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Novel Insights on Oral Anticoagulants in Clinical Practice

Focus on Acenocoumarol



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Oral Anticoagulants: From Discovery to Clinical Practice

K Damodara Rao Kodem, Mrinal K Das

INTRODUCTION TO ORAL ANTICOAGULANTS

Today there is a need for chronic anticoagulation therapy, due to the rising prevalence of atrial fibrillation (AF), artificial heart valves, and malignancy among the aging population. Anticoagulant treatment is indicated for the treatment and prevention of arterial and venous thromboembolic disorders, such as stroke, pulmonary embolism (PE), venous thromboembolism (VTE), and acute coronary syndrome. Patients with AF have a fivefold higher risk of stroke-related fatality or disability. Oral anticoagulants have been mainly indicated for stroke prevention in AF patients. There is also a significant need for anticoagulation therapy in patients undergoing orthopedic surgeries (hip or knee replacement), due to a higher risk of PE or VTE.[1]

In the past two decades, the interest in antithrombotic compounds with a distinct mode of action on the coagulation pathway has lead to the approval of anticoagulants such as low molecular weight heparins, indirect factor Xa inhibitors, and direct thrombin inhibitors. However, factors such as higher cost of therapy and the need for parenteral administration have resulted in oral vitamin K antagonists being the only alternative anticoagulant for patients requiring chronic anticoagulation therapy.[2] The commonly used vitamin K antagonists in clinical practice are coumarin preparations.[3]

In this chapter, we will discuss the history of coumarin derivatives: from their discovery to their use as anticoagulants in clinical practice.

Vitamin K antagonists are among the most commonly used anticoagulants in clinical practice.

HISTORY OF TWO DISCOVERIES THAT LED TO THE AVAILABILITY OF CLINICAL ANTICOAGULANTS

Two different lines of research in the 1920s and 1930s led to the discovery of vitamin K and its antagonists.[4]

Discovery of Vitamin K[5]

Between 1928 and 1930, unexpected symptoms of hemorrhage and delayed coagulation in chicks being reared for metabolic studies prompted Henrik Carl Peter Dam and his coworkers to further investigate the cause. During

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Henrik Carl Peter Dam


Edward Adelbert Doisy

the course of the investigation, they found that an unrecognized factor in the diet of the chicks was able to prevent hemorrhagic symptoms. In 1935, this factor was characterized as a new fat-soluble vitamin and designated vitamin K [the letter K stands for Koagulation (coagulation)]. Edward Adelbert Doisy elucidated the chemical structure of vitamin K over the next 10 years, and reported its method of synthesis.[4]

In 1943, Henrik Dam and Edward Doisy jointly won the Nobel Prize for their contributions to the understanding of blood clotting, especially the role of vitamin K.

Discovery of Coumarin Anticoagulants[6,7]

The Epidemic of Sweet Clover Disease

Between 1920 and 1922, the cattle population of the Canadian and North American prairies faced a fatal epidemic of generalized bleeding diathesis. The hemorrhagic disease that manifested within 15 days of ingestion of moldy sweet clover hay, and led to death within 30–50 days, was termed sweet clover disease. Frank W Schofield, a Canadian pathologist, proved that the causative


Frank W Schofield

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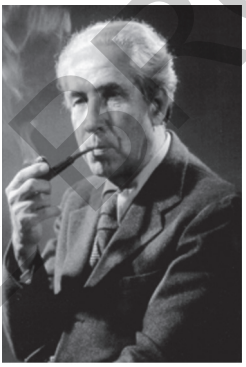
factor was a substance found in moldy sweet clover hay. He further proved that the disease condition was potentially reversible if the offending hay was removed from the diet or the animals transfused with fresh blood.

Isolation of Anticoagulant from the Rotten Clover

Between 1933 and 1939, Karl Paul Link and his colleagues attempted to isolate the anticoagulant present in the rotten clover. In 1939, they were finally able to crystallize the substance, which was proven to be dicoumarol [3,3′-methylene-bis(4-hydroxycoumarin)], a product formed due to the oxidation of naturally occurring coumarin in sweet clover. Consequently, they demonstrated that vitamin K could counter the anticoagulant action of dicoumarol.

