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REVIEW

Renal function and venous thromboembolic diseases

Fonction rénale et maladies tromboemboliques veineuses

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Summary Anticoagulant agents have been approved by international regulatory agencies to prevent and treat venous thromboembolism (VTE). However, chronic kidney disease (CKD) is: (1) highly frequent in VTE patients; (2) strongly linked to VTE; and (3) a risk factor for cardiovascular morbidity/mortality and fatal pulmonary embolism. Therefore, an increasing number of patients are presented with CKD and VTE and more and more physicians must face the questions of the management of these patients and that of the handling of anticoagulant agents in CKD patients because of the pharmacokinetic modifications of these drugs in this population. These modifications may lead to overdosage and dose-related side effects, such as bleeding. It is therefore necessary to screen VTE patients for CKD and to modify the doses of anticoagulants, if necessary.

MOTS CLÉS
Anticoagulants ;
Maladie thrombo-embolique veineuse ;
Insuffisance rénale chronique

Résumé Les anticoagulants ont été approuvés par les autorités européennes dans l'indication de traitement et de prévention des maladies thromboemboliques veineuses (MTEV). Cependant, l'insuffisance rénale chronique (IRC) est : (1) fréquente chez les patients présentant une MTEV ; et (2) étroitement liée à l'apparition des MTEV. Ainsi, il existe un nombre croissant de patients présentant une IRC et une MTEV et de plus en plus de médecins et de pharmaciens sont confrontés à la question de la gestion des anticoagulants chez ces patients à cause des modifications de la pharmacocinétique des anticoagulants. Ces modifications peuvent conduire à des surdosages

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et des effets indésirables dose-dépendants, comme des hémorragies. Il est donc nécessaire de dépister l'IRC chez ces patients et d'adapter la posologie des anticoagulants au besoin.

Chronic kidney disease: a silent deadly threat

Chronic kidney disease (CKD) is a frequent pathology. In the United States, the National Health And Nutrition Examination Survey (NHANES) study, conducted between 1999 and 2004, reported that more than 13% of subjects presented a stage 1 to 4 CKD according to the classification of the Kidney Disease Improving Global Outcomes/Kidney Disease Outcomes Quality Initiative (KDIGO/KDOQI) [1—4]. Moreover, the French study MONA-LISA reported that the prevalence of CKD, defined by a glomerular filtration rate (GFR) ranging from 60 to 15 mL/min/1,73 m^2 was 8.2% in a population aged from 35 to 75 years, in the community setting [5]. Moreover, among CKD patients, 98% did not know that they were suffering from CKD. CKD is thus under-diagnosed in France.

CKD patients are at risk of clot formation and several unique conditions to this population influence the risk of thrombosis [6]. The mechanisms for increased coagulation are multifactorial. These patients are known to have increased levels of procoagulant factors [7]. Simultaneously, a decrease in endogenous anticoagulants and fibrinolytic activity might occur [8]. Commonly used medications such as erythropoietin stimulating agents can also increase the risk of thromboembolism, but these medications are more used in patients with more advanced CKD or in cancer patients receiving chemotherapy inducing anemia [9—11]. Depending on the location, graft material, surgical technique, and the patients' own coagulable state, thrombosis of vascular access can be increased. The degree of hypercoagulability can increase as renal function declines and continues to increase during concurrent anticoagulation therapy [6]. Finally, surgery and cancer are risk factors of VTE in severe CKD patients [12].

Several studies investigated a potential link between CKD and venous thromboembolism (VTE). Wiesholzer et al were the first to report a relationship between these two diseases [13]. Thereafter, several studies showed the high prevalence of CKD in VTE patients. Cook et al. reported that 22.1% of VTE patients had a creatinine clearance (CrCl) < 60 mL/min [14]. The RIETE register (*Registro Informatizado de la Enfermedad TromboEmbólica*) showed that this prevalence was increasing over time, with 12.3% of VTE patients having a CrCl < 60 mL/min in 2006, and 18.1% in 2013 [15,16]. Therefore, there was an increase of nearly 6% in 7 years between the two publications (a relative increase of 47% when comparing 2013 to 2006). Finally, the Worcester Venous Thromboembolism study [17] reported that 36.7% of VTE patients had a GFR < 60 mL/min/1.73 m^2 when it was estimated with CKD-EPI formula [18]. Although the prevalence varied from one study to another, it is undeniable that CKD is common in VTE patients.

Moreover, other studies have shown that the relationship between CKD and VTE was in ''both directions''. Indeed, the Longitudinal investigation of thromboembolism etiology (LITE) study showed that among 19,073 patients followed for 12 years, CKD was found to be a risk factor for VTE. In this study, annual incidences of VTE increased according to the renal function: 1.9 and 4.5 per 1000 patients among stage 2, and stage 3&4 CKD patients, respectively. The relative risk (RR) (adjusted for age, sex and race of the patients) of developing VTE was 2.1 with a 95% confidence interval (95% CI) of [1.5—3.0]. Moreover, this risk appeared early in the course of CKD, appearing for a GFR below 75 mL/min/1.73 m^2 (estimated with the MDRD formula) [19]. Another study confirmed that the increased risk for VTE was beginning for a relatively high value of GFR. In this study, the risk appeared when the GFR reached 88 mL/min/1.73 m^2 in a pooled analysis of 5 prospective studies that included 95,154 patients [20]. Furthermore, the hazard ratio (HR) for VTE was increasing with the decrease in GFR (estimated with CKD-EPI). Compared to normal renal function patients, CKD is a major risk factor for VTE, at a relatively early stage of renal disease, which only increases as the renal functions deteriorate.

In addition, CKD is a risk factor for atherothrombosis [21], cardiovascular morbidity and mortality [22] and fatal pulmonary embolism (PE) in multivariate analysis [15]. CKD is also a risk factor of symptomatic PE and major bleeding [23]. In fact, CKD patients are at an increased risk of bleeding. Platelets can become dysfunctional, secondary to uremic related toxin exposure and can have further adhesion defects as a result of shear wall stress alterations during hemodialysis [6,24,25]. Blood loss and lower hemoglobin values can be a concern for dialysis efficiency in addition to providing adequate tissue oxygenation in a population prone to anemia. This may be most critical in comorbid conditions such as asthma or coronary artery disease [6].

It is therefore necessary to diagnose CKD and to monitor the progression of renal disease in order to optimize the management of these patients and to adjust their drug dosages, when necessary.

Prescriptions and ATHIR rules

Prior to prescribing anticoagulant treatments such as unfractionated heparin (UFH), low molecular weight heparin (LMWH), fondaparinux, vitamin K antagonists (VKA) and direct oral anticoagulants (DOACs), a diagnosis needs to be made, followed by an assessment of the renal function (which will also be made during the treatment).

When prescribing anticoagulant agents, a biological evaluation of the feasibility of starting the therapy in daily practice is possible with the ATHIR rule [26]:

- A as anemia: full blood count, because anemia is a significant bleeding risk factor;
- T as thrombocytopenia: platelet count, because an unknown thrombocytopenia is a haemorrhagic risk factor