Acenocoumarol: A Review of Anticoagulant Efficacy and Safety

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Abstract

Anticoagulant treatment is required for the treatment and prevention of thromboembolic disorders. Vitamin K antagonists are commonly used oral anticoagulants worldwide. Acenocoumarol is mono-coumarin derivative with racemic mixture of R (+) and S (-) enantiomers. Efficacy and safety of acenocoumarol has been evaluated in atrial fibrillation, cardiac valve replacement, after myocardial infarction, treatment of deep vein thrombosis, after major surgeries and after critical illness requiring prolonged hospitalization. Acenocoumarol is effective and safe in all age groups. It offers an advantage over warfarin in terms of better stability of anti-coagulant effect. Due to its economic advantage acenocoumarol may be suitable oral anticoagulant for long term use in countries like India.

Introduction

Anticoagulant treatment is indicated for the treatment and prevention of recurrent thromboembolic disorders.¹ Vitamin K antagonists are widely used oral anticoagulants worldwide.²,³ Vitamin K antagonists act by inhibition of vitamin K epoxide reductase and are often used for long-term anticoagulation.³ The benefits of oral anticoagulants have been clearly established in well-designed clinical trials. Coumarin preparations are commonly used vitamin K antagonists in clinical practice.⁴ Warfarin, phenprocoumon and acenocoumarol, the mono-coumarin derivatives are racemic mixtures of R (+) and S (-) enantiomers.

Acenocoumarol is structurally different from warfarin. The difference is characterized by nitro group in para position of the phenyl ring (Figure 1). (R+) acenocoumarol is more potent anticoagulant compared to S (-) acenocoumarol.⁵

Acenocoumarol inhibits 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 mechanism of action of acenocoumarol is depicted in Figure 2.

Pharmacokinetics

Acenocoumarol is rapidly absorbed from the gastrointestinal tract resulting in peak concentration (Cmax) of 0.3 (±0.05) mcg/ml in 2-3 hours. Acenocoumarol is highly bound to serum proteins; only 1.52% is free in the plasma. The mean %AUC and half-life of acenocoumarol are 3.9 (±0.7) mcg ml/hr and 10.9 (±1.5) hours respectively. After the oral administration, maximum effect of rise in prothrombin time is seen between 24-30 hours.⁶ The CYP2C9 isoenzyme is most important enzyme for the clearance of warfarin while its role in acenocoumarol clearance is less.³ Acenocoumarol is excreted rapidly.⁷

A comparative study (n=103) showed that warfarin does not provide better performance than acenocoumarol in terms of PT level within therapeutic range (62% vs 59%; p=0.4).⁸ Acenocoumarol has been criticized for risk of factor VII fluctuations because of shorter half-life. The study conducted by Barcellona and colleagues has clearly shown that it is not true. The results revealed higher factor VII levels with both drugs 24 hours after administration compared to 16 hours after administration.

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Fig. 2: Mechanism of action of acenocoumarol

Intake of vitamin K affects the level of factor VII rather than the half-life of drug.\(^8\)

Warfarin’s longer half-life of approximately 36 hours theoretically would provide more stable anticoagulation.\(^8\) Despite the short half-life pharmacodynamic activity of acenocoumarol is stable after achieving the steady state. The results of a clinical trial among hospitalized patients with deep-vein thrombosis, who received either daily dose or twice daily doses, demonstrated that acenocoumarol can be administered once daily. Twice-daily use is not required.\(^9\)

**Dose**

A cenocoumarol is usually administered as once daily oral dose\(^1\) given at the same time every day. Because of differing sensitivity to anticoagulant effect, regular testing of prothrombin time (PT)/ international normalized ratio (INR) is required to adjust the dosage. In settings of unavailability of such facility, use of acenocoumarol should be avoided. In adult patients, with normal thromboplastin time, acenocoumarol should be given 4 mg per day. If the patient is on heparin, dose may be reduced. Loading dose is not required if the PT/INR values are normal. On the second day, acenocoumarol dose ranges between 4-8 mg. Therapy should be started carefully, if initial thromboplastin time is abnormal. Older patients or malnourished people may need lower dose. The maintenance dose (usually 1-8 mg/day) should be determined on regular laboratory parameters and adjusted based on INR estimations.

