Improve the results of phase II trials of thromboprophylaxis with the new oral anticoagulant drugs

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In the current issue of *Thrombosis and Haemostasis*, Weitz et al. describe the first dose-finding study of a novel oral factor Xa inhibitor, TAK-442, for the prevention of venous thromboembolism (VTE) in orthopaedic surgery (1). TAK-442 was tested on a wide range of doses, from 10 mg twice-daily (bid) to 80 mg bid. There was a dose-dependent reduction in the incidence of VTE but there was no relation with dose regarding the safety endpoint, major bleeding in comparison with enoxaparin. TAK-442, 40 mg once-daily (qd) to 80 mg bid, had comparable efficacy and safety than enoxaparin 30 mg bid. Based on these results, one could suggest that this new oral anticoagulant is well tolerated and has a large therapeutic window.

The trial did identify ineffective dose-regimens (dose of TAK-442 that produced lower efficacy than enoxaparin) but did not identify the highest tolerable dose regimen. Thus future trials are warranted to define an optimal regimen to be tested in a confirmatory trial. The developments of previous anticoagulants have provided valuable information which is worth considering in the design of these future studies with TAK-442.

Dose-ranging studies are designed to demonstrate a significant effect on efficacy. Orthopaedic surgery, in particular primary knee arthroplasty, is an ideal clinical setting for investigating the antithrombotic potential of anticoagulant agents because it is associated with high rates of asymptomatic VTE. However, dose-ranging studies are often underpowered for safety as the rate of major bleeding events are roughly ten times lower than the rate of VTE detected by mandatory venography. Based on the sole results of the TAK-442 dose-ranging study, it would probably be too early to conclude that TAK-442 has a large therapeutic window. Of note, the 2008 European Medicines Agency (EMEA) guidelines recommend major bleeding as the main safety criteria, and also states that other bleeding related parameters should be recorded during the study. Pending a much more important median for calculated blood loss or postoperative allogeneic transfusion, the difference between dose regimens could be easier to demonstrate and this would simplify the quest for a statistical difference (2).

Unfortunately these bleeding events were not reported in the TAK-442 dose-ranging study.

To define an optimal regimen, the choice of the most appropriate dose for efficacy and safety is of course essential. At the time when low-molecular-weight heparins were under development, the necessity of conducting powerful dose-ranging studies had not yet been clearly recognised. Whilst different doses of enoxaparin were tested in phase III studies, a correlation between doses and clinical events was never established. Thus, the optimal dose of enoxaparin is still unknown, as illustrated by the different dose regimens recommended between Europe and North America (3, 4). Since then, large dose-ranging studies have been performed with the more recent anticoagulant agents. Some trials have provided sufficient data to perform confirmatory studies (5, 6), whereas others have required additional dose-ranging studies or *post hoc* analyses to evaluate the optimal regimen. For example, four dose-ranging studies were performed with rivaroxaban to eventually decide that 10 mg qd was the dose to be tested in future studies (7–9).

Another approach, which may save time and money, is to use the data gathered in the phase II study and perform a concentration-response analysis with the use of pharmacokinetic and pharmacodynamic modelling based on a population approach. In the BISTRO II and APROPOS studies (10, 11), there was a significant correlation between a biological marker (maximum concentration after the first dose of dabigatran and daily steady-state area under the plasma concentration-versus-time curve of apixaban), and various efficacy and safety criteria. These concentration-effect relationships were more informative than the dose-effect relationship and allowed selection of doses that were successfully tested in phase III studies (12–14).

Baseline characteristics of the patients included in a dose-response study are also to be considered. It is important to emphasise that a parallel dose-response study gives group mean dose-responses, not individual dose-response curves. Thus, the results of a dose-response study may not be applicable in a population with different characteristics. Indeed, patients included in phase II trials are often homogeneous patients and highly selected, with a low risk of adverse events. Hence, the majority of patients included in the TAK-442 dose-ranging study were young-elderly obese patients. The study by Weitz et al (1) showed that 10 and 20 mg bid were ineffective regimens. However it cannot exclude that these latter doses are inappropriate for very elderly patients with low body-weight and renal impairment.
Population modelling allows investigating the potential covariates that can explain part of the inter-subject variability of a drug's pharmacokinetic parameters, as well as the risk of drug accumulation. For example, simulation suggests that an approximately equivalent efficacy/safety balance for apixaban would be maintained in subjects with moderate renal impairment as compared with subjects with normal renal function, despite the higher apixaban exposures in patients with renal impairment (11). Yet, a pharmacokinetic model will depend on the characteristics of the patients forming the basis of its building. As a result, pharmacokinetic simulations of “extreme” patients may be limited and should only generate hypothesis. Indeed, a recent study questioned the validity of the fondaparinux model based on data from phase II/III studies to adequately predict pharmacokinetics in special populations encountered in everyday practice (15). In orthopaedic surgery, baseline demographic factors are also so different in knee arthroplasty compared with patients under- going hip arthroplasty or hip fracture surgery. Thus, future studies with TAK-442 should include a sufficient amount of patients at risk of drug accumulation.

Moreover, there is strong evidence that the timing of first administration relative to surgery may affect the benefit-risk ratio of anticoagulants (16–18). In the phase III studies with dabigatran, RE-NOVATE and RE-MODEL (12, 13), the drug was initiated 1–4 hours postoperatively, as in its phase II study, BISTRO II (10). The results showed that dabigatran was not inferior to enoxaparin 40 mg once daily in reducing VTE. However, in the RE-MOBILIZE study, in which dabigatran was initiated 12–24 hours postoperatively (19), dabigatran was found to be statistically inferior to enoxaparin 30 mg twice daily in reducing VTE. Thus, the difference of efficacy of dabigatran in this example may be due to the different regimen used with the comparator. Nevertheless, it appears crucial that studies should be planned to investigate the combined effect of dose and timing. This was previously done in a phase II study using a factorial design for another antithrombotic, NAPC2 (20). Starting TAK-442 the day after surgery, as it has shown to be effective with apixaban (14), should perhaps be tested.

Given that the choice of the dose-regimen to be tested in a first phase-II study is not an easy task, the results of the TAK-442 dose-ranging study provides some evidence that this anticoagulant is promising. Future trials are evidently warranted but we should not neglect the lessons learnt from the past. Given the diverse range of the many new oral anticoagulants in development for VTE and other indications (21–25), those involved in drug development may best take heed of such advice.

References