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REVIEW

Clinical considerations on the posology of direct oral anticoagulants☆

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Abstract The efficacy of dicoumarin anticoagulants has been shown in patients with nonvalvular atrial fibrillation. However, they have drawbacks such as the need to adjust the dosage and the interaction with drugs and food. Direct oral anticoagulants are an effective and safe alternative and have a less complicated clinical management. There is considerable debate on the selection criteria for the posology regimens of direct oral anticoagulants. The differences among them and their administration regimens have raised questions about the clinical, pharmacokinetic and pharmacodynamic selection criteria that support the posology. This review critically analyses the available evidence and its impact on the final selection of the dosage regimen.

PALABRAS CLAVE
Inhibidores del factor Xa;
Farmacocinética;
Farmacodinamia;
Esquema de administración;
Fibrilación auricular

Consideraciones clínicas sobre la posología de los anticoagulantes orales de acción directa

Resumen Los anticoagulantes dicumarínicos han demostrado su eficacia en pacientes con fibrilación auricular no valvular. Sin embargo, presentan desventajas como la necesidad de ajustar la dosis y la interacción con fármacos y alimentos. Por su parte, los anticoagulantes orales de acción directa se presentan como una alternativa eficaz y segura con un manejo clínico menos complejo. Existe un considerable debate sobre los criterios de selección de las pautas posológicas de los anticoagulantes orales de acción directa. Las diferencias entre ellos

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y sus pautas de administración han despertado dudas sobre los criterios de selección clínicos, farmacocinéticos y farmacodinámicos que avalan dicha posología. Esta revisión analiza de forma crítica las evidencias disponibles y su impacto en la selección final del esquema posológico.

Background

The characterization of the dose–response and dose–safety profile of medicinal products is an essential element in their development. The dose–concentration–response assessment increases the chances of obtaining a favorable risk–benefit ratio. For oral anticoagulants, an optimal treatment regimen should maintain an appropriate anticoagulant activity and safety profile over time, with no oscillations or the need for periodic laboratory monitoring.[1,2]

The assessment of the dose–concentration–effect relationship has varied dramatically in recent years, such that the classical approach (phase II of the clinical development of medicinal products) is less delimited now and is frequently accelerated due to the need to optimize clinical development in a highly competitive environment. Techniques such as pharmacokinetic–pharmacodynamic (PK/PD) modeling[3,4] and the assessment of 2 dosage regimens in ''pivotal'' studies tend to replace the classical dose-finding studies. However, the time and cost savings is coupled with a notable increase in uncertainty. In these circumstances, the safety and efficacy studies on the target population are the ones that determine whether the chosen dosage regimen shows a favorable risk–benefit profile. However, we cannot rule out the possibility that other alternative regimens could have been reasonable.

Direct oral anticoagulants (DOAs), both thrombin inhibitors (dabigatran) and factor Xa inhibitors (rivaroxaban, apixaban and edoxaban), are not exempt from this complexity. The accepted dosage regimens for each of them (which are different one from the other) reflect the previously mentioned uncertainties. In this review, we analyze the evidence underlying the final selection of the dosage regimen, taking into account its relevance for guiding the clinical decision-making process for prescribers in daily clinical practice. To this end, we address the general foundations for selecting the dosage, subsequently analyzing the selection of the dosage regimen during the clinical development of each drug.

General pharmacokinetic and pharmacodynamic principles for selecting the dosage regimen

For the characterization of PK/PD, we must consider 2 fundamental factors: the concentration reached in plasma, in the target organ or the target tissue (biophase) and the duration of the effect. The course of the plasma concentrations is determined by the processes of absorption, distribution, metabolism and excretion.[5] From the plasma, the drug must be distributed to the biophase to cause its effect. Therefore, the concentration and half-life in the biophase will determine the temporal profile of the effect to a greater degree than the plasma concentration. There are numerous factors (genetic, physiological and pathological) that determine the degree of variability in the pharmacokinetic processes. The dosage needs to be adjusted for each individual situation when these factors of variability involve relevant intrapatient and interpatient changes in plasma concentrations and the biophase, and these changes have clinical repercussions.

In the case of DOAs, given that the target consists of plasma coagulation factors, the plasma concentrations constitute a direct measure of concentrations in the biophase. However, the temporal profile of the effect not only depends on the pharmacokinetic factors but also on the mechanism of action, given that based on this mechanism, the effect could last longer than the presence of the drug. An example of this is antivitamin K drugs, whose anticoagulant effect is maintained sufficiently long so that once the antagonism on the vitamin K disappears sufficient quantities of new active coagulation factors are synthesized. In addition to the mechanism of action, there are other pharmacodynamic factors such as potency, intrinsic activity, pharmaceutical tolerance and genetic polymorphisms[5] that can affect the magnitude and duration of the effect regardless of the plasma concentrations and elimination half-life.

It is also important to consider the relationship of pharmacokinetic and pharmacodynamic factors. Studies on DOAs in healthy volunteers observed an acceptable parallelism between the curve of plasma concentrations and pharmacodynamic parameters, such as the activated partial thromboplastin time (aPTT), the thrombin time and the ecarin clotting time. Despite this parallelism, however, the concentration–time and effect–time curves were not similar. In these cases, the anticoagulant effect persisted into the terminal phase of the curve of elimination.[6–9]

It is important to note that the concentration–effect relationship is not always linear and direct and is not equal for all pharmacodynamic parameters.[10] In studies with healthy volunteers, for example, the aPTT analysis showed a pharmacodynamic behavior compatible with a sigmoid Emax model (the graphical representation of the concentration–effect relationship shows a sigmoid curve), while other parameters such as thrombin time, ecarin clotting time and prothrombin time (PT) fit with greater precision to a linear Emax model. Although the tendency was similar, differences were observed in the average values depending on the drug, dosage and study.[11–20] Therefore,