Intern Emerg Med (2013) 8:371–372
DOI 10.1007/s11739-013-0949-3

IM - DEBATE

Laboratory tests during direct oral anticoagulant treatment? Yes

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Received: 23 March 2013 / Accepted: 20 April 2013 / Published online: 21 May 2013

Warfarin is still the most used oral anticoagulant; in Italy approximately 650,000 subjects were taking warfarin in 2006 with an annual increase of 5 % [1]. The main drawback of warfarin is the high interindividual variability in the dose–response [2]. Variability depends on both environmental factors (e.g., diet and interfering comedications) and endogenous factors (e.g., age, gender, height, weight, comorbidities and genetic). *VKORC1*, *CYP2C9* and *CYP4F2* gene polymorphisms are clearly involved in determining the variation in warfarin dose. [3]. Less variability is reported for direct oral anticoagulants although trough plasma concentration varies individually on maintenance treatment [4]. As the increase in drug concentrations is closely related to bleeding events, it is suggested to monitor their effect through specific coagulation tests. The aim would be to find out the best dose for each patient. However, direct oral anticoagulants have shown a fairly predictable effect with no need for routine coagulation monitoring [5]. Moreover, Phase III clinical studies of direct anticoagulants on stroke prevention in atrial fibrillation have clearly shown the efficacy and safety of fixed dose of direct anticoagulants [6].

This is one of the main advantages of using these new drugs. According to this assumption, physicians will follow their patient only from a clinical point of view to assure adherence and compliance to treatment. It could be argued that in specific situations assessment of patient anticoagulant status may be useful [7]. Ecarin clotting time (ECT) or diluted thrombin time (dTT) or aPTT (if the previous ones are not available) is recommended for dabigatran. Prothrombin time (PT) in comparison to control PT is a sensitive and reliable test for rivaroxaban whereas no routine coagulation test seems to be suitable for apixaban. Possible indications for laboratory testing are the following (Table 1): (1) evaluation of coagulation tests when the patient reaches a steady state, (2) evaluation of possible over- or underdosing the anticoagulant due to drug interactions, (3) assessment of anticoagulant effect in frail patients. As recommended by Italian Federation of Thrombosis Centers (FCSA) appropriate coagulation tests should be performed after 2–3 months from the initiation of therapy in order to have a steady-state laboratory value that may be useful if future adverse clinical events (bleeding, thrombosis) occur. Interaction of novel anticoagulants with other drugs is apparently much lower than that of warfarin. However, dabigatran, rivaroxaban and apixaban are substrates of the P-glycoprotein (P-gp) transporter, one-third of rivaroxaban is metabolized by the liver via CYP3A4/CYP3A5 and CYP2J2-dependent pathways and apixaban which has predominant non-renal clearance is eliminated via the CYP3A4, CYP1A2 and CYP2J2-dependent pathways. Therefore, the possibility exists that drug interactions may interfere with the anticoagulant effect of these agents. In frail patients prescribed with multiple drugs as for example with elderly patients with atrial fibrillation it might be wise to perform adequate coagulation tests at regular intervals comparing them with those initially obtained at steady state. In this way, the extent of drug interaction can be measured when a potential interfering drug is added on top of their usual therapy. Definite indications to laboratory testing comprise the following: (1) major or life-threatening bleeding, (2) renal or liver impairment, (3) urgent or elective surgery or invasive manoeuvres at high risk of bleeding. Under these circumstances, if the drug used is not known, coagulation

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Table 1 Need for coagulation tests during direct anticoagulant treatment

Possible	Definite
At steady state	Major or life-threatening bleeding
Drug interactions	Renal or liver impairment
Frail patients	Surgery or invasive manoeuvres at high risk of bleeding

tests may help to establish whether dabigatran (marked prolongation of the dTT) or rivaroxaban (marked prolongation of the Prothrombin Time) has been used whereas such a possibility does not exists for apixaban. Emergency physicians should also assess how the procedures to counteract the anticoagulant effect are working as no drug-specific antidote is available. Direct Xa Inhibitors but not dabigatran are (partially) antagonized by non-activated four factor prothrombin complex concentrates [8] that contain Factor II–VII–IX–X and dosage could be 50 UI/kg by one shot administration [9]. Other situations in which coagulation tests are needed are renal or liver impairment. Dabigatran is excreted unchanged by the kidneys (80 %). One-third of rivaroxaban is cleared unchanged via the kidneys and the remaining two-thirds are metabolized by the liver via CYP3A4/CYP3A5 and CYP2J2-dependent or independent pathways (one-third each, respectively). Apixaban, which has predominant a non-renal clearance, is eliminated via the liver and intestinal excretion, by over 70 %. Renal and liver function decline with age and the same drug dosage of novel anticoagulants may be inappropriate during long-term treatment [10]. Another important issue is treatment withdrawal before surgery or invasive maneuvers. In case of emergency surgery a reversal of anticoagulation could be evaluated by coagulation tests. If elective surgery at standard bleeding is performed, a 1- to 3-day drug suspension of dabigatran depending on renal function is mandatory. If elective surgery at high risk of bleeding is considered (neurosurgery, cardiovascular surgery), it is advisable that the active anticoagulant drug should be absent in the circulation. This is definitely assessed by the normalization of specific coagulation tests.

Conflict of Interest None.

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