Revista Electrónica de Biomedicina
Electronic Journal of Biomedicine

ISSN: 1697-090X

Rev Electron Biomed / Electron J Biomed 2012;2:11-15.

Editorial:

NEW ORAL ANTICOAGULANTS

Beatriz Cuevas Ruiz MD, PhD

Department of Hematology and Hemotherapy

Complejo Asistencial Universitario de Burgos

Burgos. Spain

bcuevas @ hgy.es

Version en español

Until the recent introduction of the new anticoagulants, oral anticoagulant treatment was based exclusively on the administering of the coumarin drugs derivatives of 4-hydroxycoumarin and indandiones.

The basic premise of oral anticoagulant treatment is that the modification of haemostasis reduces the morbidity and mortality of the thromboembolic disease.

The use of these drugs was preceded by a series of findings. In 1922 Schofield [1] described the so-called sweet clover disease, which affected farm cows and sheep in Alberta (Canada). These animals suffered severe bleeding after castration or dehorning.

The substance present in this sweet clover and responsible for the bleeding condition was isolated by Link in 1941 and was called dicoumarol[2].

In the subsequent years the possibility of using dicoumarol as an

anticoagulant was evaluated, with Butt et al[3] being those who treated the first patient in 1941. Warfarin was subsequently introduced into clinical use in 1953[4].

The use in patients demonstrated that oral anticoagulant therapy required careful analytical monitoring due to the narrow therapeutic margin, since excessive doses could cause bleeding, and ineffective doses would not prevent the thromboembolic complications.

This led to a great debate among coagulation specialists, and drove the search for a test that would help in this control. The prothrombin time was shown to be the ideal test but given the variability of using reagents of different sensitivity a mathematical model was produced that allowed comparable results to be obtained. This model gave a value called the International Normalised Ration (INR)[5].

The use of warfarin and coumarins since the 1950's has demonstrated a reduction in the rate of ischaemic stroke in patients with atrial fibrillation, but they are drugs that require frequent dose adjustments and monitoring[6].

The new oral anticoagulants have a different mechanism of action to the anti-vitamin K anticoagulants such as warfarin and the coumarins, and do not require the use of the INR to monitor them, as they do not need to be monitored since they are given at fixed doses. Thus, there is less interaction with drugs and diet, conditions that give a more constant and predictable anticoagulation, characteristics that lead to an improvement in the quality of life of the patients.

Dabigatran is a thrombin inhibitor with an indication in the prevention of thromboembolic events in adults who have been subjected to elective hip or knee replacement surgery, and its efficacy has also been demonstrated in the prevention of systemic embolism in patient with atrial fibrillation[7].

Rivaroxaban is a direct inhibitor of activated factor X that besides having the indications of dabigatran, has demonstrated its usefulness in the treatment of deep venous thrombosis, and the prevention of recurrent thrombosis and pulmonary embolism after deep venous thrombosis in adults[8].

Apixaban is a reversible direct and selective inhibitor of activated factor X, with an indication in the prevention of thromboembolic events in adults who have been subjected to elective hip or knee replacement surgery, and its use has also been demonstrated in the prevention of cerebral infarction in atrial fibrillation[9].

The new anticoagulants have some disadvantages, such as a higher incidence of dyspepsia and gastrointestinal bleeding, the lack of an effective antidote, and the accumulation in cases of renal failure, with severe renal failure being a contraindication[10].

Although these drugs lack an antidote, Eerenberg et al, have demonstrated that the prothrombin complex immediately reverts the anticoagulant effect of rivaroxaban in healthy subjects[11].

As regards cost, numerous studies have analysed this aspect, highlighting the Canadian study that demonstrated that dabigatran was a very cost-effective alternative in the prevention of stroke and systemic clots in patient with atrial fibrillation[12].

Deitelzweig et al, in a sub-analysis of the RE-LY, ROCKET-AF and ARISTOTLE trials, showed a reduction in the cost per patient / years (excluding the cost of the drug) for dabigatran, rivaroxaban and apixaban compared to warfarin, with apixaban being the drug that showed the greatest reduction[13].

