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DEBATE

New oral antithrombotics: a need for laboratory monitoring. For

P. MISMETTI*†‡ and S. LAPORTE*‡

*University Jean Monnet of Saint-Etienne, EA3065, F-42023, Saint-Etienne; †Department of Therapeutic Medicine, Teaching Hospital of Saint-Etienne, F-42055, Saint-Etienne; and ‡Department of Clinical Pharmacology, Teaching Hospital of Saint-Etienne, F-42055, Saint-Etienne, France

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Introduction

In general, the need for laboratory monitoring depends on the properties of the drug considered, monitoring being warranted if the following five criteria are met:

Criterion #1 (inter-individual variability). The inexplicable inter-individual variability (i.e. variability between subjects) is high, justifying identification of the optimal dose for each patient at the start of treatment. This criterion may be waived if Criterion #2 is met (or vice versa).

Criterion #2 (intra-individual instability). The unpredictable intra-individual instability in drug exposure (i.e. variability in the same patient) over time is high and could adversely affect the benefit-to-risk ratio of the drug. This variability over time could reflect a pathophysiological change, a drug-drug or food-drug interaction, or an unknown factor.

Criterion #3 (assay method). The variability of the assay method used to assess the drug concentration or effect is low and reproducible, and the optimal timing between drug administration and assessment of its concentration, or effect, is well established.

Criterion #4 (correlation). The correlation between the drug concentration, or effect, and clinical events (efficacy and safety endpoints) is well established, allowing identification of an optimal therapeutic range between the minimum effective dose and the maximum tolerated dose, and this therapeutic range is sufficiently narrow to necessitate dose adjustment in view of the variability defined in Criteria #1 and #2.

Criterion #5 (validation). Therapeutic drug monitoring as a basis for dose increase or decrease has been shown to prevent thromboembolic events and/or hemorrhagic events.

All these criteria should be met to justify the need for laboratory monitoring of a given drug.

Correspondence: Patrick Mismetti, Department of Therapeutic Medicine, Teaching Hospital of Saint-Etienne, Avenue Albert Raimond, 42270 Saint-Priest en Jarez, France.
Tel.: + 33 4 77 12 02 85; fax + 33 4 77 12 78 20.
E-mail patrick.mismetti@chu-st-etienne.fr

The need for laboratory monitoring: the story with anticoagulant drugs

To illustrate the need for laboratory monitoring, vitamin K antagonists (VKA), the first oral anticoagulants, are perfect candidates.

The best candidates – VKA (Table 1)

With respect to Criterion #1 (inter-individual variability), the optimal dose required to reach the target INR value, even in stable patients, must be determined for each individual. In fact, age, sex, genetic polymorphism (2C9, VKORC) and drug-drug interactions explain only 60% of the inter-individual variability, hence the need to monitor the effect of VKA to determine the optimal dose for each patient [1].

As regards Criterion #2 (intra-individual variability), several drug-drug and food-drug interactions with VKA, as well as several pathological conditions, have been reported to influence VKA response in the same patient. Apart from these potential sources of variability, the highly unstable response to vitamin K antagonists has been extensively described. Even in the more recent clinical trials, including highly selected populations, patients remained within the therapeutic range for approximately 60% of the time [2].

The inter-laboratory variability of assay methods (Criterion #3) has been greatly reduced by the use of INR values instead of percentage activity, significantly improving the uniformity of anticoagulation level measurements. Several studies have demonstrated the validity of the INR/ISI system [3–5]. A further advantage of this laboratory test is that it does not depend on sampling time, due to the very long pharmacodynamic half-life of VKA.

Over the past years, several randomized studies and reviews have examined the risk of bleeding and thromboembolic events with different intensities of oral anticoagulant therapy in patients with venous thromboembolism or non-rheumatic atrial fibrillation (Criterion #4 – correlation). A model developed on the basis of these data, suggested that each unit increase in INR raises the risk of bleeding 3.5-fold [6]. This prediction has since been confirmed by several studies [7,8].

Table 1 Respect of the criteria supporting laboratory monitoring by current and new anticoagulants

	Current anticoagulants			New oral anticoagulants
	VKA	UFH	LMWH fonda parinux	Dabigatran, edoxaban, apixaban, rivaroxaban
Criterion #1. Intra-individual instability in drug level	X	X		
Criterion #2. Inter-individual variability in drug level → optimal dose finding at the start of treatment	X	X		X
Criterion #3. Low variability and reproducibility of the assay method	X		X	X
Criterion #4. Correlation between drug level and clinical events → optimal therapeutic range	X			X
Criterion #5. Value of therapeutic drug monitoring demonstrated	X			

VKA, vitamin K antagonist; UFH, unfractionated heparin; LMWH, low-molecular-weight heparin.