Tapering of dosage is generally not required during withdrawal; however, some high risk patients may need gradual lowering of the dose.\(^10\)

In children with mechanical heart valves, acenocoumarol has been given initially in oral doses of 0.7-2 milligrams daily (average 1.5 milligram/day) in combination with aspirin 150 to 500 milligrams daily (average 250 milligrams/day) started on the third day of surgery. Subsequent dose adjustments are done based on prothrombin time ratio and activated partial thromboplastin time.\(^11\)

If INR is less than 1.3, 1 mg per day should be added while for level between 1.4-2, dose of 0.5 mg should be added. Dose can be maintained if INR falls between 2.1-3.0. If INR ranges between 3.1-3.5 and 3.6-4, then dose should be reduced by 0.5 mg and 1 mg per day respectively. INR should be repeated after one week in all cases if the dose is altered. If INR crosses 4, then drug should be temporarily discontinued for three days and if remains above 4, then drug should be stopped.\(^3\)

For most of the conditions the INR target is 2-3 while post-myocardial infarction patients may need INR between 3.0 to 4.0.

Based on the genotyping of polymorphisms specific algorithm has also been proposed for more accurate acenocoumarol dosage prediction.\(^12\)

**Contraindications**

A cenocoumarol should not be used in severe renal or hepatic impairment. It should be carefully used in mild to moderate impairment. A cenocoumarol should not be used in pregnancy, hypersensitivity to acenocoumarol/ excipients or coumarin derivatives, and conditions where the risk of haemorrhage is more than the potential benefit.\(^10\)

**Warnings and Precautions for Use**

Missed dose of acenocoumarol should be taken as early as possible on the same day; but should not be doubled to make up the missed dose. Sometimes quick anticoagulation is required and in such cases heparin should be preferably used while acenocoumarol may be started simultaneously or afterwards. Normal dose of heparin should be given for minimum four days after starting acenocoumarol. Heparin should be continued till INR is in the target level for minimum two days. While stopping heparin, close monitoring of coagulation profile is recommended. During major surgery or other procedure where there is risk of bleeding, close supervision of coagulation status is required. Minor surgical procedures where local hemostatic precautions and treatment is possible can be done without high risk of bleeding. Risks and benefits should always be considered while stopping the therapy or using other anticoagulant treatment. Careful monitoring with repeated
Acenocoumarol has rapid onset of action\(^7,13\) while the effect lasts for 15 to 20 hours. Acenocoumarol causes therapeutic hypoprothrombinemia in most patients after about 36 hours of initial dose and almost all patients in ≤48 hours. The average maintenance daily dose of acenocoumarol is 5.9 mg.\(^7\)

### Efficacy and Safety

**Efficacy and safety of acenocoumarol** has been studied in wide conditions requiring prevention and treatment of thromboembolism including atrial fibrillation,\(^14-16\) cardiac valve replacement,\(^17\) after myocardial infarction,\(^7\) prophylaxis of deep vein thrombosis after major surgeries,\(^18,19\) and after critical illness leading to prolonged hospitalization.\(^3\) The data related to cardiac indications for use of acenocoumarol after acute myocardial infarction (MI),\(^20\) chronic heart failure,\(^21\) atrial fibrillation,\(^14-16\) stenting after cardiac bypass surgery\(^22\) and cardiac valve replacement\(^17\) is briefly discussed here.

