cranial trauma (unless the CT scan is normal), uncontrolled severe arterial hypertension (with diastolic serial pressure above 120 mmHg), esophageal varices, not healed peptic ulcer, serious changes in the hepatic synthesis, haemorrhagic syndrome, severe kidney insufficiency (with creatinine clearance below 20 mL/minute) and for the first and third quarter of pregnancy. There are relative contraindications as recent surgical interventions, the elderly and patients with biliary pathology, bowel infection (destroying the usual intestinal flora) and with moderate kidney and liver failure.

Adverse effects

The main complication of such therapy is haemorrhaging influenced not only by the anticlotting intensity but also by the patient's pathology and the concomitant use of platelet antiaggregants (not only because it interferes with the platelets function but also for the risk of gastric erosions). Patients with a higher risk of haemorrhage are patients aged 65 years or older, previous history of CVA, high blood pressure, gastric intestinal haemorrhage history and associated pathology (kidney failure, severe anaemia, myocardial acute infarction). In the elderly therapy should start with small doses, gradually increased according to the needs, as the warfarin clearance decreases with age.[3,4]

As non-haemorrhagic complications, the main one is cutaneous necrosis. This is a rare situation, occurring between the third and eight days of therapy corresponding to wide thrombosis located in the subcutaneous fat venules and capillaries. It results of a decrease on C protein (with a shorter half-life) making part of the proteins promoting natural anticlotting mechanisms and that acting along with thrombomodulin, present essentially in the capillaries (reason for thrombosis location) leading to its reduction which will favour thrombosis. In individuals with a previous deficit in C protein the reduction is more marked, being frequently exposed to such situation. These lesions are similar to those found in

neonatal purpura fulminans, which complicates the C protein homozygotic deficiency. In such patients, therapy should be started with very small warfarin dosages, covered by heparin in therapeutic dosages, with a slow and gradual increase, for several weeks, after warfarin dosage in order to avoid an abrupt fall of C protein before than other factors.[2,3,4]

Warfarin crosses the placental barrier, therefore it should not be used during pregnancy, mainly in the first quarter due to its teratogenic potential and during the first quarter for increasing the intralabor haemorrhage risk. If from a clinical point of view anticoagulation therapy must be implemented during pregnancy, warfarin should be replaced by heparin, mainly low molecular weight heparin, already well proven in clinical practice. Warfarin does not seem to induce an anticlotting effect in breastfed children, therefore there are no contraindications to be used during breastfeeding.[3,4]

Conclusions

Oral anticlotting therapy is an important therapeutic resource to control hypercoagulability conditions. Due to the clinical increased prevalence of such conditions, we should be reminded the practical aspects of its use, as well as its potential complications. Oral anticlotting therapy is the most used method when a chronic anticoagulation is envisaged, not only because it is easy to administer, but also because it is simple to monitor. For all these reasons, oral anticlotting therapy remains an effective and widely used method requiring however the patient periodic surveillance. ■

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