

Acenocoumarol in Geriatric Population

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Commentary

Thromboembolic disorders which are common across the globe have been associated with a high mortality rate [1]. Prevention and treatment of recurrent thromboembolic disorders necessitates the use of anticoagulants [2]. Treatment with anticoagulants has been the mainstay to prevent/treat deep vein thrombosis, pulmonary embolism, acute coronary syndrome and stroke prevention in valvular and non - valvular heart disease [1].

The elderly population is not only characterized by being at a higher thromboembolic risk but also with a higher bleeding risk, Hence physicians are prone to underuse anticoagulants either due to underestimation of thromboembolic risk or fear of bleeding or both within this geriatric population [3].

Oral anticoagulation therapy is as effective in the elderly as in younger patients. Elderly patients are more prone to thromboembolism than younger because younger patients are more physically active, a higher velocity of blood flow and results in better emptying effect and less stasis of blood. Secondly there is more sinus rhythm in the young thirdly heart is smaller in young, making stasis less likely [4].

Benefits of anticoagulation in geriatric population

Geriatric peoples are more vulnerable to venous and arterial thromboembolism because of increased in clotting factor concentration and activity as well as platelet activity and declined in fibrinolytic activity. Elderly are more likely to undergo surgeries like cardiac, knee and hip surgeries [4].

Since the elderly population is more likely to be afflicted with various co-morbidities, impaired renal function, risk of fall, altered pharmacodynamics of VKAs, antiplatelet agents it is imperative to keep this in mind while treating them with anticoagulants [3].

Acenocoumarol and warfarin are most frequently used oral anticoagulants in India. Both in India and Europe acenocoumarol is widely available and prescribed. Acenocoumarol acts by inhibiting reduction of vitamin K, preventing carboxylation of glutamic acid residues of vitamin K dependent clotting factors, an important step in the process of clotting.

The monograph for acenocoumarol has been documented in the Indian Pharmacopoeia and its tablets ranging from 0.5-6 mg has been approved by the Regulatory authorities to be marketed in India for the prophylaxis and management of thromboembolic disorders.

Therapeutic Indications of acenocoumarol are for the prophylaxis and treatment of venous thrombosis and its extension, the treatment of stroke prevention in atrial fibrillation with embolization, the

prophylaxis and treatment of pulmonary embolism, and as an adjunct in the treatment of coronary occlusion [5,6].

Dosage of acenocoumarol

Acenocoumarol is to be taken as a single dose at a fixed time each day.

In adults initial dosage: When the thromboplastin time is within the standard range prior to initiating treatment, the below dosing plan is recommended:

Day one: Initial dose of 4 mg/day (lower doses may be necessary if patients are receiving heparin). There may be no need for a loading dose if the PT/INR value prior to treatment falls inside the therapeutic range. Day two: 4 to 8 mg. one should proceed with caution during treatment if the initial thromboplastin time is abnormal.

Elderly patients, patients with liver disease or severe heart failure with hepatic congestion or malnourished patients may require lower doses during treatment initiation and maintenance.

Maintenance therapy: the maintenance dose of Acenocoumarol differs from one patient to another and should be calculated based on the patients' blood coagulation time done during regular laboratory checks.

Alteration of the maintenance dose can only be made by checking the Quick value of international normalized ratio (INR) at consistent intervals, confirming that the dosage stays inside the therapeutic range. The maintenance dose usually lies between 1 to 8 mg daily depending on the individual.

Prior to the start of treatment, till the time the coagulation valency is stabilized within the optimal range, regular measurement of the thromboplastin time must be done daily in the hospital.

The INR is defined as the ratio of the patient's plasma thromboplastin time to the normal thromboplastin time raised to a power determined for a reference thromboplastin. When the Quick value declines, the patient's thromboplastin time rises and the INR is greater. The therapeutic range normally lies between INR values of 2 to 4.5. Most patients show no risk of severe haemorrhagic complications or a recurrence of thrombosis within the normal range.

Mostly, after withdrawal of Acenocoumarol, there is commonly no danger of reactive hypercoagulability and therefore it is not essential to give progressively diminishing doses. Though, in very rare cases, in some high risk patients (e.g. after myocardial infarction), withdrawal must be gradual.

