Editorial

Coumarins, a Class of Drugs with a Unique Contribution to Medicine: The Tale of Their Discovery

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For more than half a century, medicine has depended upon vitamin K antagonists, known as coumarins, to protect patients against dangerous thrombosis. New anticoagulants have been developed recently and are likely to predominate in the coming years. Perhaps it is not yet time to say farewell to coumarins and let them "rest in peace". However, we can take the opportunity to revisit the adventure of their discovery and their significant contribution to medicine. Readers who are interested in seeking details of the coumarin story will certainly be rewarded for their efforts.[1] The present article will just provide a brief summary of that story.

During the winters of 1920-22, cattle on the vast prairies of Canada and the northern United States suffered an epidemic of deaths due to generalised bleeding diathesis. The pathologist of the Ontario Veterinary School in Canada, Frank W. Schofield, undertook to study the phenomenon and was convinced that the afflicted cows had consumed stored hay that contained a kind of clover, of the *melilatus* species. However, the cows had been eating the same grass fresh on the prairie all through the year without coming to any harm. After many observations and experiments, Schofield proved that the poison was a substance found in this clover after it had rotted. The fresh clover contained the substance coumarin, which gave it its characteristic smell and was harmless. However, when the clover was spoiled, the coumarin was altered, and Schofield proved that the altered coumarin was the culprit ingredient that caused the haemorrhagic disease in the cows (sweet clover disease).[2,3] It remains a question for historians why Schofield, after these meticulous experiments, abandoned his research and finally ended up in Korea, working to organise veterinary studies there.

For the sequel we move to North Dakota, to the Agricultural Experimental Station of Fargo town, where the star is Lee M. Roderick. Roderick was concerned about bleeding diathesis in cows that had consumed spoiled clover and, together with his associate, Arthur F. Schalk, he determined that the sick animals exhibited a prolonged prothrombin time, which improved following a transfusion from healthy animals, but not from affected animals. Through experiment, he ruled out other mechanisms of bleeding diathesis and concluded that the disease was due to a lack of prothrombin.[4-6]

The next step was taken by Karl Paul Link, whom the literature describes as a talented man with a lively and restless personality, who had studied agricultural chemistry at the University of Wisconsin and had completed postgraduate studies

in Scotland, Austria, and Switzerland under Nobel prize-winning tutors (Fritz Pregl and Paul Karrer).[7,8] Link returned to Wisconsin, where he became Professor of Biochemistry. One freezing Saturday evening, in February 1933, as he vividly described himself,[1] a farmer arrived at his lab with a dead heifer, a bucket full of unclotted blood, and a pile of half-rotted hay. The local vet had told the farmer that his barn had been affected by a classic case of sweet clover disease. The farmer rejected the diagnosis, since he had been feeding his cattle the same clover for four years, and the vet advised him to go to the Agricultural Experimental Station for a second opinion. However, the Station was closed, and the farmer ended up by chance at the Biochemistry building, where he bumped into Professor Link. The good professor recalled earlier related publications and recommended that the farmer stop feeding his cattle the spoiled hay. However, his curiosity was aroused, particularly after emotional urging by his German-speaking senior student, Wilhelm Schoeffel, who had kept the bundle of hay and the pail of unclotted blood that the farmer had abandoned when he left in disappointment. From 1933 to 1939, Link and his students attempted to isolate the anticoagulant contained in the rotten clover, which the first analyses showed to contain a cocktail of known and unknown organic compounds.

Finally, in 1939, they managed to isolate the first crystals of the substance dicoumarol, to perform biological tests on this substance, and to define its chemical structure. At the same time, Link's laboratory demonstrated that vitamin K was able to counter the anticoagulant action of dicoumarol. In 1939, Vitamin K had only just been discovered, independently, by two researchers who shared a Nobel prize for it in 1943. Ultimately, the University of Wisconsin was able to patent dicoumarol under the name "warfarin", from the initials of the Wisconsin Alumni Research Foundation and the last letters of "coumarin".

These discoveries were not enough to convince clinicians that dicoumarol was really a vitamin K antagonist, and the substance was considered far too toxic to be used in medicine. However, it was used as a rat poison from 1948 on,[9] and it is still so used today – not always without consequences for wildlife, since rat bait is also consumed by other animals.

Eventually, in 1953, warfarin was introduced as a drug for use in clinical medicine, and one of the first prominent patients to whom it was given was Dwight D. Eisenhower, President of the USA, when he suffered a myocardial infarction in 1955.

Since then, coumarin anticoagulants have found extremely widespread application, and many similar molecules that act as vitamin K antagonists have been produced. They have permitted the use of artificial heart valves, they are used in the treatment of venous thromboses and pulmonary emboli, and in the prevention of cardiac embolism, especially in the large population of patients with atrial fibrillation, where they cut the risk of cerebrovascular stroke by an average of 64%.

