Cardiovascular Pharmacology: Open Access

Trailokya, Cardiovasc Pharm Open Access 2015, 4:4
DOI: 10.4172/2329-6607.1000157

Review Article Open Access

Acenocoumarol in Thromboembolic Disorders

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Abstract

Thromboembolic disorders are common worldwide, frequently a leading cause of death. Judicial use of Anticoagulant plays an important role in the prevention and treatment of Venous and arterial thromboembolic diseases like deep vein thrombosis, pulmonary embolism, Stroke prevention in valvular and Non-valvular heart disease, and Acute coronary syndrome. Vitamin K antagonists, e.g., acenocoumerol and warfarin are commonly used as oral anticoagulants worldwide. The clinical use of oral anticoagulants has come a long way since their discovery over 50 years ago and Acenocoumarol is a coumarin derivative with pharmacological features closer to an ideal oral anticoagulant. Acenocoumarol is a drug with over 50 years of clinical experience and has been the subject of numerous clinical studies Acenocoumarol is prescribed once every day orally, as the anticoagulant is applied in various thromboembolic disorders. Amongst the coumarone, acenocoumarol is unique, with its rapid onset and offset of action and well documented efficacy and safety. Acenocoumarol has been shown to be superior to warfarin in maintaining INR stability within therapeutic range and efficacy. Despite the development of several new oral anticoagulants, coumarin anticoagulants remained unchallenged. Their efficacy has been established beyond doubt and they have long years of clinical experience. Forever 50 years since its discovery, acenocoumarol still continues to be widely used in India and various parts of the world.

Keywords: Thromboembolic disorders; Acenocoumarol; PT/INR; Oral anticoagulant; VKA

Introduction

Venous and arterial thromboembolic diseases are still the most frequent cause of death and disability in high-income countries, and their incidence is dramatically increasing also in middle- and low income countries [1]. Anticoagulant treatment has been cornerstone in preventing various thromboembolic disorders like deep vein thrombosis, pulmonary embolism, Stroke prevention in valvular and Non valvular heart disease, and Acute coronary syndrome.

Venous Thromboembolism (VTE) is potentially a fatal disease, consisting of Deep Vein Thrombosis (DVT) and Pulmonary Embolism (PE). DVT and PE are life threatening complications that involve major surgery and medication, leading to prolonged immobility. Venous thrombosis is common among more than 50% of patients that undergo surgical procedures, particularly those involving the hip and knee and 10% to 40% of patients that undergo abdominal or thoracic operations [2]. DVT occurs less frequently in the upper extremity than in the lower and the initial aim of treatment of DVT is to prevent thrombus extension and PE. The need for a systemic thromboprophylax is necessary for the surgical patients based on the high prevalence of postoperative DVT and PE. Frequent presentation of VTE has the potentiality to develop major adverse events. Clinical efficacy studies with acenocoumarol have shown the drug to be effective in the prophylaxis of DVT.

Atrial fibrillation (AF) is one of the most commonly encountered tachyarrhythmia in clinical practice, and affects 5% of people older than 65 years and nearly 10% of those over 80 years of age [3]. AF contributes to substantial morbidity and mortality due to stroke, thromboembolism, and heart failure, adversely affecting the quality of life. It is a condition of clinical and economic importance to an increasing number of aging populations. Patients with atrial fibrillation and valvular heart disease have a substantial risk of stroke and other thromboembolic events. AF increases the risk of stroke from four to five folds across all age the groups, accounting for 10–15% of all ischaemic strokes, in people aged more than 80 years [3]. Mitral valve stenosis is a substantial risk causing stroke and thromboembolism. In 9–20% of patients, of which 75% may develop cerebral emboli [3]. The risk of thromboembolism is increased by 3–7 times in patients with mitral stenosis in sinus rhythm with atrial fibrillation [3]. Presence of atrial fibrillation without any valve disease may increase the risk of stroke and thromboembolism by five times [3]. Large randomised trials have established the value of antithrombotic treatment for non-valvular atrial fibrillation. However, anticoagulation remains generally underused in clinical practices [3]. Recent observations have showed that only 56.5% of patients that are taking anticoagulants are at very high risk of stroke in the community and a large proportion of patients affected with atrial fibrillation remained untreated [3].

