Med Intensiva. 2015;39(3):167–171

medicina intensiva

www.elsevier.es/medintensiva

POINT OF VIEW

New oral anticoagulants in severe trauma patients: Enemy at the gates?☆

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Received 6 July 2014; accepted 10 September 2014

KEYWORDS
New oral anticoagulants;
Trauma;
Bleeding;
Reversion;
Prothrombin complex concentrate

Abstract The high incidence of trauma, especially in elderly people anticoagulated with new oral anticoagulants (NOAs), has become a major challenge, particularly in critical situations with life-threatening bleeding. Under these circumstances, urgent NOA reversion becomes mandatory. Prothrombin complex has become a frequent indication in critical situations in which rapid reversal of anticoagulation is needed and where the use of fresh frozen plasma is limited. This study offers our point of view regarding the usefulness of NOAs, not only in the prevention of cardioembolic events but also as regards their emergent reversion in cases of severe bleeding associated to trauma.

PALABRAS CLAVE
Nuevos anticoagulantes orales;
Trauma;
Hemorragia;
Reversión;

Nuevos anticoagulantes orales en el paciente traumatizado grave: ¿enemigo a las puertas?

Resumen La alta incidencia de los traumatismos, especialmente en aquella población mayor previamente anticoagulada con nuevos anticoagulantes orales (NACO), se ha convertido en un gran desafío, sobre todo en aquellas situaciones críticas en las que existe una hemorragia grave que pueda comprometer la vida del paciente. En estos casos se hace necesaria la aplicación urgente de medidas de reversión. El empleo de complejo protrombínico es una indicación cada

☆ Please cite this article as: Egea-Guerrero JJ, Quintana Díaz M. Nuevos anticoagulantes orales en el paciente traumatizado grave: ¿enemigo a las puertas? Med Intensiva. 2015;39:167–171.

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2173-5727/

Complejo concentrado de protrombina

vez más frecuente en estas situaciones de urgencia, en las que se necesita una reversión rápida de la anticoagulación y en las que el uso de plasma fresco congelado es limitado. El objetivo de este trabajo es dar nuestro punto de vista sobre la utilidad de los NACO, no solo en la prevención de enfermedades cardioembólicas, sino en su reversión emergente en aquellos casos de hemorragia grave asociada al trauma.

Traumatisms are a serious worldwide public health problem. Although the last World Health Organization (WHO) reports on the importance of trauma are separated by a period of almost 10 years, they continue to alert us to the magnitude and importance of the problem, and its possible future consequences (Document TDR/Gen/96.1; update 2008). It must be underscored that we are witnessing a change in the epidemiology of trauma, with an increase in the number of accidental falls among elderly people with comorbidities–a situation that results in increased mortality.[1] This scenario points to the need to introduce primary and secondary prevention strategies referred to traumatisms in general, and indicates that care must be optimized in patients who suffer serious injuries.[2]

Bleeding is known to be one of the main causal factors of mortality associated to accidents (30–40% of all cases). However, a priori, bleeding produced by trauma should be regarded as a potentially reversible cause of mortality provided surgical damage control measures are adopted or coagulopathy associated to trauma is avoided.[3,4] Nevertheless, if the patient is under the effects of some anticoagulant medication, the risk of bleeding increases–especially if anticoagulation cannot be quickly reverted.

Warfarin is prescribed in about 12.8% of the patients in the United States, mostly in elderly individuals over 65 years of age with chronic atrial fibrillation (AF), with the purpose of avoiding cardioembolic phenomena, among other problems.[5] The development and increasingly widespread use of new oral anticoagulants (NOAs) imply a change in management strategy when patients who use these drugs suffer severe bleeding, independently of its spontaneous or traumatic origin.[6,7] At present, the lack of effective means for reverting the effects of NOAs in non-scheduled situations such as after traffic accidents, casual falls or aggressions, where a ''wait and see'' approach is not possible, but constitutes the most critical issue regarding these new anticoagulant drugs. Although the half-life of all NOAs is about 12 h, there are a number of situations such as those commented above in which we cannot wait for spontaneous reversion of their effects.[6,7] In contrast, when classical anticoagulants are used, such as the vitamin K antagonists, their reversion according to the available time window is well known. Such a reversion or antagonization can be performed using vitamin K, fresh frozen plasma (FFP), or prothrombin complex concentrate (PCC).[3]

We obviously cannot forget that anticoagulation, in the context of AF, constitutes the main reversible cause of ischemic stroke.[5] Since 1972, when Miller Fisher published a series of recommendations on the management of AF, many studies have attempted to define safer strategies for reducing the risk of embolic events.[8,9] Between 1989 and 1993 a total of 6 clinical trials evaluated the usefulness of warfarin versus aspirin or placebo in preventing stroke in patients with arrhythmias of this kind. The data obtained from the global 2900 patients enrolled in these trials showed warfarin use to result in a decrease in cardioembolic phenomena.[9] In this regard, we have established the main advantages and problems associated with the use of vitamin K antagonists. As positive aspects, mention must be made of their reasonable cost, good efficacy, the possibility of knowing their effects upon coagulation, the development of point of care devices that facilitate monitoring of treatment efficacy, dosing optimization through patient genetic studies, and the possibility of practically immediate reversion in the event of bleeding or the need to perform some urgent procedure.[10] As inconveniences, the vitamin K antagonists take time in reaching optimum therapeutic levels (24–72 h), with a narrow target range (INR 2–3), a renal clearance of 90%, unpredictable between- and within-patient responses, the existence of interactions with certain foods and other drugs, and a purported inherent increase in bleeding risk.[11] Because of the above, routine monitoring of coagulation becomes mandatory in this group of patients.

The above inconveniences, together with the high worldwide prevalence of AF associated to population aging (between 3 and 4%), have probably incentivized the study and development of new drugs that optimize and facilitate adequate prevention of cardioembolic phenomena.[5] In this regard, since 2009 a total of four large clinical trials on the use of NOAs have been published.[12–15] Table 1 summarizes the main advantages and properties of these new drugs. Firstly, NOAs have been shown to offer better prevention of ischemic stroke and embolic events compared with warfarin.[14–18] Secondly, a decrease in severe spontaneous bleeding is observed, especially as regards intracranial hemorrhage. However, it must be noted that dabigatran has been associated to an increased risk of gastrointestinal bleeding.[14] Their effects do not require monitoring, thereby improving patient comfort – though this may be a problem in individuals with treatment adherence problems. It must be emphasized that in the case of important bleeding, excessive dosing, or administration before surgery, we can monitor the effects of these drugs upon coagulation.[6] Nevertheless, no laboratory value has yet been found to reliably determine NOA activity, since some specific parameters may be under- or overestimated (Table 1).

In the same way as with the classical anticoagulants, NOAs can interact with other drugs associated to glycoprotein P including diltiazem, verapamil, atorvastatin, etc.[7] Recently, Ruff et al. published the results of a study