LETTERS TO THE EDITOR

Comments on: Laboratory tests for the management of major bleeding complications and emergency surgery in patients on long-term treatment with direct oral anticoagulants: Proposals of the Working Group on Perioperative Haemostasis (GIHP)

Tests de laboratoire dans la prise en charge des saignements majeurs et la chirurgie urgente chez les patients sous traitement anticoagulant oral direct au long cours : propositions du Groupement d’intervention en hémostase périopératoire (GIHP)

Keywords: Direct oral anticoagulants; Surgery; Laboratory tests
Mots clés : Anticoagulants oraux directs ; Chirurgie ; Test de laboratoire

We read with interest the proposal of the Working Group on Perioperative Haemostasis (GIHP), published in a recent issue of Archives of Cardiovascular Diseases by Pernod et al. [1]. One of the aims of the proposal was to provide information on the use of coagulation tests carried out at the time when emergency surgery is required in patients treated with the direct oral anticoagulants (DOACs) dabigatran or rivaroxaban. The authors pointed out correctly that the data available at the moment are scanty and do not allow firm recommendations. Nevertheless, specific plasma concentrations of dabigatran or rivaroxaban below which urgent surgery can be carried out have been reported [1]. Furthermore, the authors propose that when plasma concentrations are not available, one can rely on the results of the two most commonly available coagulation tests, prothrombin (PT) and activated partial thromboplastin time (aPTT) [1]. Specifically, the authors mentioned that < 30 ng/mL for either drug is safe and surgery can be carried out without significant bleeding risk. Likewise, they proposed that a PT or aPTT ratio < 1.2 can be taken as a threshold limit to perform surgery [1]. We understand and appreciate how it is important to provide information at the time when these drugs will be used and patients may need to be subjected to emergency surgery. Nevertheless, we wish to comment on the value of such proposals.

Drug concentrations

As stated by the authors, the proposed threshold values for dabigatran or rivaroxaban do not stem from clinical observations and are based largely on the drug’s pharmacokinetics [1]. According to the European Medicine Agency Annexes Summary of Product Characteristics for both drugs [2,3], the steady-state concentration of plasma dabigatran expected on the basis of the interindividual variability spans from 117 ng/mL to 275 ng/mL at the peak level, and from 61 ng/mL to 143 ng/mL at the trough level, both taken as the 25th to 75th percentile range [2]. Likewise, the plasma concentrations of rivaroxaban vary from 22 ng/mL to 535 ng/mL at the peak, and from 6 ng/mL to 239 ng/mL at the trough level, both taken as the 90% prediction interval [3]. It is unclear where these values come from and how they have been determined. However, one may assume that they come from the clinical trials and that the method of determination was mass spectrometry. Also, it was not specified which the values were or not associated with clinical bleeding.

All in all, the above observations point to the fact that threshold values for safe emergency surgery are presently unknown. If this is the case, we wonder whether providing threshold values (although with some caveats) as the authors did in their proposal is not detrimental to patient management as these values may give a false reassurance to those who are not particularly familiar with the effect of DOACs.

PT and aPTT

The threshold presurgical prolongations for PT and aPTT provided by the working group (i.e. a ratio < 1.2) are based largely on considerations stemming from the relative half-life of the circulating drugs and on the relative responsiveness of aPTT or PT reagents stemming from results obtained by spiking in-vitro normal plasmas with known and increasing concentrations of either drug [4–7]. It should be mentioned that the situation might be different when one investigates plasmas from patients treated with either drug. Such observations are now available. Hawes et al. [8] have in fact investigated plasmas from patients treated with dabigatran. According to their results, the PT and
aPTT are often normal in spite of therapeutic dabigatran plasma levels. Furthermore, there was a relatively large between-reagent variability in the response to dabigatran. As an example, when the aPTT was run with a particular reagent, 35% of the aPTT ratios were in the normal range when the dabigatran plasma concentration was up to 100 ng/mL. Rodgers et al. [9] investigated patients on rivaroxaban and found that the recombinant thromboplastin they used was adequately responsive to rivaroxaban. On the contrary, van Veen et al. [10], while investigating their patients on rivaroxaban with another recombinant thromboplastin, found that it was unresponsive to rivaroxaban. These results clearly demonstrate that providing presurgical cut-off values without taking into proper consideration the responsiveness of the aPTT or PT tests to dabigatran or rivaroxaban may create a dangerous situation for patient management.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

References


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Comments on: Laboratory tests for the management of major bleeding complications and emergency surgery in patients on long-term treatment with direct oral anticoagulants: Proposals of the Working Group on Perioperative Haemostasis (GIHP): A rebuttal

Observation sur laboratoire tests for the management of major bleeding complications and emergency surgery in patients on long-term treatment with direct oral anticoagulants: Proposals of the Working Group on Perioperative Haemostasis (GIHP): une réfutation

Keywords: Direct oral anticoagulants; Surgery; Laboratory tests; Haemorrhages
Mots clés: Anticoagulants oraux directs; Chirurgie; Laboratoire; Hémorragies

Dear editor,

We appreciate the pertinent comment from Dr Tripodi [1] on the proposals of the Working Group on Perioperative Haemostasis, regarding management of major bleeding and emergency surgery in patients on long-term treatment with direct anticoagulants [2]. Several clarifications need to be made.

As highlighted by Dr Tripodi, recommendations cannot be established because of the lack of data in the emergency situation. Therefore, several mundane proposals can be put forward, such as: ‘ideally, surgery must be delayed’; but how many times, and for what purpose? In our working group, we decided that experts must develop an opinion precisely for such cases where there is no clear guidance. Moreover, we addressed the proposals for

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