Finally, the effectiveness of therapeutic drug monitoring (Criterion #5) has been demonstrated in several clinical trials [9,10]. For example, the risk of thromboembolic events was 2.8-fold higher in patients randomized to the INR 1.5–2 group compared with those randomized to the INR 2–3 group [9].

All the criteria indicating a need for laboratory monitoring are therefore met for VKA. The situation is less clear for unfractionated heparin (UFH) and low-molecular-weight heparin (LMWH) or fondaparinux and we would like to discuss here the problems encountered in clinical practise when the need for laboratory monitoring is still debated. All these points warrant elucidation before considering the case of new oral anticoagulants.

A recent controversy – UFH (Table 1)

Laboratory monitoring has always been advocated for unfractionated heparin (UFH) in view of the high inter-individual and intra-individual variability observed with this compound (Criteria #1 and #2). However, the other criteria listed are not respected. For example, Criterion #3 (assay method) is not met, given the high variability in aPTT measurements, and at least 300 assay methods are employed. Even if this variability could be reduced by using the calibration curve established on the basis of anti-factor X activity (anti-Xa), the instability in drug levels could be directly related to laboratory variability [11]. As the recommended therapeutic range clearly depends on the assay method (e.g. aPTT ratios of 1.5–2.5, 2–3, etc., for the treatment of venous thromboembolism), Criterion #4 (correlation) cannot be verified. In fact, although the study performed by Hull *et al*. [12] showed that a fixed low-dose regimen was not effective in treating VTE, an association between low aPTT results and recurrent venous thromboembolism, or between high aPTT results and bleeding, in the UFH group was not clearly demonstrated. This issue was discussed by Anand *et al*., [13], who suggested that a sufficiently high initial dose regimen of UFH is more important than close monitoring of aPTT for avoiding VTE recurrences. This attitude is partially supported by the MATISSE study, in which a standardized initial dose regimen was recommended in the UFH group, resulting in an aPTT ratio above 1.5 for 93% of the time on the first day of treatment. [14]. At present, the value of laboratory monitoring (Criterion #5) is questionable, considering the results of the randomized trial FIDO in patients with acute venous thromboembolism [15]. This study showed that fixed-dose, unmonitored, subcutaneous UFH was as effective and safe as fixed-dose, unmonitored, subcutaneous LMWH, challenging the value of aPTT monitoring in patients treated with UFH at the currently recommended doses. However, both the FIDO and MATISSE studies were open-label and the populations included were highly selected. Moreover, the systematic use of anti-Xa for monitoring might have reduced assay-related variability. The current debate on laboratory monitoring for UFH is probably inspired simply by the lack of strong evidence. This applies even more to LMWH.

A current debate – LMWH (Table 1)

With LMWH, the intrinsic variability is small compared with UFH and VKA, so Criteria #1 and #2 do not plead for laboratory monitoring. In view of this advantage, no effort has been spared to demonstrate that laboratory monitoring is unnecessary, particularly as Alhenc-Gelas *et al*. [16] showed in 122 patients that adjustment of dalteparin doses according to anti-Xa levels (target therapeutic range 0.5–1.0 IU) compared with fixed dalteparin doses of 100 IU/kg twice daily resulted in an increased risk of thrombosis without significantly reducing the risk of bleeding. Based on this study alone, and on the low expected variability, the development of LMWH was performed without drug monitoring.

In addition, at the time of LMWH development, the necessity of conducting randomized and powerful dose-ranging studies had not yet been clearly established. Thus,

unfortunately, very few dose-ranging phase II studies were performed to identify the optimal doses of LMWH to be assessed in phase III trials, and a correlation between doses and clinical events or between drug concentration or coagulation parameters and clinical events was never established (Criterion #4). The only large, randomized dose-ranging study was the MEDENOX trial, showing that a reduced fixed-dose regimen was associated with a dramatic loss of efficacy [17].

In view of this lack of evidence, it is not surprising that the concept that no laboratory monitoring is needed for LMWH has been challenged by data derived from clinical practise and pharmacovigilance. The use of LMWH in a non-selected population was associated with an excess bleeding risk in patients with characteristics favouring bio-accumulation of LMWH, such as renal insufficiency, advanced age, low body weight and/or therapeutic dosage. Up to now, based on a population pharmacokinetics approach and Bayesian estimation, approaches not widely used at the time of LMWH development, it has been acceptable to propose a reduced dose regimen for the treatment of acute coronary syndrome, based on creatinine clearance and anti-Xa level [18–20]. This resulted in a significant reduction in bleeding risk, but the effect on thromboembolic risk was not clear [21,22] and Criterion #5 (validation) was not strictly verified. However, an optimal target for anti-Xa was chosen, even though no sufficiently powered trials had been performed to detect a potential association between anti-Xa level and the risk of clinical events [23,24] (Criterion #4). Moreover the anti-Xa level was measured at a time corresponding to the maximum effect (i.e. 4 h after subcutaneous administration), a precise timing difficult to respect in clinical practise. The minimum effect measured just before the next administration might be less variable and a correlation might be easier to establish than with the maximum effect. Finally, recent guidelines still recommended the same anti-Xa target for all LMWH, even though anti-Xa values depend greatly on the type of LMWH [25].

