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Editorial

Monitoring Direct Oral Anticoagulants: Longing for the Days When We Were in Control?

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See article by Kawabata et al., pages 736–743 of this issue.

For 6 decades, health care professionals and patients, felt "in control" of oral anticoagulation. Warfarin dosing was titrated to values of prothrombin time (PT) within a range of international normalized ratios (INRs). Lamentably, this control was, in part, an illusion. Dose adjustments were made according to art and experience to retrospectively correct abnormal INRs that had been out of range for an unknown period of time between the last 2 INR measurements. Too many patients found frequent INR measurements objectionable and often avoided testing. Dose adjustments were not governed by knowledge of the patient's personal pharmacology and the pharmacodynamic responses to dose adjustments were delayed, because the site of warfarin action is well upstream from the coagulation event in a complex cascade of clotting factors.

To achieve appropriate anticoagulation, the initial warfarin dose needed to be found by trial and error to compensate for each patient's genetically-bestowed profile of warfarin metabolism and vitamin K epoxide sensitivity. When anticoagulation was established, patients' dose requirements could change abruptly under the influence of disease, drug interaction, or altered vitamin K exposure. This required skilled attention to changes in the patient's disease-therapy environment or luck in timing INR measurements to guide dose adjustments before outside factors could cause INR shifts and possibly bleeding or thrombosis. Nevertheless, with no alternate oral anticoagulation available, we had no choice but to become moderately adept at INR monitoring. With these challenges, achieving a 50% average time in therapeutic INR range was the norm to be expected.

Loss of Control

More recently on the market are new medications that act directly on the coagulation cascade (direct oral anticoagulants or DOACs, also known as NOACs or non-vitamin K targeting anticoagulants). These agents eliminate lag in time to onset of anticoagulant effects and greatly reduce interindividual variability in the degree of anticoagulation, properties that permit the use of unadjusted, fixed dosing, and eliminate the requirement for serial monitoring of anticoagulation effects. Massive preregistration trials and a decade of experience have shown that standard-dose DOAC therapy is safe and effective in most patients, the proviso being that those patients do not have pharmacokinetic contraindications (eg, renal failure).[1] Nonetheless, some health care professionals and patients feel uncomfortably out of control without the ability to monitor their anticoagulant medication. That uncertainty prompts the question, "Couldn't we just use a laboratory test to be sure that this patient is correctly anticoagulated?"

Can Measuring Coagulation Parameters Increase Control of DOAC Therapy?

The longing to monitor anticoagulants persists, because the penalty for over- or undertreatment can be major bleeding or thromboembolic events. Clinically, the temptation is to fall back on the familiar coagulation tests, despite the fact that they do not reliably quantify the effects of DOACs. This conundrum is illustrated by the report of Kawabata et al.,[2] in this issue of the *Canadian Journal of Cardiology*, who retrospectively examined a population of nonvalvular atrial fibrillation patients taking DOACs to determine the prevalence, causes, and consequences of excessively prolonged PT and activated partial thromboplastin time (APTT), defined as PT or APTT > 2 SDs over the median. Of the 1521 patients they identified with records of PT or APTT associated with DOAC therapy, excessive prolongation occurred in 88 (5.8%). Compared with the rest of the population, these patients had a > fourfold increase in major bleeding events after a median follow-up of 8.9 months (5.7% vs 1.3%; $P = 0.01$). Patients with excessively prolonged PT or APTT measurements were older (69 vs 66 years; $P = 0.012$), had lower body weights (60 vs 66 kg; $P = 0.0001$), and had lower creatinine clearance (66 vs 76 mL/min; $P = 0.002$). Although they also had higher **C**ongestive Heart Failure, **H**ypertension, **A**ge (≥ 75 years), **D**iabetes, **S**troke/Transient Ischemic Attack, **V**ascular Disease,

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Age (65-74 years), **S**ex (Female) (CHA_2DS_2-VASc) scores (2.8 vs 2.3; $P = 0.011$), and higher **H**ypertension, **A**bnormal Renal/Liver Function, **S**troke, **B**leeding History or Predisposition, **L**abile INR, **E**lderly (> 65 Years), **D**rugs/Alcohol Concomitantly (HAS-BLED) scores (1.6 vs 1.3; $P = 0.017$), in multivariate analysis only body weight $\leq$ 60 kg (odds ratio, 2.12; 95% confidence interval, 1.20-3.72; $P = 0.016$) and the use of higher than recommended DOAC dosages (odds ratio, 2.29; 95% confidence interval, 1.17-4.50; $P = 0.016$) were independently associated with excessively prolonged PT or APTT. Of the 58 patients investigated for associated coagulation disorders: 47% had no identifiable disorders, 28% had antiphospholipid antibodies; 11% were receiving higher than recommended doses of DOACs; 8% had coagulation factor deficiencies; and 6% had severe liver disease.