From Test Tube to Rat Poison

In 1945, Link dwelled upon the idea of using the hemorrhagic property of a coumarin derivative as a rodenticide. The slow-acting characteristics of dicoumarol led Link and his colleagues to test several variations of naturally occurring coumarin in search of a fast-acting compound. Warfarin was the product of this effort, and was promoted as a rodenticide in 1948.[6]



Karl Paul Link

From Rat Poison to Clinical Use

The success of warfarin as a rodenticide, and its apparent advantages over heparin and dicoumarol, coupled with its high water solubility and oral bioavailability, supported its use in clinical conditions. Warfarin was not used frequently until 1955, when it was administered to President Dwight D Eisenhower following a myocardial infarction. This led to the widespread prescription of the drug.[6] Earlier in 1941, the Mayo Clinic had reported the successful use of dicoumarol in the prophylaxis of deep-vein thrombosis after surgery.[8]

This is the fascinating journey of coumarin anticoagulant, which went from being a test tube discovery to being promoted as a rat poison and eventually becoming a wonder drug for the prevention and treatment of thromboembolic disorders.

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YET ANOTHER BREAKTHROUGH: THE DEVELOPMENT OF ACENOCOUMAROL

In an effort to develop the perfect anticoagulant, Stoll and Litvan (Ciba Geigy) developed Nicoumalone (acenocoumarol) in 1953. Acenocoumarol found clinical use in Europe in 1955 followed by the United States in 1956.[8]

Some of the features of acenocoumarol that established its superiority over other anticoagulants include:[3]

- Rapid onset of action
- Long-term anticoagulation effect lasting 15–20 hours
- Superior anticoagulation stability compared to warfarin
- Rapid reversal of anticoagulant action with relatively small doses of vitamin K1
- Reduced dependence on CYP2C9 enzyme than on warfarin for metabolism.

Acenocoumarol is used in the treatment of various thromboembolic disorders and has well-documented safety and efficacy.

The clinical use of oral anticoagulants has come a long way since their discovery in 1943. Following over 50 years of clinical experience and numerous clinical studies, acenocoumarol could be considered close to an ideal oral anticoagulant. The well-documented safety and efficacy of acenocoumarol, and its efficacy and superiority over warfarin in maintaining international normalized ration stability within the therapeutic range, have made it a drug of choice in the treatment of various thromboembolic disorders.[8] It also finds a mention in several reputed medical books, such as:

Goodman and Gilman's The Pharmacological basis of Therapeutics, 12th Edition
"Acenocoumarol has a short half-life (10–24 hours), more rapid effect on the prothrombin time and short duration of action (2 days)."
Martindale: The Extra Pharmacopoeia, 36th Edition
"Acenocoumarol is used in the management of thromboembolic disorders."
Essentials of Pharmacology by KD Tripathi
"Acenocoumarol is considered among the suitable and well tolerated anticoagulants."
Postgraduate Haematolog, 6th Edition
"Studies with acenocoumarol have demonstrated better safety profile in patients with venous thromboembolism."

KEY POINTS

- Efforts to identify the hemorrhagic factor responsible for sweet clover disease led to the discovery of coumarin anticoagulants
- Coumarin derivatives were initially promoted as rodenticides, but later developed for use in clinical therapeutics
- The well-documented safety and efficacy of acenocoumarol make it a favorable option in oral anticoagulant therapy.

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Novel Insights on

Oral Anticoagulants in Clinical Practice

Focus on Acenocoumarol

Key Features

- This title highlights the latest development in anticoagulant therapy in clinical practice
- Pharmacology and safety of available and new anticoagulants have been discussed
- Begins with chapters on overview, history of anticoagulants from discovery to clinical practice
- Subsequent chapters discuss role of anticoagulation in different populations and situations such as pregnancy, geriatrics, pediatrics, chronic kidney disease, cancer, major or minor surgeries, and dental surgeries
- In summary, a must read book for cardiologists, physicians, and postgraduate students.

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