However, these drugs have serious disadvantages. They have a slow onset and a prolonged action, as well as an unpredictable dose–effect relationship, so that they require close monitoring and adjustment of the dose. They also have a narrow therapeutic range: an international normalised ratio (INR) below 2 does not protect, while for an INR above 4 the risk of haemorrhage increases significantly. For these reasons, treatment is not always successful and is not without risk.[10] It has been estimated that less than half the patients who have an indication for anticoagulant medication receive treatment, while of those who take anticoagulant medication only about 40% remain within the therapeutic range.[11,12] This is especially true for Greece, as clinical trials have shown.[13,14] The success of anticoagulant medication is defined in terms of the proportion of time for which the patient remains within therapeutic limits: the "time in therapeutic range" (TTR). In the recent ACTIVE trial in various Greek centres, the mean TTR (i.e. with INR 2-3) ranged between 15% and 75%, with a mean value of around 45% (personal communication). Under the very strict monitoring in the RELY trial, Greek participants managed a TTR of 56%.[15] In everyday practice the success of anticoagulation is by no means guaranteed.

The need for a better therapy has been apparent for some time, and attempts have been made to find one. Coagulation follows two pathways, the intrinsic and the extrinsic, which finally converge to a single one. The final common pathway is controlled by factor X. When this factor is activated and becomes Xa, it converts prothrombin to thrombin, which in turn converts fibrinogen to fibrins, which form the thrombus. Because of the primary role played by factor Xa and thrombin, pharmaceutical research efforts have been focused on these. The two new categories of anticoagulants that have been developed are the direct antithrombins and the anti-Xa agents.

We now have the first three alternative drugs – dabigatran, rivaroxaban, and apixaban – that have

been approved and appear to offer attractive alternative treatments, with the following reservations:

- Experience of these drugs is in some cases mainly limited to controlled clinical trials, while general use can sometimes spring surprises.
- There is no practical laboratory method of monitoring their anticoagulant action and there is so far no specific antidote, although there are such products under investigation. Another very important limiting factor is the cost of treatment.[16,17]

Coumarin drugs – vitamin K antagonists – have been widely used in medicine for 60 consecutive years. Few drugs have shown such resistance to time. They have disadvantages and they are difficult to use, but they bear the stamp of long experience. With the new drugs, the physician now has a choice.

For now, the recommendation is that in patients who are well controlled under coumarins, this therapy should not be replaced. The newer drugs have an indication when control of the INR is not successful, or close monitoring is not feasible. Nevertheless, even patients who are being treated with the new drugs should be followed up regularly.

References

1. Link KP. The discovery of dicumarol and its sequels. Circulation. 1959; 19: 97-107.
2. Schofield FW. Damaged sweet clover: the cause of a new disease in cattle simulating hemorrhagic septicemia and blackleg. Am Vet Med Assoc. 1923-24; 64: 553-575.
3. Schofield FW. A brief account of a disease in cattle simulating hemorrhagic septicemia due to feeding sweet clover. Ca Vet Record. 1922; 3: 74-78.
4. Schalk, AF. Cattle disease resulting from eating damaged or spoiled sweet clover hay or silage. Agric Exp Sta Bull North Dakota Agricultural College, Fargo. 1926; Circular 27 pp 1-13.
5. Roderick LM. A problem in the coagulation of the blood. Sweet clover disease of cattle. Am J Physiol. 1931; 96: 413-425.
6. Roderick LM, Schalk AF. Studies on sweet clover disease. Agric Exp Sta Bull North Dakota Agricultural College, Fargo. 1931; 250.
7. Behm D, Link KP. A Biographical Memoir, Wisconsin Alumni Research Foundation, Madison WI. 1979.
8. Ballou CE. Karl Paul Gerhardt Link 1901-1078. Adv Carbohydr Chem Biochem. 1981; 39: 1-12.
9. O'Connor JA. The use of blood anti-coagulants for rodent control. Research. 1947; 1: 334-336.
10. Optimal oral anticoagulant therapy in patients with nonrheumatic atrial fibrillation and recent cerebral ischemia. The European Atrial Fibrillation Trial Study Group. N Engl J Med. 1995; 333: 5-10.
11. Gottlieb LK, Salem-Schatz S. Anticoagulation in atrial fibrillation. Does efficacy in clinical trials translate into effectiveness in practice? Arch Intern Med. 1994; 154: 1945-1953.
12. Sudlow M, Thomson R, Thwaites B, Rodgers H, Kenny RA. Prevalence of atrial fibrillation and eligibility for anticoagulants in the community. Lancet. 1998; 352: 1167-1171.
13. Korantzopoulos P, Andrikopoulos G, Vemmos K, Goudevenos JA, Vardas PE. Atrial fibrillation and thromboembolic risk in Greece. Hellenic J Cardiol. 2012; 53: 48-54.
14. Farmakis D, Pipilis A, Antoniou A, et al. Clinical profile and therapeutic management of patients with atrial fibrillation in Greece: results from the Registry of Atrial Fibrillation to Investigate New Guidelines (RAFTING). Hellenic J Cardiol. 2013; 54: 368-375.
15. Direct thrombin inhibitors in acute coronary syndromes: principal results of a meta-analysis based on individual patients' data. Lancet. 2002; 359: 294-302.
16. Andrikopoulos GK, Fragoulakis V, Maniadakis N. Economic evaluation of dabigatran etexilate in the management of atrial fibrillation in Greece. Hellenic J Cardiol. 2013; 54: 289-300.
17. Goudevenos J, Pipilis A, Vardas P. Novel oral anticoagulants in atrial fibrillation: will the benefit outweigh the cost? Hellenic J Cardiol. 2012; 53: 137-141.