**After Acute Myocardial Infarction**

A randomized, multicentre, double-blind study\(^23\) has shown that in selected elderly patients (n=878), long term oral anticoagulant therapy after myocardial infarction significantly reduces the risk of recurrent myocardial infarction and cardiac death. In elderly patients on anticoagulants after primary myocardial infarction were randomized to receive treatment with placebo or continuation of the anticoagulant treatment for two years. The total two year mortality (7.6% vs 13.4%; \(p = 0.017\)) and incidence of recurrent myocardial infarction (5.7% vs 15.9%; \(p = 0.0001\)) was significantly less with oral anticoagulant therapy compared to placebo. The rate of intracranial event was less with anticoagulant, but not statistically significant (5.6% vs 3.1%; \(p = 0.18\)). There were no fatal extracranial haemorrhages (5.6% vs 3.1%; \(p = 0.18\)).

Acenocoumarol therapy started early i.e. preferably within five weeks after acute MI is significantly effective in resolution of left ventricular thrombus. Two-dimensional echocardiography assessed the effects of acenocoumarol on left ventricular thrombosis after acute MI. A total of 38 post MI patients with left ventricular thrombi were treated with either acenocoumarol (n=19) and results were compared with 19 non-treated patients. At 15 days and one year post treatment (n=17) thrombus was completely resolved in 52.9% and 88.2% patients respectively. In control group only two patients had resolution of thrombus at 15 days and four at one year. Reduction in thrombus size was seen in another four patients in control group. However, thrombus was unchanged in 52.9% patients in control group (Figure 3).\(^20\)

The size of thrombi in patients treated with acenocoumarol also reduced consistently during follow up.

**Long-term anticoagulant therapy** can reduce mortality rate in chronic heart failure (CHF). Patient who did not receive anticoagulant or antiplatelet therapy (n=150) had an annual death rate of 4% compared to 1.2% in patients who received acenocoumarol (n=75) or aspirin (n=250), indicating reduced mortality rate in patients with CHF class III-IV NYHA with anticoagulant or antiplatelet therapy.\(^21\)

### Atrial Fibrillation

Antithrombotic prophylaxis is essential in patients with atrial fibrillation at risk of developing cerebral stroke.\(^14\) It has been documented that prolonged oral anticoagulation with proper control of INR significantly reduces the risk of cerebral stroke.\(^24\) However outcome also depends on the patient’s cooperation, an important parameter in long term oral antithrombotic therapy.\(^14\)

In patients with atrial fibrillation acenocoumarol therapy should be preferred over aspirin (dose to provide maximal inhibition of platelet function) considering its benefits. One year follow of patients showed acenocoumarol lowers D-dimer and prevents and improves the breakdown of left auricular thrombus formation. It also lowers the risk of ischemic stroke and thromboembolism. On the other hand, aspirin does not reduce D-dimer levels, or promote breakdown of left auricular thrombi. Aacenocoumarol is superior to aspirin in prevention of ischemic stroke.\(^25\)

### Non-valvular Atrial Fibrillation

Nonvalvular atrial fibrillation is another indication for long-term oral anticoagulation treatment because of high risk for thromboembolic complications. A randomized trial (n=117) showed average INR values with both warfarin and acenocoumarol in the therapeutic (2-3) range [2.12 (±0.61) and 2.26 (±0.79) respectively] with average total weekly dose of 27.89 (±12.34) and 20.44 (±9.94) mg respectively.\(^15\)

Kulo and colleagues evaluated the treatment quality between warfarin and acenocoumarol in patients with nonvalvular atrial fibrillation in a one year study. In both groups, all average monthly INR values were within therapeutic

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**Fig. 3: Comparative response (complete resolution of thrombus) post MI**
Vein Thrombosis Prophylaxis and Treatment of Deep

After Cardiac Valve Replacement

Strict anticoagulation therapy is essential for maintaining patency of graft after stent implantation as shown by analysis of 46 stents (n= 24) in 35 lesions. In these patients activated partial thromboplastin time was maintained at 2-3 times control level by giving intravenous heparin till thrombostest values were reduced 5-10% by using acenocoumarol. Adequate anticoagulation was observed in all except two patients who were successfully treated with coronary artery bypass grafting.22