Could clinical judgement have identified patients with higher bleeding risk during DOAC treatment, or is laboratory screening a valuable option? Kawabata et al.[2] found that only the 2 abnormalities, both easily detected clinically without laboratory screening, were the most commonly identified abnormalities associated with excessive PT or APTT measurements: (1) higher than recommended dose of DOAC; and (2) low body weight.[1] The independent predictive values of these 2 associations could imply that lower dosing is needed for low body weight and/or reduced renal function. The most commonly associated occult abnormality was the presence of antiphospholipid antibodies. However, none of these patients had a major bleeding or thromboembolic event during follow-up, and no alterations in therapy were required. Therefore, determining this information did not change clinical care.

Otherwise, screening for excessively high values of PT or APTT identified only 4 patients with coagulation factor deficiencies and 25 patients with no identifiable associated disorder (0.26% and 1.6% of the total study population). Overall, the clinically actionable results of screening for excessive prolongation of PT or APTT were extremely low.

Nonetheless, the nagging question persists as to whether we could implement monitoring to do a better job of determining DOAC dose. Certainly, laboratory monitoring and dose adjustment of DOACs is a topic of discussion in the contemporary literature.[3-5] To be valuable, screening should identify risks that can be corrected by dose adjustment or by choice of other therapy. Such screening should also reduce adverse outcomes sufficiently enough to justify the additional screening costs, or at least increase the number of patients who could be safely and effectively managed with DOACs.

What Monitoring Strategy to Adopt

If we chose to monitor DOACs, what is the goal of our monitoring? What monitoring parameter best supports that goal? What guidance does that parameter give to adjusting personal dosing? How often does it need to be done?

Importantly, we must keep clear in our minds that DOACs are not like warfarin.[6] Whereas DOACs are true anticoagulant agents for which increasing concentrations at the effect site correlate directly with degree of effect,[1] warfarin does not interfere with clot formation itself, but rather it is an antimetabolite, interfering with the vitamin K supply/regeneration critical to production of several clotting proteins. The effect of this complex interaction cannot be directly predicted by simply knowing warfarin concentration.

Next, one must choose the goals of monitoring. Situational monitoring is often used sequentially, with the goal of adjusting dose as often as needed to accommodate for changing responses to medications, especially those with a relatively narrow therapeutic window. However, baseline screening for inherent differences in pharmacokinetics, either genetically imbued or functionally acquired, has the goal of identifying patients in whom the "standard dose" of drug is not optimal. Because of the contemporary focus on personalized medicine, the sum total of individual differences in a patient's pharmacokinetics could be referred to as "personal pharmacokinetics." A strategy to adjust personal dose to accommodate the effect of personal pharmacokinetics on drug concentration reduces the incidence of therapeutic misadventure in the population as a whole and, because it does not require frequent repetition, can use fewer resources.

Warfarin management uses situational monitoring for frequent verification of drug effect to mitigate its variable interplay with environmental effects on cytochrome P450 2C9 (CYP2C9) metabolism, vitamin K epoxide (VKOR) activity, and vitamin K exposure.[6] Without guided dose adjustment, rates of bleeding or thrombosis would be unacceptable. This kind of monitoring is also used in assessing whether an acutely bleeding patient is overanticoagulated or a patient needs reversal of anticoagulation before surgery. In these situations, the monitoring parameter must accurately reflect the degree of anticoagulation and have a rapid turnaround. However, because the goal in this situation is a simple decision to continue/hold/reverse warfarin dosing, no guidance regarding magnitude of dose adjustment is actually needed. Such pharmacodynamic monitoring is discussed in a review by Eikelboom et al.[5]

