

Generic Anticoagulant, Antithrombotic and Thrombolytic Agents. Are There Any Specific Guidelines?

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Thrombosis represents a complex pathophysiological syndrome with multifactorial etiologies. Anticoagulants, antiplatelet and thrombolytic drugs have been used for the treatment of various thrombotic disorders and for prophylaxis in patients admitted for medical, surgical and interventional indications. These drugs play a valuable role in the treatment of various disorders such as myocardial infarction, thrombotic stroke and pulmonary embolism. The mechanisms by which these drugs produce their effects are complex and not completely understood at this time. Most of the effects produced by these drugs are indirect and may involve the modulation of plasmatic, vascular and target organ specific effects. Moreover, some of these drugs produce the release and generation of certain endogenous antithrombotic mediators.

Recently the generic versions of oral anticoagulants (eg. coumadin), low molecular weight heparins (eg. dalteparin and enoxaparin), antithrombin agents (eg. argatroban), antiplatelet drugs (eg. clopidogrel) and thrombolytic drugs (eg. streptokinase) have been introduced. Regulatory compliance guidelines from WHO, USFDA, EMEA and other agencies for the manufacture of these drugs are ambiguous and thus the generic versions of these drugs are not manufactured using the stringent biological and chemical controls applied to the branded products. Moreover, several non-WTO member countries do not acknowledge the intellectual property protection rights of the innovator company for the purpose of patent protection. Generic products are manufactured by uncontrolled means and may result in compromised quality and undesirable clinical implications.

The oral anticoagulant drugs such as warfarin exhibit a narrow therapeutic index and show a non-linear pharmacokinetics. Moreover, these agents are bound to proteins (>98%). Small changes in the patients condition and pathophysiologic predispositions can result in considerable changes in the anticoagulant responses. Recently, several generic versions of branded LMWHs such as enoxaparin and dalteparin have become available. A comparison of generic and branded LMWHs has shown significant pharmacological difference despite chemical equivalence. Generic versions of antiplatelet drugs like clopidogrel have weak antiplatelet activity and require additional dosing of this drug. In a recent study, 21 samples of generic streptokinase were tested and only 3 samples were found to perform as per the information listed on the label. This striking discrepancy between claimed and actual performance of these critical drugs may result in life threatening situations for severely ill patients. To address these important issues a defined preclinical screening program is in place in various laboratories. In the future, peer review and group consensus will be required to develop guidelines for the acceptance of generic antithrombotic drugs. Until that time the interchange between generic and branded anticoagulant, antiplatelet and antithrombotic drugs should be considered with caution.

References

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