After Cardiac Valve Replacement

In patients with cardiac valve replacement acenocoumarol plus aspirin (330 mg) and dipyridamole (75 mg) twice daily INR of 2-3 is safer and also provides good protection against thromboembolism compared to INR of 3-4.5.17

Prophylaxis and Treatment of Deep Vein Thrombosis

A total of 101 patients undergoing total hip replacement were studied in a prospective study. The patients were randomized to receive treatment with either of the two regimens; acenocoumarol 3 mg once day started four days before surgery or on the day of the surgery; Acenocoumarol 3 mg was started on preoperatively with dose adjustment to yield an INR of 1.5-1.6 during surgery and thereafter 2.1. There was no difference between two groups in the incidence of proximal localized deep venous thrombosis (11/51 vs 12/50). No cases of postoperative hemorrhagic complications or fatal pulmonaryembolism occurred during the study.18

In another study patients with more than 40 years of age undergoing major gynaecological surgery (n=145) were randomized to receive acenocoumarol stabilized over five days before operation and continued during second postoperative week (n=48), subcutaneous low-dose heparin (n=49) or subcutaneous saline (n=48). The incidence of DVT evaluated by 125I-fibrinogen scanning was almost similar to heparin (Figure 6). The incidence of haemorrhage was similar in all groups.19

A small study from India evaluated the safety and efficacy of acenocoumarol in DVT prophylaxis among 39 critically ill patients who were treated with low molecular weight heparin and acenocoumarol 2 mg for five days. The dose was adjusted to maintain INR of 2-3. Once therapeutic level of INR was achieved, heparin was stopped and only acenocoumarol was continued. These patients needed prolonged mechanical ventilation with mean duration of 38.57 (±9.23) days. During the mean duration of intensive care unit (ICU) stay of 47.73 (±16.22) days. During ICU stay or three months after, no patient developed complication related to acenocoumarol treatment. No patient developed deep vein thrombosis during ICU stay as evaluated by symptoms or Doppler. The cost of acenocoumarol including the cost of INR monitoring was only 330 Indian rupees for thirty day therapy. Acenocoumarol can be a good alternative for prevention of DVT in critically ill patients.1

Treatment of Symptomatic Venous Thromboembolism

A randomized, comparative study among 4289 patients with symptomatic venous thromboembolism who received three month treatment with one of the four oral anticoagulants (warfarin, acenocoumarol, phenprocoumon or fluindione) started within 72 hours of episode with dose adjustment to achieve a target INR of 2.0-3.0 showed lower incidence of recurrent venous thromboembolism with acenocoumarol compared to warfarin (2.5% vs 4.6%) with similar safety.26 Warfarin resistance defined as dose requirements of >70 mg weekly to maintain target INR level could be another indication for use of acenocoumarol. At the moment, this indication is not studied in well designed clinical trials, but found useful in a case report.27

Long Term Use

A Spanish study documented ten year experience with use of acenocoumarol in ambulatory patients. The most common indication for the use of acenocoumarol in this cohort was atrial fibrillation. A total of 73% patients received acenocoumarol for atrial fibrillation. Analysis of 1,086 patients with median age of 74 years receiving acenocoumarol showed INR in the therapeutic range (2.0-3.0) in 82.5% patients. Overall bleeding rate (2.27/100 patients-year) and thrombotic event rate was low (0.2/100 patients-year) was
low. Acenocoumarol can be safely used in elderly. The analysis of Spanish cohort showed age and is not associated with higher risk of bleeding. 28

Cost is a concern for long term therapy with any disease especially in countries like India. Acenocoumarol can be an economic option for long term anti-coagulant therapy. According to an Indian study, the cost of acenocoumarol including the cost of INR monitoring is about 330 Indian rupees for one month. 1