Coagulation and Antithrombotic Prophylaxis

Vitamin K1 is essential for normal blood coagulation. Coagulation factors II, VII, IX and X and the anticoagulant proteins C and S are synthesized mainly in the liver and are biologically inactive unless 9 to 13 of the γ-amino-terminal glutamate residues are carboxylated to form Ca^{2+}- binding γ-carboxyglutamate residues. With the carboxylation of the protein precursors, the reduced vitamin cofactor is converted into vitamin K 2,3-epoxide, converted into Vitamin K epoxide reductase, which along with the postulated enzyme vitamin K quinone reductase, are highly sensitive to inhibition by coumarin drugs. Vitamin K1 must be regenerated from the biologically inactive epoxide by vitamin K1 epoxide reductase for the continued synthesis of activated clotting factors, Acenocoumarol and the coumarin anticoagulants are structurally similar to vitamin K and are competitively able to inhibit the enzyme vitamin K-epoxide reductase. These drugs exert

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Received August 26, 2015; **Accepted** September 22, 2015; **Published** October 05, 2015

Citation: Trailokya A (2015) Acenocoumarol in Thromoembolic Disorders. Cardiovasc Pharm Open Access 4: 157. doi:10.4172/2329-6607.1000157

their anticoagulant action by preventing the regeneration of reduced vitamin K by interfering with action of vitamin K epoxide reductase. Coumarins are irreversible inhibitors of these enzymes and it is believed that this inhibition is responsible for their anticoagulant effect [4]. Antithrombotic prophylaxis is essential for patients with atrial fibrillation at the risk of cerebral stroke. Introduction and monitoring of prolonged anticoagulation may be considered more important for the patients than taking a decision about the conversion of atrial fibrillation to a normal sinus rhythm [5]. Prolonged oral anticoagulation with proper INR control decreases the risk of a cerebral stroke by 2/3 times and prevents the permanent disability among patients with atrial fibrillation. Vitamin K antagonists acenocoumarol, phenprocoumon and warfarin reduces the risk of stroke by more than 60% in patients with nonvalvular atrial fibrillation oral anticoagulation .However, single or double antiplatelet therapy is much less effective and sometimes associated with a similar bleeding risk as vitamin K antagonists [6].

Discovery of Coumarin Anticoagulants

In 1921, an epidemic of serious hemorrhagic diathesis of cattle was reported in North Dakota, USA. In 1924, Frank Schofield found that cattle bled only when they were fed mouldy sweet clover. The hemorrhagic disease, known as 'sweet clover disease', became manifested within 15 days of ingestion and killed the animal within 30–50 days. The disease could be reversed if the mouldy hay was removed or if fresh blood was transfused. I In 1940 Karl Link identified the active principle that caused the sweet clover disease – coumarins (3,3'-methylene-bis[4-hydroxycoumarin]). The natural coumarin was found to get oxidized in mouldy hay, to form the substance that later became better known as dicoumarol [7].

In 1945, Karl Link proposed the use of dicoumarol as a rodenticide to prevent the death of cattle due to internal hemorrhage. However, dicoumarol proved to be too slow. Further research in this field has led to the development of warfarin, which was promoted as ratpoison by 1948 [8,9].

In 1941, the Mayo Clinic reported the successful use of the dicoumarol for first time in the prophylaxis of deep vein thrombosis, following surgery. President Eisenhower received warfarin following a myocardial infarction in 1955.Thus, a substance that was hitherto used as a rat poison became a clinical medicine in the prevention and treatment of thromboembolic disorders [8,9].

Following the introduction of dicoumarol in 1943, efforts were in the development of a perfect anticoagulant. Stoll and Litvan (Ciba Geigy developed the "Nicoumalone" (acenocoumarol) by 1953 was an effort in this direction, and a drug that is rapid-acting but not very long-acting came into clinical usage in the form of Acenocoumarol in Europe (1955) and USA (1956). Since then, acenocoumarol is widely used in the prevention and treatment of thromboembolic disorders worldwide [10,11].

