Increased risk of bleeding is a serious adverse effect – can monitoring of therapy involving the new oral anticoagulants (therapeutic drug monitoring) enhance drug safety?

Useful and necessary about new anticoagulants

In the Norwegian Prescription Database and other drug statistics (1) we see that an increasing number of patients are treated with the new anticoagulants called "non-vitamin K oral anticoagulants» (NOACs) or "direct oral anticoagulants» (DOACs). In this edition of the Journal of the Norwegian Medical Association, Henriette Johansen et al. (2) provide useful information about the risk of bleeding with concomitant use of these drugs and antiplatelet agents, while Halvor Lundgaard et al. discuss the necessity of monitoring of the use of these drugs in therapy (3).

Atrial fibrillation, pulmonary embolism, deep vein thrombosis, myocardial infarction and hip fracture are relatively common diagnoses, particularly in the elderly. Elderly people may also have impaired renal function, multimorbodity and extensive polypharmacy. It is precisely this patient population that is often treated with the new anticoagulants. Dabigatran, apixaban and rivaroxaban were approved for inclusion on the Norwegian national health free list in 2013. The indication was prevention of stroke and embolism with atrial fibrillation not due to heart valve disease and in the presence of more than one risk factor. The drugs were also to be used for prophylaxis and treatment of pulmonary embolism and deep vein thrombosis and for post-operative thrombosis prophylaxis after hip and knee surgery. Rivaroxaban has in addition been approved for treatment of acute coronary disease. Dabigatran (coagulation factor II inhibitor), rivaroxaban and apixaban (factor X inhibitors) are selective, reversible inhibitors that are simple to dose compared with warfarin. They are substantially more costly than warfarin, but their use could be justified financially because therapeutic drug monitoring was regarded as unnecessary. The Norwegian Directorate of Health has issued guidelines for their use (4, 5). Examples of contraindication are severely impaired renal function, liver disease associated with coagulopathy, increased risk of bleeding and drug interactions.

The drugs in the NOAC group act differently from antiplatelet agents such as acetylsalicylic acid (aspirin) and clopidogrel. Drugs with different points of action on the same physiological system may increase the risk of bleeding, as confirmed by the literature review of Johansen et al. (2). They conclude that the combination of new anticoagulants and antiplatelet agents increases bleeding risk and in most cases should be avoided. Johansen et al. recommend that the combination should only be used in clinical situations where treatment with current standard regimens is difficult. The duration of this treatment is given, but without further medical grounds or documentation. At present, the standard treatment for cerebral and myocardial infarction without concurrent atrial fibrillation or deep vein thrombosis remains a combination of aspirin and clopidogrel. The authors also point out that the observation period for combinations of new anticoagulants and antiplatelet agents following orthopaedic surgery has been short, and this may explain the limited risk of bleeding that has been observed.

Lundgaard et al. (3) ask whether monitoring serum concentration may make treatment with new anticoagulants safer. Monitoring can be carried out at several laboratories – albeit using different methods such as liquid chromatography tandem mass spectrometry (LC-MSMS) and functional assays (antifactor Xa for rivaroxaban and apixaban and modified thrombin time for dabigatran). Drug monitoring is expensive, and not all analytical methods are performed around the clock. The article briefly discusses which methods should be used under which circumstances, and the LC-MSMS method is cited as the gold standard.

So far there are no health economic analyses of drug therapy monitoring in connection with the use of the new anticoagulants. The serum concentrations are only guides, and further studies should be made with respect to effects/side effects. The authors argue convincingly for the suitability of the NOACs for therapeutic drug monitoring (6). The drugs have a narrow therapeutic window, selective and reversible effects and high interaction risk, and their use may potentially have serious consequences if their concentration becomes too high (bleeding) or too low (thrombosis). Use of serum concentration monitoring combined with clinical findings in the event of suspected overdose may provide grounds for termination of therapy and possibly antidote treatment in hospital. An antidote to dabigatran, idarucizumab, is now available for use in hospitals (7). Antidotes for rivaroxaban and apixaban have been developed, but not yet approved. Guidelines for therapeutic drug monitoring must be introduced, and analytical practice established at our hospitals.

Monitoring of the new anticoagulants could improve drug safety, and increased attention to avoiding concomitant use of these drugs and antiplatelet agents will probably result in fewer side effects. In the meantime, we bring a reminder that the Norwegian Medicines Agency has the new anticoagulants under special observation because of the risk of bleeding and thrombosis.

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