In contrast, the goal of baseline screening of drug concentrations is to adjust for the naturally occurring population variation in effect site concentration of drug (ie, the intrinsic spread in steady-state peak drug concentrations developed in response to fixed-dose therapy in the population). Adjusting drug dose to optimize concentration is a reasonable strategy for patients starting treatment with a DOAC, because drug effect is proportional to concentration for directly acting medications. A measure of steady-state peak concentration developed after a given dose can guide dose adjustment, moving less typical patients into a band of concentrations associated with successful therapy (Fig. 1). Adding a measure of trough concentration permits calculation of personal elimination rate, commonly expressed as half-life. Because DOACs have linear pharmacokinetics in the clinical dosing range, change in concentration is proportional to change in dose. Successful examples of guided DOAC dose adjustment in patients with unusual pharmacokinetics have been reported.[7,8]

What to Monitor

Because pharmacology predicts a graded relationship between effect and drug concentration,[9] monitoring (screening) at inception of DOAC therapy could offer 3 benefits: (1) screening after initial dosing could identify patients with personal pharmacokinetics atypical enough to

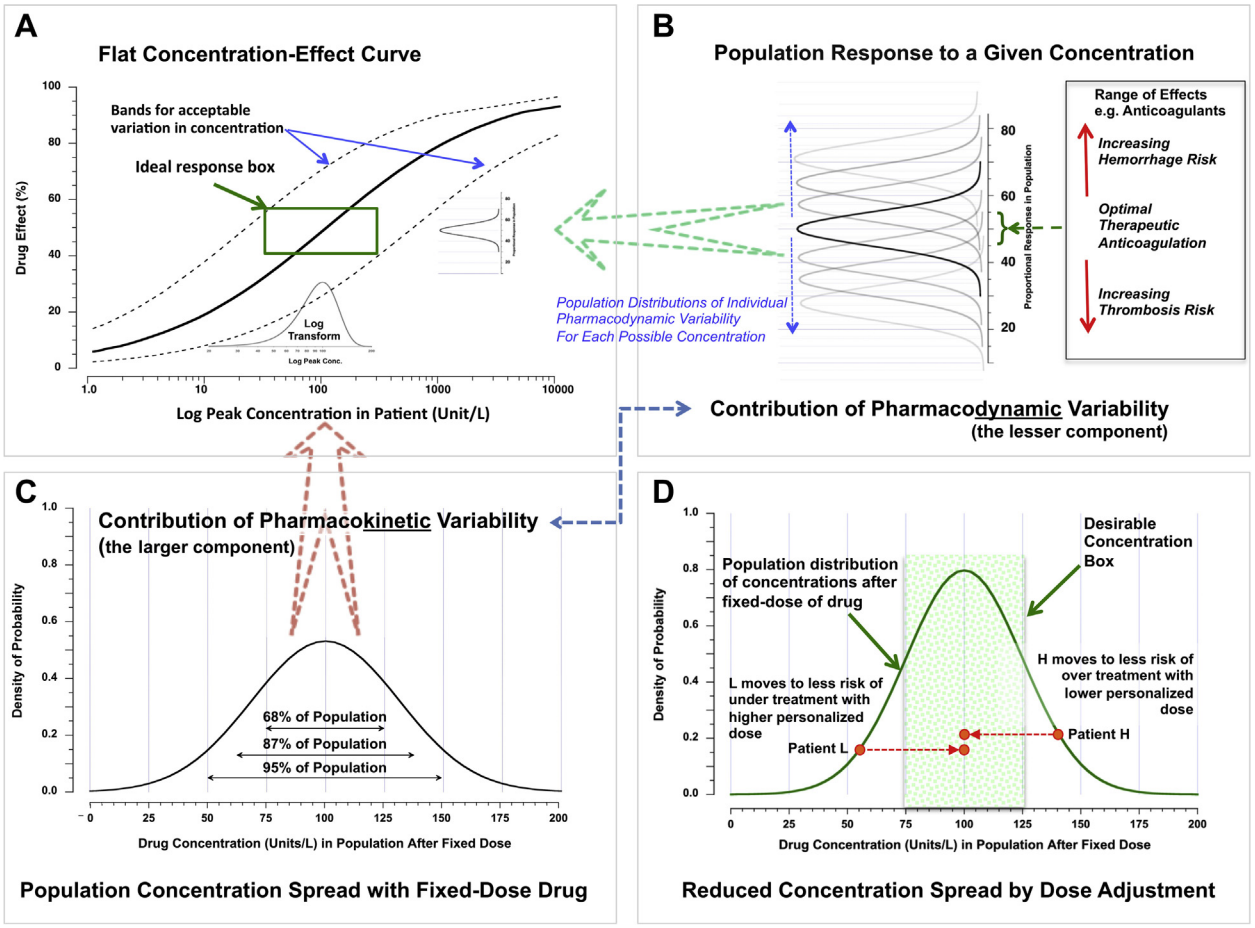

Figure 1. Simplified schematic of main sources of variability in population response to any fixed-dose therapy. Diagram does not pertain to any particular drug, but illustrates sources of variability in drug outcomes. (**A**) Concentration-response curve showing relatively flat degree of change in effect with shift in concentration, as seen with β-blocker therapy or direct oral anticoagulants/non-vitamin K targeting anticoagulants. Ideal response occurs when the dose administered causes a patient's personal pharmacokinetics to generate serum concentrations close to the typical values in the **green box**. (**B**) Relatively narrow population distribution of pharmacodynamic response to any given concentration. Each concentration outside the typical will have a similar distribution of individual responses shown as upward and downward shifts of response distribution curve. For direct oral anticoagulants optimal response in the **green box** would be slowing the rate of coagulation enough to reduce thrombosis risk, but not enough to excessively increase risk of hemorrhage. (**C**) Distribution of serum concentrations in a population given fixed-dose drug therapy. Variations in personal pharmacokinetics produce a relatively broad array of concentrations. (**D**) Effect of personalized dose adjustment for patients who are outside acceptable variation in concentration. A patient who develops a low concentration with fixed-dose, "Patient L," can be moved up into the desirable concentration range by increasing their dose above the norm. Those with high concentration, such as "Patient H," can be moved down into safe concentration range by decreasing their dose. Adjusting dose for patients with atypical personal pharmacokinetics reduces the spread of concentrations in the population. As such, more patients can achieve concentrations in the range associated with successful therapy.