Acenocoumarol in Children

Anticoagulant treatment with acenocoumarol is not difficult even in children. Woods A et al reported long term experience of acenocoumarol plus aspirin in 31 children (5 months-16 years) with cardiac valve replacement (mitral n=20; aortic and mitral-aortic n=4 each; tricuspid n=3) followed up for 1336 months. With adequate anticoagulation, the embolism was seen in 0.74/1000 patient-months. Close to 94% patients did not have thromboembolism up to 96 months of follow-up. The incidence of minor and major haemorrhage was 1.49/1000 and 0.74/1000 patient-months. 11

Superior Anticoagulant Stability with Acenocoumarol

In the SPORTIF-III substudy acenocoumarol was compared with warfarin (W) in 74 patients with chronic atrial fibrillation. Treatment was started with warfarin and changed to acenocoumarol. The patients were followed for three months on warfarin and acenocoumarol each. The percentage of patients with INR in therapeutic range (2-3) was significantly higher with acenocoumarol compared to warfarin (56 ±26.8% vs 49 ±22.6%; p < 0.05) while supratherapeutic values occurred more commonly on warfarin compared with acenocoumarol (28± 20% vs 19± 19%; p<0.001). 29

Conversion Factor for Dose from Warfarin to Acenocoumarol

The SPORTIF-III substudy has shown a good correlation between doses of warfarin and acenocoumarol. The dose ration of warfarin to acenocoumarol is 2.18±0.78. 29

In another study the transition factor between acenocoumarol and warfarin is shown to be 1.85. The transition factor helps to calculate the maintenance dose when patient is required to be switch from acenocoumarol to warfarin. 2

Comparison of Acenocoumarol with Warfarin

The differential features of acenocoumarol with warfarin are given in table 1.

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<td><strong>Acenocoumarol</strong></td>
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Acenocoumarol monograph has been described in the Indian Pharmacopoeia. 33 Various strengths of acenocoumarol tablets from 0.5-6 mg are available in India for prophylaxis and treatment of thromboembolic disorders.

Overall Advantages

1. Rapid onset of action. 7,13
2. The effect lasts for 15-20-hours. 7
3. Less dependence on CYP2C9 for metabolism. 3
4. Better anticoagulation stability than warfarin. 16,29
5. Rapid reversal of anticoagulant action with relatively small amounts of vitamin K1. 7

Adverse Events

The most serious complication with oral anticoagulation is bleeding. An Italian study involving 2745 patients (warfarin 64%, acenocoumarol 36%) with follow up of 267 days had bleeding complication rate of 7.6 per 100 patient-years of which 0.25 per 100 patient-years were fatal. These results show that oral anticoagulation is safer with proper monitoring. 34

Acenocoumarol is well tolerated when given orally. The risk of bleeding is significantly high in patients with INR more than five. The risk of bleeding could be higher in patients with mechanical prostheses and
drug interaction. The other risk factors for bleeding are history of intercurrent disease in the last month, and non-compliance.²

Cases of hematuria have been reported when acenocoumarol was used for acute myocardial infarction which resolved after vitamin K administration.⁷

Coumarin preparations cause overall similar haemorrhagic complications in older or younger age.⁴ The challenges for the use of vitamin K antagonists include narrow therapeutic index and unpredictable dose-response pattern.⁵ Vitamin K, given orally can antagonise effect of acenocoumarol within three to five hours and may be required in case of moderate to severe haemorrhage. Higher dose of vitamin K, (usually more than 5 mg) can lead to resistance to anticoagulant effects. In life-threatening haemorrhagic conditions, intravenous blood transfusion or recombinant factor VIIa may also be required.¹⁰

Summary

Anticoagulation is indicated for the treatment and prevention of various recurrent thromboembolic disorders including atrial fibrillation, after cardiac valve replacement and for prophylaxis of DVT in critically ill patients. Acenocoumarol is a good alternative for long term anticoagulation because of its rapid onset of action and long duration of action. Despite short half-life acenocoumarol provides stable anticoagulant effect. Its long term safety has been well established. Vitamin K, in small dosage when used to counter the effect provides results in few hours.

References

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