Other authors, applying the RE-LY study to Danish clinical practice, and analysing the cost of using dabigatran for life in patients with atrial fibrillation compared to warfarin. Using the analysis of the quality of life adjusted for years as the measure of efficacy, they showed that dabigatran was a cost-effective alternative to warfarin treatment[14].

The new anticoagulants are going to cause a revolution in the world of oral anticoagulation, achieving a great improvement in the quality of life of the patients, and this heralds a promising future.

REFERENCES

1.- Schonfield Fw. Damaged sweet clover; the cause of a new disease in cattle simulating haemorrhagic septicemia and blackleg. J Am Vet Med Ass 1924; 64: 553-6

2.- Link KP. The Discovery of dicumarol and its sequels. Circulation 1959; 10; 97-107

3.- Butt HR, Allen EV, Billman JL. A preparation from spoiled sweet clover, [3,3'methylene-bis- (4 hydroxycoumarin)] which prolongs coagulation and prothrombin time of the blood: preliminary report of experimental and clinical studies. Proc Staff Meet Mayo Clinic. 1941; 16: 388-395.

4.- Shapiro S. Warfarin sodium derivative: (coumadin sodium); an intravenous hypoprothrombinemia-inducing agent. Angiology 1953; 4: 380-390

5.- Kirkwood TB. Calibration of reference thromboplastins and standardisation of the prothrombin time ratio. Thromb Haemost. 1983; 49: 238-244.

6.- The Boston Area Anticoagulation Trial for atrial fibrillation investigators. The effect of low-dose warfarin on the risk of stroke in patients with nonrheumatic atrial fibrillation. N Engl J Med 1990; 323: 1505-1511.

7.- Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, Pogue J, Reilly PA, Themeles E, Varrone J, Wang S, Alings M, Xavier D, Zhu J, Diaz R, Lewis BS, Darius H, Diener HC, Joyner CD, Wallentin L; RE-LY Steering Committee and Investigators. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med 2009; 361: 1139-1151.

8.- Romualdi E, Donadini MP, Ageno W. Oral rivaroxaban after symptomatic venous thromboembolism: the continued treatment study (EINSTEIN-extension study). Expert Rev Cardiovasc Ther 2011; 9: 841-844.

9.- Granger CB, Alexander JH, McMurray JJ et al. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med 2011; 365: 981-992.

10.- Reddy P, Atay JK, Selbovitz LG et al. Dabigatran: a review of clinical and pharmacoeconomic evidence. Crit Pathw Cardiol 2011; 10: 117-127.

11.- Eerenberg ES, Kamphuisen PW, Sijpkens MK et al. Reversal of rivaroxaban and dabigatran by prothrombin complex concentrate: a randomized, placebo-controlled, crossover study in healthy subjects. Circulation 2011; 124: 1573-1579.

12.- Sorensen SV, Kansal AR, Connolly S, Peng S, Linnehan J, Bradley-Kennedy C, Plumb JM. Cost-effectiveness of dabigatran etexilate for the prevention of stroke and systemic embolism in atrial fibrillation: a Canadian payer perspective. Thromb Haemost 2011; 105: 908-919.

13.- eitelzweig S, Amin A, Jing Y, Makenbaeva D, Wiederkehr D, Lin J, Graham J. Medical Cost Reductions Associated with the Usage of Novel Oral Anticoagulants vs. Warfarin Among Atrial Fibrillation Patients, Based on the RE-LY, ROCKET-AF and ARISTOTLE Trials. J Med Econ. 2012 Mar 27. [Epub ahead of print]

14.- Langkilde LK, Bergholdt Asmussen M, Overgaard M. Cost-effectiveness of dabigatran etexilate for stroke prevention in non-

valvular atrial fibrillation. Applying RE-LY to clinical practice in Denmark. J Med Econ 2012 Mar 22. [Epub ahead of print]

CORRESPONDENCE:
Beatriz Cuevas Ruiz MD, PhD
Department of Hematology and Hemotherapy.
Complejo Asistencial Universitario de Burgos
Burgos. España
Mail: bcuevas @ hgy.es