The absence of any need for drug monitoring with LMWH was postulated without specific investigation of the value of such monitoring based on a proper dose-ranging study, a pharmacokinetic-pharmacodynamic study, demonstration of a correlation between laboratory testing and clinical events and validation of dose-adjusted regimens. Due to the low variability associated with LMWH, this approach is successful for the large majority of patients, but some epidemiological and clinical trial data have indicated that drug monitoring could be useful and effective in patients at high risk of bio-accumulation. However, in view of the lack of evidence in support of such monitoring, this could result in certain patients being deprived of the benefit of these drugs. In particular, patients who are elderly and/or present with renal insufficiency are very difficult to manage because they have a very high risk of adverse events. Due to the potential risk of bio-accumulation, they are often treated with UFH, so in fact the most complex treatment is reserved for the patients most difficult to manage, resulting in an increase in bleeding risk [26,27]. The need for laboratory monitoring for LMWH is therefore still open to discussion.

The need for drug monitoring with new oral anticoagulants should be evaluated on the basis of previous experience with VKA and heparins. The assessment should be easier for these new drugs, because their clinical development was based on proper dose-finding studies and *a priori* planned pharmacokinetic and pharmacodynamic modelling based on a population approach during phases II and III. These data allow verification of Criteria #1 to #5 listed at the beginning of this article.

New oral anticoagulants: a need for laboratory monitoring

The new oral anticoagulants have several advantages compared with VKA in that their pharmacokinetics (shorter half life) and pharmacodynamics (direct inhibition) are simpler and less variable [28,29]. In view of these advantages, with probably more than 80% of the population presenting a low variability, is it really worth discussing the need for laboratory monitoring? The clinical trials performed in current drug development programmes enrolled large, even if frequently selected, populations, including enough patients to enable identification of those at risk of variability (e.g. the elderly and patients with renal insufficiency, even in the case of drugs not excreted solely via the kidneys, such as rivaroxaban), who could benefit from drug monitoring (Criteria #1 and #2, Table 1). This could be particularly important in that we have already identified some drug-drug interactions with these new compounds (interaction with the P-glycoprotein system and/or cytochrome P450 isoenzymes) [30,31]. Some of these drug-drug interactions are sufficiently clinically relevant to result in contraindications or precautions for use (protease and some antifungal drugs for rivaroxaban, quinidine for dabigatran, etc.). Other interactions or polymorphism of the P-glycoprotein and/or cytochrome P450 system could also prove to be clinically relevant in clinical practise in non-selected populations and could necessitate dose adjustments, possibly based on drug monitoring. This drug monitoring, if necessary, should be performed simply to determine the initial optimal dose for a particular patient and repeated only in the event of introduction or withdrawal of a drug significantly interacting with the oral anticoagulant administered.

Due to the direct mechanisms of action of these agents, it should be relatively simple to identify a suitable coagulation parameter and to develop an accurate and reproducible assay method capable of determining their pharmacodynamic and pharmacokinetic-pharmacodynamic relationships (Criterion #3). This could be a specific test based on a chromogenic method, such as anti-IIa for dabigatran or anti-Xa for rivaroxaban, apixaban and edoxaban. It could also be a global coagulation test, such as ecarin clotting time (ECT) for dabigatran or prothrombin time expressed as the INR for direct anti-Xa inhibitors. All these methods are currently performed in all laboratories and could be used if monitoring is needed.

Regarding Criterion #4, dose-ranging studies and PK-PD modelling have already provided data showing a significant

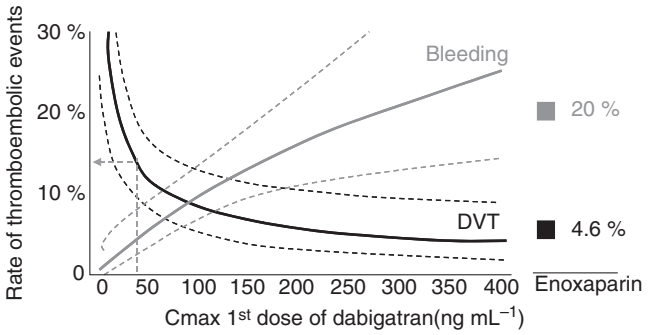

Fig. 1. Dose-effect relationship of dabigatran in major orthopedic surgery.