Acenocoumarol has a shorter $t_{1/2}$ (10–24 hours), a more rapid effect on the PT, and a shorter duration of action (2 days). The maintenance dose is 1–8 mg daily.

Dosage in geriatric patients

The dose of acenocoumarol required to achieve a therapeutic prothrombin ratio (1.8 to 2.7) may decrease with increasing age, with decreases being most evident from the third to the fifth decade. This may be linked to increased intrinsic sensitivity of oral anticoagulants in the ageing [7,8].

Acenocoumarol offers numerous benefits over warfarin, like: More rapid onset of action provides better stability of prothrombin time, shorter half-life, and Swift reversal of anticoagulant action, with relatively smaller dose of vitamin K1. It is also less dependent of CYP2C9 enzyme for its metabolism [9].

The most important factors associated with bleeding in geriatric patients are degree of anticoagulation, presence of organic lesions, duration of therapy and most important patient compliance. In geriatric patients it is important to keep the INR range at the lowest effective level to reduced risk of bleeding. Try to keep anticoagulation course short but unfortunately, many of the conditions VKAs indicated in geriatric patients for lifelong. While using VKAs (acenocoumarol) in elderly please exclude the presence of organic lesions like genitourinary, gastrointestinal pathology as these conditions could present with haematuria, hematemesis or malena. Close management with regular monitoring of PT/INR needs to be carried out to ensure compliance in geriatric patients [4].

Special attention should be given to avoid over anticoagulation to reduce haemorrhagic complications once the elderly patients have been prescribed oral anticoagulants. The advantage in terms of bleeding risk in decreasing anticoagulant strength is not broadly accepted, and target INR should be the same as in younger patients (2.0–3.0 for almost all indications). One of the chief difficulties regarding anticoagulation in ageing patients is that those at maximum risk for bleeding are those who would have maximum benefit from anticoagulation [7].

Thromboembolic and haemorrhagic prediction scores can aid physicians balance the risk-benefit ratio for anticoagulation in specific patients. Patient's inclinations should also always be taken into account [10]. Several medical conditions are known to escalate bleeding risk during VKA therapy, including hypertension, diabetes, serious heart disease cerebrovascular disease, ischemic stroke, renal insufficiency, alcoholism and liver disease [11]. Many of these conditions have a greater occurrence among elderly patients, and should be taken into account while assessing risk-benefit ratio of oral anticoagulation.

Elderly patients also display amplified pharmacodynamics response to VKAs for numerous reasons: they might have reduced synthesis of clotting factors due to liver disease; their dietary vitamin K consumption (contained mainly in leafy green vegetables) may be low, the level of vitamin K produced by intestinal bacteria may be reduced by broad-spectrum antibiotics; concomitant use of drugs interacting with platelet function plus nonsteroidal anti-inflammatory drugs (NSAIDs) or aspirin is more frequent and raises bleeding risk; hypermetabolic states such as fever (perhaps through increased catabolism of vitamin K-dependant clotting factors) may increase

response to VKAs (Like warfarin & Acenocoumarol) in larger extent in frail elderly patients with poor vitamin K storage [12,13].

In trying to start and sustain safe and stable anticoagulation with VKAs (Acenocoumarol) in the elderly, physicians should be mindful of increased response to warfarin in this age group. Moreover, physicians and patients should keep in mind potential key effects of dietary changes and drug interactions (even over-the-counter and herbal medicines) on anticoagulation intensity. INR should be meticulously monitored each time changes occur in dietary habits or concomitant medications [13].

Ideally, patient education about oral anticoagulation should be part of the therapy similar to how diabetic patients are managed. Indeed, Kagansky et al. identified that poor quality of education was a major risk factor for anticoagulation-associated bleeding problems in the elderly.

Conclusion

Patients who require anticoagulation therapy should not be denied such therapy because of age. Always assess the risk/benefit ratio for the patients. Check renal and liver function to minimize the effect of the reduction of VKAs clearance that occurs because of ageing. Whenever required start with low dosage of VKAs (Acenocoumarol) and frequent monitoring is recommended.

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