Desired tests for monitoring new anticoagulation drugs

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The new oral anticoagulants dabigatran and rivaroxaban have major influence on almost all coagulation assays. With the forthcoming wide-spread clinical use in therapeutic dosage every lab will be faced with these interferences. Additionally, in special patient groups and clinical situations monitoring of drug levels will be required.

These facts raise two questions. First, how can one assess the coagulation status (e.g. bleeding tendency or DIC) of a patient under therapy with the new drugs? And second, which assays are best suited for therapeutic drug monitoring?

The in-vitro influence of the new anticoagulants on coagulation assays does not necessarily reflect the in-vivo anticoagulant effect of the drug. We performed a systematic evaluation of the influence of the drugs on an extensive profile of routine and special coagulation assays using plasma pools of normal population, ICU and cumarin patients with dabigatran or rivaroxaban concentrations ranging from 31.25 µg/l to 1000 µg/l. Drug concentrations of 31.25, 250 and 1000 µg/l were selected as representative for through level, Cmax and overdosage/cumulation. Even within the normal therapeutic range of the drugs (Cmax of 250 µg/l) deviations from baseline values between 37% and 290% were observed. In overdosage levels deviation ranged from 1% to 765%! Only through level samples showed moderate deviations between 80% and 146%. The extent of deviation dependeds on the drug, the assay type and the assay manufacturer used. In conclusion, at Cmax levels and in overdosage/cumulation a reliable measurement is almost impossible. Most reasonable for available assay types seems to be measurement at through levels taking assay characteristics and a deviation of about -20 to +50% into account.
Future assay development should focus on assays insensitive to drug interference as well as on assays which better reflect the in-vivo situation.

In contrast to previous launchings of new (anticoagulant) drugs, in case of dabigatran and rivaroxaban the manufactures considerably support assays development for therapeutic drug monitoring in cooperation with scientific institutions. These activities include production of calibrators and controls as well as assay optimization. Currently, a modified thrombin time is promoted for monitoring of dabigatran and anti-Xa-activity assays for monitoring of rivaroxaban. However, relevant experiences with these assays in clinical situations are sparse as the new drugs are not yet approved for therapeutic use and the need for monitoring in prophylactic use is very limited. Future assay development should focus on assays with a good correlation to clinical status of the patients as risk of bleeding or thrombosis and outcome.