correlation between a biological marker and clinical events. This was observed during the development of dabigatran for the prevention of VTE in major orthopedic surgery: in this study, the concentration-effect relationship was often more informative than the dose-effect relationship [32]. A logistic regression analysis model of the maximum concentration (Cmax) following administration of the first dose of dabigatran indeed showed a strong correlation with efficacy and safety outcomes (Fig. 1). On the basis of this relationship, we determined that a predicted optimal Cmax of dabigatran of 40 ng/mL corresponded to a first postoperative dose of 75 mg. These data were useful not only for drug development but also for drug monitoring. Because there is a direct relationship between drug concentration and ECT or anti-IIa [33], it should be possible to determine the optimal prophylactic range for this parameter based on the data from this phase II study. Similar findings were observed with another oral anticoagulant, edoxaban, in a different indication (atrial fibrillation) [34]. In this study, the incidence of bleeding events increased significantly with increase in edoxaban exposure and was strongly correlated with the minimum concentration observed at steady state, just before the next drug administration (Cmin), whatever the event considered (major bleeding, major and clinically relevant bleeding,or total bleeding). The results also demonstrated that Cmin was a more robust predictor than Cmax [34].

All these data indicate the feasibility of laboratory monitoring, if needed.

Despite an appropriate methodology, the estimated dose-effect relationship is sometimes not very informative, as it is not highly discriminative during the interval between two doses (due to the flat profile). This could signify that the therapeutic range of the drug is sufficiently wide, but nevertheless hampers choice of the optimal dose. It could also mean that the population included in the phase II studies was too 'normal', lacking 'extreme' patients with regard to risk factors for thromboembolism or bleeding. In this case, a novel concept in new oral anticoagulant development is to select two effective doses, rather than only one, for phase III studies, to take into account the uncertainty of the estimations based on phase II studies and the inclusion of highly selected patients, generally considered to be at low risk of adverse events, in these studies compared with the patients enrolled in phase III trials. This applied to dabigatran in the context of orthopedic surgery [35–37] and atrial fibrillation [2] and will also apply to apixaban in the treatment of VTE (AMPLIFY extension), edoxaban in atrial fibrillation (ENGAGE-TIMI 48) and rivaroxaban in acute coronary syndrome (ATLAS 2). In the RELY study, the lowest dose (110 mg bid) was as effective as and safer than warfarin and the highest dose (150 mg bid) was more effective and as safe as warfarin [2]. The lowest dose could be proposed for patients considered to be at risk of bleeding, and the highest dose for patients at risk of thromboembolism. However, patient characteristics often include risk factors for both thromboembolism and bleeding, in which case laboratory testing could considerably facilitate the difficult choice of dose. The same observation could apply to orthopedic surgery, especially in patients at risk, such as renally impaired patients, the lowest dose being safer than, and at least as effective as LMWH, the highest dose being at least as safe as, and more effective than LMWH [38]. This could be considered as the first step in validation of Criterion #5, but warrants confirmation in specific clinical trials including non-selected populations. If the results observed with dabigatran are confirmed with other oral anticoagulants, it should be possible to identify several dosages for each compound, allowing dose adjustment in clinical practise.

Conclusion

The first results observed during the clinical development of new oral anticoagulants have shown that the inexplicable variability of drug response is quite low in highly selected populations, so there is no sense in recommending drug monitoring for such patients. However, we have already identified some sources of inter- and intra-individual variability, such as renal and/or hepatic function, advanced age, and certain clinically relevant drug-drug interactions. These criteria concern a restricted population, but one at very high risk of clinical events. Laboratory monitoring should be assessed for these patients, to avoid denying them treatment with these very promising compounds.

Such drug monitoring appears to be feasible, because we now have available new modelling techniques allowing determination of an optimal therapeutic range based on common, simple and reproducible pharmacodynamic parameters such as ECT, INR or chromogenic assays. Moreover, several of these new compounds are being developed for various indications at different doses. Drug monitoring should provide a very useful and clinically effective means of determining an optimal and effective dose regimen for each individual. In certain circumstances, such as the presence of a potential drug-drug interaction or pathophysiological fluctuation of renal or hepatic function, this monitoring could be repeated to enable adjustment of the initial dose.

In conclusion, all the relevant factors are or will soon be available to plan any laboratory monitoring required to ensure the safest possible use of new oral anticoagulants.

Laboratory monitoring in patients at risk of instability should of course be envisaged, but we definitely need more data from postmarketing risk management plans and clinical practise concerning non-selected patients in order to identify those likely to benefit from drug monitoring. The final step will be to validate the benefit of laboratory monitoring for these particular patients.

Disclosure of Conflict of Interests

The authors state that they have no conflict of interest.

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