Acenocoumarol monograph is described in the Indian Pharmacopoeia and the Regulatory authorities have approved the manufacturing of acenocoumarol tablets ranging from 0.5 mg up to 6 mg is to be marketed in India for the prophylaxis and management of thromboembolic disorders [12].

Oral Vitamin K Antagonists

Vitamin K antagonists (VKA) include various substances that include acenocoumarol with a short half-life, warfarin with intermediate life and phenprocoumon with long life. VKA blocks the synthesis of four plasma coagulation factors (prothrombin or factor II, FII, FVII, FIX, and FX) by the liver. Appropriately stable level of anticoagulation cannot be reached before 4 to 7 days due to the relatively long half-life of circulating factors [13]. Vitamin K antagonists of the coumarin type are widely used as oral anticoagulants. Though ifferent coumarin derivatives available worldwide, warfarin, acenocoumarol and phenprocoumon are the most frequently used [8]. Acenocoumarol is frequently used in many European countries [14].Close monitoring of VKA treatment is necessary as it is complicated due to factors like genetically induced metabolic variability, influence of vitamin K content on food, and the narrow therapeutic window [7]. Standardised monitoring of the therapeutic level corresponds to an INR between 2 and 3. There is a risk of thromboembolic recurrence in Below INR 2.0, and above INR 3.0, as there is a very high risk of bleeding is evident.

Five Cs of anticoagulation – complications, compliance, confidence, convenience and cost plays an important role in the anticoagulation management.

Acenocoumarol/nicoumalone

Nicoumalone is the earliest name given as per the BAN (British Approved Name) and it is uttered at present as Acenocoumarol as per the recommendations of rINN (recommended International Non-Proprietary Name). Acenocoumarol's rapid onset of action within15- to 20-hour duration of effect is great advantages in its clinical use. In a clinical study, at the end of 43 hours, 94 per cent of patients receiving acenocoumarol were in the therapeutic range [15]. The drug was found to be well tolerated when administered orally. Data suggests that it will induce a therapeutic prothrombin level in most of the patients in 36 hours after the initial dose. Its therapeutic effect can be easily maintained if it is given as a single dose daily. It is rapidly excreted and the elimination of 1 dose usually results in a prompt return of the prothrombin to normalicy. Vitamin K1 in relatively small dosage counteracts its effect within a few hours. The dosage is relatively constant in a given patient but, as with all anticoagulants, may vary with changes in the clinical condition of the patient. The dose required to maintain the therapeutic level varies greatly from patient to patient. Limited experience suggests that it is an ideal anticoagulant than any of the commonly used coumarin derivatives [9].

Pharmacokinetics of acenocoumarol

Absorption: Following the oral administration, acenocoumarol is rapidly absorbed; at least 60% of the administered dose is systemically available. Peak plasma concentrations are achieved within 1 to 3 hours after a single dose of 10 mg and AUC values are proportional to the size of the dose with a dosage range of 8 to 16 mg. Correlation between plasma concentrations of acenocoumarol and apparent prothombin levels cannot be established due to the variation of plasma drug concentrations between patients Plasma drug concentrations are generally higher among patients of 70 years and above when compared to the younger patients.

Distribution: Over 98% of acenocoumarol is protein-bound, mainly to albumin. The calculated apparent volume of distribution is 0.16-0.18 L/kg for the R(+) enantiomer and 0.22-0.34 L/kg for the S(-) enantiomer.

Metabolism: Acenocoumarol is extensively metabolised, although the metabolites appear to be pharmacologically inactive in man.

Elimination: The elimination of half-life of the acenocoumarol from the plasma is 8 to 11 hours. 29% of the drug is excreted in the form of faeces and 60% in urine [16].

Dose and administration

First day: Acenocoumarol should be given as a single oral dose at a particular time every day. Because of the differing sensitivity to anticoagulant effect in people, regular testing of prothrombin time (PT)/INR is required to adjust the dosage without which Acenocoumarol should not be used.

Adults

Initial dosage: If the thromboplastin is within the normal range at the time of initial treatment, the starting dose should be 4 mg/day (lower doses may be required if patients are receiving heparin).

