Korean J Gastroenterol Vol. 65 No. 4, 197-198
http://dx.doi.org/10.4166/kjg.2015.65.4.197
pISSN 1598-9992 eISSN 2233-6869

EDITORIAL

"다비가트란 *vs.* 와파린" 이제는 바꿔야 하나?

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Dabigatran *vs.* Warfarin; Is It Time to Change?

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Article: Gastrointestinal Bleeding with Dabigatran, a Comparative Study with Warfarin: A Multicenter Experience **(Korean J Gastroenterol 2015;65:205-214)**

Long-term anticoagulation is required in patients with atrial fibrillation (AF), mechanical heart valves, pulmonary embolism, and deep vein thrombosis.[1] A vitamin K-dependent antagonist such as warfarin is the most commonly used oral anticoagulant and is effective for prophylaxis and treatment of various thromoboembolic complications. However, warfarin has several limitations that complicate its use in clinical practice. It has a narrow therapeutic and safety margin and thus requires frequent laboratory monitoring. In addition, the anticoagulation effects of warfarin are altered by diet, medications, and genetic variations. These limitations have led to development of novel anticoagulants (NOACs).[1]

Unlike warfarin, which inhibits multiple coagulation factors, NOACs specifically target factor Xa or thrombin. NOACs as a group have a rapid onset and offset of action. There are few drug-drug interactions and dietary interactions, which results in a more predictable anticoagulant response. Routine coagulation monitoring is not necessary for NOACs. Dabigatran, one of the NOACs, exerts its effect by reversibly binding to thrombin. It is primarily eliminated by the kidneys and dose modification is required in patients with impaired renal functions. Dabigatran is currently approved by the US Food and Drug Administration (FDA) for the prophylaxis of thromboembolic complications in non-valvular AF.

In a meta-analysis comparing NOACs with warfarin, the development of stroke, systemic embolic events, and intracranial hemorrhage was reduced in NOAC groups.[2] However, the benefits of NOACs came at the expense of increased gastrointestinal bleeding (GIB) compared to warfarin.

The report by Sherid et al.[3] in this issue provides insight into the risk of GIB in patients taking dabigatran compared with those taking warfarin. A total of 417 patients, 208 were on dabigatran and 209 were on warfarin, were identified and assessed for development of GIB. GIB occurred in 4.8% in the dabigatran group and 10.1% in the warfarin group. Multivariate analysis revealed patients who were on dabigatran for less than 100 days, age over 65 years, and history of GIB as risks of GIB. The results of this study are contradictory with those

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Financial support: None. Conflict of interest: None.

of previous trials. As the authors pointed out, the dosage of dabigatran may have been the reason for these results. Studies that reported increased GIB mainly used dabigatran 150 mg twice daily while 20% of patients in this study used doses of 75 mg twice daily.[3] Major GIB from dabigatran seems to occur more frequently in the first three months of usage and decreasing renal function with increasing age may be the cause of increased GIB in elderly patients. While previous studies reported higher incidence of GIB with concomitant administration of aspirin and/or clopidogrel, the authors reported that concomitant administration of anti-platelet agents did not increase the risk of GIB.[4] The small sample size compared to the previous studies and the lower dose used in this study may have been the reason for these results. Interestingly, although the authors used lower doses than the recommended dose by the FDA, there was no occurrence of venothromboembolic events in any patients taking dabigatran., suggesting that a lesser dose may be equally effective with fewer adverse events.

The exact mechanism of development of GIB with dabigatran use is uncertain. One hypothesis is that active drugs in the gastrointestinal tract promote bleeding through a topical effect.[5] Although the incidence of GIB was lower in the dabigatran group compared to the warfarin group, dabigatran is a drug without an antidote. Also, lower GIB occurred more frequently in the dabigatran group compared to the warfarin group. Endoscopic procedures may not be easily accessible in cases of lower GIB associated with dabigatran .

Hundreds of studies on the effect of new oral anticoagulants have been published in the past decade. There are still debates on whether these new oral anticoagulants have benefit on GIB compared to warfarin. From the current study we cannot conclude whether or not "it is time to change!". However, this study is indeed "another step towards the end of the warfarin era". More prospective studies with longer observation period are anticipated and gastroenterologists should be alert to these new anticoagulants since consumption of these drugs is expected to increase along with the aging population. The more out patients take oral anticoagulants, the greater the chance of performing emergency endoscopy at night.

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