make nonstandard dosing optimal; (2) chronic physiological abnormalities or drug-drug interactions affecting DOAC concentration at baseline (or even later on recheck) could be identified and adjusted for early during treatment; and (3) some patients with slow drug elimination, who might otherwise be excluded from DOAC therapy, might be managed with a simple dose adjustment.

While convenient to focus on peak concentrations, we must also remember that the effect of DOACs is not constant over the dosing interval. Serum DOAC concentrations might fluctuate anywhere from 2- to 8-fold between doses. Yet, for most patients, the degree of thrombosis inhibition over the course of the day is sufficient to tip the overall balance in favour of clot resolution through natural fibrinolysis. This means that, although no 2 patients have the same concentration profile, most patients achieve successful anticoagulation without excessive bleeding.

Because the ratio of change in anticoagulation effect to change in DOAC concentration is relatively modest, the concentration-response curve can be characterized as "flat" (Fig. 1A). The advantage of a flat response is that, even with the population variation in concentrations produced by a fixed-dose drug, acceptable therapy is still achieved in most patients. For example, if a given DOAC provides successful therapy at a range of concentrations within ± 1.5 SDs of the mean produced by fixed-dose therapy, then 87% of the population would be therapeutic with fixed dosing (Fig. 1C). Patients developing concentrations at the lower end of the desirable range would be more prone to clotting, whereas those at the upper end would be more prone to

bleeding. How best to identify patients who develop concentrations inconsistent with desirable clinical effect? For most pharmacokinetic problems, the best assessment is to measure drug concentration at steady state at a defined time after a defined dose of drug and compare it to a population standard. Trying to adjust dose according to pharmacodynamic parameters such as PT only adds an extra layer of variability.

Monitoring Conclusions

Pharmacology is founded on the theory that effects are proportional to interactions between receptors and agonist/antagonist molecules, a concept less than a century old.[9] Modern understanding of a drug's effects involves knowledge of its pharmacodynamics and pharmacokinetics. Pharmacodynamics is dependent on the expression of genetically encoded receptor proteins and their sensitivity to variations in drug concentration, which in turn are determined by pharmacokinetics. The concentration to which a receptor is exposed is dependent on: (1) drug dose in the context of: (2) personal pharmacokinetics (genetic variations in absorption, distribution, metabolism, and elimination); under the influence of: (3) external modifiers (drug-drug-food interactions, disease-anatomic-drug interactions).