The administration of a loading dose may not be necessary if the PT/INR value is within the therapeutic range at the time when treatment begins.

Second day: 4 to 8 mg

If the initial thromboplastic time is abnormal, treatment should be instituted with caution.

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

Maintenance therapy: The maintenance dose of Acenocoumarol varies from patient to patient and must be determined on the basis of regular laboratory estimations of the patient's blood coagulation time.

Adjustment of the maintenance dose can only be made by monitoring the Quick value of the international normalised ratio (INR) at regular intervals, ensuring that the dosage remains within the therapeutic range. Depending on the individual, the maintenance dose generally lies between 1 to 8 mg daily (Table 1)

Treatment discontinuation: Generally, there is no danger of reactive hypercoagulability after the withdrawal of acenocoumerol, and therefore it is not necessary to give gradual diminishing doses. However, in extremely rare cases, in some high risk patients (e.g., after myocardial infarction), withdrawal should be gradual.

Missed dose: The anticoagulant effect of acenocoumerol persists beyond 24 hours. If the patient forgets to take the prescribed dose of acenocoumerol at the scheduled time, the dose should be taken as soon as possible on the same day. The patient should not take the missed dose by doubling the daily dose to make up the loss and they should follow doctor's advice in this regard for further action [15].

Special populations

Renal impairment: Acenocoumerol is not recommended for the patients with severe renal impairment due to increased risk of haemorrhage. Caution should be exercised in patients with mild to moderate renal impairment

Hepatic impairment: Acenocoumerol is not recommended for the suffering patients suffering from severe hepatic impairment due to increased risk of haemorrhage. Caution should be exercised in patients with mild to moderate hepatic impairment.

Heart failure: In severe heart failure, a very cautious dosage schedule must be adopted, as hepatic congestion may reduce the activation of gamma-carboxylation of coagulation factors. However with reversal of the hepatic congestion, it may be necessary to raise the dosage.

Haematological: Caution should be exercised for the patients with known or suspected (e.g., abnormal bleeding after injury) protein C or protein S deficiency.

Special populations: In paediatric and elderly patients (≥ 65 years), caution and more frequent monitoring of prothrombin time and INR is recommended.

Miscellaneous: Strict medical supervision should be there for the cases where the disease or condition may reduce the protein binding of Acenocoumerol (e.g., thyrotoxicosis, tumours, renal disease, infections and inflammation).Disorders affecting gastro-intestinal absorption may alter the anticoagulant activity of Acenocoumerol. During treatment with anticoagulants, intramuscular injections may cause haematomas and should be avoided. Subcutaneous and intravenous injections may be given without such complications. Meticulous care should be taken where it is necessary to shorten the PT/INR (thromboplastin time) for diagnostic or therapeutic procedures (e.g., angiography, lumbar puncture, minor surgery, tooth extractions etc.).

Conversion from heparin therapy: In clinical situations which require rapid anticoagulation, initial treatment with heparin is preferred since the anticoagulant effect of Acenocoumarol is delayed. Conversion to Acenocoumarol may begin concomitantly with heparin therapy or may be delayed depending on the clinical situation. To ensure continuous anticoagulation, it is advisable to prescribe the full dose heparin therapy for at least 4 days after initiation of Acenocoumarol and to continue heparin therapy until the INR has been in the target range on at least two consecutive days. During the transition phase close monitoring of anticoagulation is necessary.

Treatment during dentistry and surgery

Patients on Acenocoumarol that undergo surgical or invasive procedures require close surveillance of their coagulation status under certain conditions. For example, when the operation site is limited and accessible to permit effective use of local procedures for haemostasis, dental and minor surgical procedures may be performed during continued anticoagulation, without undue risk of haemorrhage. The decision to discontinue Acenocoumarol, even for a short period of time, should be considered by carefully analyzing the individual risks and benefits. The introduction of bridging anticoagulant treatment with heparin should be based on careful assessment of the expected risks of thromboembolism and bleeding.

Contraindications

Pregnancy

Patients that are unable to cope with the treatment due to Hypersensitivity to acenocoumarol and related coumarin derivatives or to the excipients of Acenocoumarol must be treated careful, unsupervised therapy is not advisable for patients that are affected due to dementia, alcoholics and patients with psychiatric disorders. All conditions where the risk of haemorrhage exceeds possible clinical benefit, e.g., haemorrhagic diathesis and/or haemorrhagic blood dyscrasia immediately prior to, or after surgery on the central nervous system or eyes and traumatising surgery involving extensive exposure of the tissues; peptic ulceration or haemorrhage in the gastro-intestinal tract, urogenital tract or respiratory system; cerebrovascular haemorrhages; acute pericarditis; pericardial effusion; infective endocarditis; severe hypertension (due to occult risks); severe hepatic impairment or severe renal impairment and in cases of increased

Indication	Recommended INR
Prophylaxis and treatment of venous thromboembolism (including pulmonary embolism)	2.0–3.0
Atrial fibrillation	2.0–3.0
Post-myocardial infarction (with increased risk for thromboembolic complications)	2.0–3.0
Bio-prosthetic heart valves	2.0–3.0
Secondary prophylaxis in patients with anti-phospholipid syndrome	2.0–3.0
Anti-phospholipid syndrome patients with venous thromboembolism on therapeutic vitamin K antagonist	2.0–3.5
Mechanical heart valves	2.0–3.5

Table 1: Recommended INR* for oral anti-coagulant therapy.

fibrinolytic activity following operations on the lung, prostate or uterus etc. must be considered after the careful assessment of the situation.

Interaction with other medicinal products and other forms of interaction

There are many possible interactions between coumarins and other drugs; we have mentioned those of clinical relevance below. Many of these are isolated reports only or have been reported with warfarin rather than acenocoumarol and we have included all of the sake of providing comprehensive information. The mechanisms of these interactions include disturbances of absorption, inhibition or induction of the metabolising enzyme system (mainly CYP2C9, and reduced availability of vitamin K1, necessary for gamma-carboxylation of prothrombin–complex factors. It is important to note that some drugs may interact by more than one mechanism. Every form of therapy may involve the risk of interaction, although not all of them would be significant. Thus careful surveillance is important and frequent coagulation tests (e.g., twice weekly) should be carried out when prescribing any drug initially in combination with Acenocoumarol, or while withdrawing a concomitantly administered drug.

Adverse events

Haemorrhage, in various organs, is the most common side-effect associated with Acenocoumarol; its occurrence is related to the dosage of the drug, the patient's age and the nature of the underlying disease (but not the duration of treatment). Possible sites of haemorrhage include the gastro-intestinal tract, brain, urogenital tract, uterus, liver, gall bladder and the eye. If haemorrhage occurs in a patient with a thromboplastin within the therapeutic range, diagnosis of such condition must be clarified.

Antidote: Vitamin K1 (phytomenadione) may antagonise the inhibitory effect of Acenocoumarol on hepatic gamma-carboxylation of the vitamin K-dependent coagulation factors within 3 to 5 hours. In cases of clinically insignificant haemorrhages, such as a brief nose-bleed or small isolated haematomas, a temporary reduction or omission of the dose of Acenocoumarol is often sufficient. In cases of moderate to severe haemorrhage, Vitamin K1 can be given orally.

Doses of Vitamin K1 in excess of 5mg can cause resistance to further anticoagulant therapy for several days. If an anticoagulant is required, heparin may be used temporarily, although oral anticoagulant therapy should be resumed at the same time and heparin withdrawn once the therapeutic range has been reached.

In the case of life-threatening haemorrhage, intravenous transfusions of fresh frozen plasma or whole blood, complex concentrate or recombinant factor VII must be supplemented with vitamin K1 can abolish the effects of Acenocoumarol.

Acenocoumarol should be resumed when INR is within the target range in case of moderate to severe haemorrhage (Table 2).

The favourable pharmacokinetic properties of acenocoumarol are as follows:

Acenocoumarol has a rapid onset of action, and the effect is maintained for 15-20 hours. Such properties offer great advantages to its clinical use. In most of the patients, it induces the therapeutic prothrombin level 36 hours after the initial dose. The anticoagulant effect of acenocoumarol can be counteracted within few hours with relatively smaller dose of vitamin K1.