We rely on medication to be supplied in dosage sizes that produce a safe and effective range of concentrations in most of the population receiving it. Dose is merely a tool that the health care worker uses to achieve desirable drug concentrations, not a magic number that makes receptors respond in the proper fashion. For patients who do not achieve desirable serum concentrations with a "normal" dose, the ability to achieve optimal concentrations through guided dose adjustment would allow more of them to be included inside the "successful therapeutics tent." As already pointed out by Gulilat et al., the proviso is "Because of the extent of inter-individual variation in the metabolism and clearance of [DOACs], it is likely that a greater range of [DOAC dosing sizes] will be needed to more precisely treat our patients."[10]

The effect site in anti-Xa and antithrombin pharmacology is an enzyme. Evolutionary preservation of these proteins is essential to life, meaning prevalence of clotting factor abnormalities (eg, hemophilia) is low. In contrast, systems responsible for absorption and excretion of exogenous substances have evolved variations to best adapt to the organisms' localized environment. This explains why a larger population variation is seen in personal pharmacokinetics than in pharmacodynamics. As such, most of the variation in response to a given dose of a DOAC will be driven by variation in pharmacokinetics (Fig. 1B vs 1C). The serum drug concentration developed in response to a fixed dose of drug is the phenotypic summation of the patient's pharmacokinetic genome. Therefore, personalized medicine can be achieved by adjusting dose for personal pharmacokinetic variation. This is best done by directly monitoring the effect of individual pharmacokinetics on concentration rather than indirectly estimating it by measuring pharmacodynamic effects. The mathematical simplicity of dose titration guided by measured concentration also makes serum drug concentration the monitoring parameter of choice. Changing the concentration of drug to which the effect site is exposed might also compensate for modification of pharmacodynamic effects by factors such as antiphospholipid antibody, something Kawabata et al. reported in 3.5% of their database.[2]

It is easy to articulate many arguments against monitoring. First, one might assert that the current situation is "good enough" for the large majority of patients (ie, unmonitored DOAC performed similarly to monitored warfarin in large randomized trials). Second, a major marketing feature of DOAC therapy is lack of a need to monitor and the resulting patient benefit of eliminating regular venipunctures for INR monitoring. Third, the laboratory capacity to measure DOAC concentrations is currently limited. Fourth, the large registration trials did not assess if there was benefit to adjusting dosage for optimal concentration, instead relying on excluding the segment of population likely to develop concentrations outside the desirable range.[1]

However, medicine should never halt progress by being complacent in the belief that current practices are good enough. Passive acceptance will not push progress. We need to counter these arguments in order to include a larger portion of the population in successful oral nonvitamin K antagonist therapy. To do that, the warfarin-inspired paradigm of regular monitoring needs to be abandoned. More effective DOAC monitoring could be achieved by screening patients for unusual dosing requirements at baseline, and retesting only when circumstances suggest a drug interaction or physiological change might be altering the patients' pharmacokinetics. We need to develop more capacity for high-performance liquid chromatography tandem mass spectroscopy, and accept that urgent turnaround is not necessary for dose adjustment at inception. Other tests will be more appropriate for acute decisions around bleeding. Finally, of paramount importance to the adoption of such a strategy is the need to study assay-guided dose adjustment for personal pharmacokinetics in a sufficient number of patients to document its practical benefit. To keep costs down, policies are needed to discourage well-meaning clinicians from drifting back to the monthly monitoring associated with warfarin therapy.

Can we return to the days of being "in control"? That might be an unattainable dream. However, Kawabata et al.[2] have suggested that we might do better by screening for "atypical" patients at baseline. Although screening for prolonged PT or APTT might contribute in identifying the $< 0.5\%$ of patients in whom risks with DOAC anticoagulation are elevated for extrinsic reasons, a much bigger return on investment could be realized from baseline screening for atypical personal pharmacokinetics in conjunction with personal dose adjustment. Such a strategy has the potential to improve therapy for 10%-20% of the population. Striving to overcome the challenges to baseline DOAC concentration screening is a logical path forward to achieving better anticoagulation therapy for the whole population requiring treatment with these newer agents.

Disclosures

The authors have no conflicts of interest to disclose.

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