Acenocoumarol offers several benefits over warfarin, such as: More rapid onset of action, shorter half-life, Offers better stability of prothrombin time, Rapid reversal of anticoagulant action, with relatively smaller dose of vitamin K1. Less dependence on CYP2C9 enzyme for metabolism [19].

Clinical Studies on Acenocoumarol

A study conducted by Swierstra BA et al. mentioned about a case study of 101 patients where acenocoumarol was administered prior to surgery and administered for 10 days for total hip replacement in both the groups. There were no postoperative haemorrhagic complications. No fatal pulmonary embolism occurred during the study. After discontinuation of the oral anticoagulants because of a negative venogram, nonfatal pulmonary embolism occurred in 3 out of 55 patients [20].

Azim A et al. conducted study among 39 neurological patients requiring prolonged mechanical ventilation underwent DVT probability risk assessment and received low molecular weight heparin along with acenocoumarol 2 mg/day for five days, followed by dosing adjustments until international normalized ratio (INR) of 2-3 was achieved. After achieving the INR, heparin was stopped and patients were maintained on acenocoumarol only. Therapy was monitored with INR, bleeding complications and lower limbs Doppler. None of the patient had any complication related to acenocoumarol therapy or any evidence of symptomatic or asymptomatic (Doppler) deep vein thrombosis during ICU stay or during follow-up of 3 months [21].

Rullo FR et al**.** was used Acenocoumarol to treat 100 hospitalized patients, with venous thromboembolism. The average initial dose of acenocoumarol was 21 mg. The average maintenance dose was 6.6 mg per day. The drug was rapidly effective and the prothrombin time was within the clinically practical range after 18 hours of dosing for over one-third of the patients. Side-effects were few; no gastrointestinal intolerance was seen, and only five patients had minor bleeding episodes [22].

Kulo A, Kusturica J et al. conducted a study among 120 patients with nonvalvular atrial fibrillation have included in two groups of 60 patients, composed according to warfarin/acenocoumarol treatment as well as the gender and age. Average monthly INR values were within the therapeutic range (2.0-3.0) in both groups. There were no significant differences either in the number of therapeutic INR values per patient or in individual quality of treatment in both groups. Significantly better

Properties	Warfarin	Acenocoumarol
Absorption	Rapid	Rapid
Bioavailability	99.4%	60%
Protein binding	Very high (99%)	Very high (98.7%)
Half-life	Distribution: 6–12 hours Elimination: 20–60 hours (mean 40 hours)	8–11 hours
Effect on PT	Within 24 hours	15–20 hours
Time to peak plasma concentration	4 hours	1–3 hours
Time to peak effect	72–96 hours	36–48 hours
Duration of action	2–5 days	48 hours
Elimination	Renal 92%	Renal 60% Faecal 29%
Preparations available	1 mg, 2 mg, 3 mg and 5 mg	0.5 mg, 1–4 mg tablets

Table 2: Comparison of acenocomerol with warfarin [17-19].

stability was determined for acenocoumarol as compared with warfarin treatment for longer period of the total observed time during which therapeutic INR values were stable (37.6% vs. 35.7%, P=0.0002) [23].

Conclusion

Anticoagulant treatment is indicated in various clinical conditions to treat and prevent the recurrent thromboembolic disorders. Vitamin K antagonists are widely used as oral anticoagulants worldwide. Acenocoumarol is a drug with over 50 years of clinical experience and has been the subject of numerous clinical studies Acenocoumarol used once daily as oral anticoagulant indicated in various thromboembolic disorders. Amongst the coumarins, acenocoumarol is unique, with its rapid onset and offset of action and have well documented efficacy and safety. Acenocoumarol has been shown to be superior to warfarin in maintaining INR stability within therapeutic range and in efficacy. Acenocoumarol monograph is described in the Indian Pharmacopoeia also. The regulatory authorities have approved manufacturing and marketing of acenocoumarol tablets ranging from 0.5 mg up to 6 mg is in India for prophylaxis and management of thromboembolic disorders. In the developing countries like India, acenocoumarol may be one of the most suitable oral anticoagulant drugs (VKA) for long term use because of its economic advantage.

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