Warfarin in Valvulopathy: How Important is Seniority?

Max Grinberg
Instituto do Coração – InCor, São Paulo, SP – Brazil

The research on new oral drugs that act on the coagulation cascade (RE-LY, 2009[1]; ROCKET, 2011[2]; ARISTOTLE, 2011[3]) reproduces, at the services that manage heart valve diseases, the hopes and fears already experienced with the indication of warfarin and the management of its adverse effects over the second half of the 20th century. Open mind aligned with ethics.

Oral anticoagulation has become one of the most complex therapeutic-preventive measures prescribed to patients with heart valve diseases in outpatient clinics[4]. The identification of signs of neither embolism nor hemorrhage during the use of the oral anticoagulant is far from being a certainty of the continuity of the clinical status, because conformity with the state of the art of warfarin application can suffer, at any time, multifactorial impacts dependent on patients' individuality. Methods belong to medicine, expertise to doctors, and results to patients.

The pioneer clinical paths of oral anticoagulation were not those idealized for innovations from the bench to the bedside. At the beginning, knowledge on warfarin belonged to the veterinary field, with the isolation of dicoumarol from sweet clover, a component of cow food preparation that caused digestive hemorrhage in the cattle. On a second phase, a most potent warfarin was developed to be used as rodent poison, culminating with the observation at an emergency room that the hemorrhage resulting from its ingestion for suicidal purposes could be controlled with blood transfusion and vitamin K administration, avoiding death. It is worth emphasizing that the oral anticoagulant showed from the beginning its hemorrhagic face, indicative of its name. One of the haphazard encounters of nature with a science-oriented mind.

The thromboembolic event associated with rheumatic disease, a late participant of the chain of cardiocirculatory abnormalities of homeostasis consequent to the immunopathological reaction to *Streptococcus pyogenes*, was better observed in patients with mitral stenosis by Harris and Levine[5] in the early 1940s. Those authors have also reported that cerebral embolism was more common in patients with no complaint of dyspnea than in those with signs of congestive heart failure, stressing the concerns on the unpredictability of the neurological manifestation. On that occasion, the anticoagulant drug was not considered an antithrombotic agent. But, at the end of that decade, Irwing Sherwood Wright (1901-1997) began to prescribe dicoumarol to prevent embolic recurrences related to cardiological conditions[6]. At that time, the options for a presumed antithrombotic success were reversion of atrial fibrillation by using quinidine and surgical resection of the atrial appendix.

Some years have passed and Szekely[7] has emphasized the first year after atrial fibrillation as the most vulnerable period to systemic embolization in rheumatic heart disease, creating the concept of primary preventive benefit of oral anticoagulation in the presence of "perpetual arrhythmia".

Emphasis was then given to additional knowledge on clinical data, while biochemical fundaments on oral anticoagulation still lacked. By the end of the 1950s, a prothrombin time over 20s, due to the use of dicoumarol, was known to drastically reduce the recurrence of thromboembolic manifestations in patients with rheumatic heart disease[8], and excesses could be reverted with the administration of vitamin K.

In the 1950s, warfarin was considered the most practical anticoagulant drug, because of the following: heparin was expensive and required several daily doses; dicoumarol took a while to begin acting; and other anticoagulants were not recommended due to their adverse effects. Given the current standards, it is surprising that warfarin would be prescribed at the initial dose of 1 mg/kg of weight up to 75 mg, via parenteral route (venous or intramuscular, ampoule with 75 mg of warfarin to be diluted into 3 mL of distilled water) or oral route; at the same time, the concept that the degree of hypoprothrombinemia depended on the maintenance dose gained momentum[9].

Reports on the first clinical observations were aimed not at assessing the antithrombotic benefit, but at assessing the frequency of the hemorrhagic event and only during the initial period of warfarin use. Regarding the safety of its use, Pollock[10] has followed up 100 patients with different indications for the mean period of 15.8 days. The patients received induction with 75 mg of intravenous or oral warfarin and maintenance doses between 4 mg and 19 mg, according to the daily analysis of the prothrombin time, targeted at 30% beyond the normal. There were eight hemorrhagic manifestations, five of which attributed to warfarin based on the prothrombin time value, and none of the four deaths was related to that drug use.

It is worth noting that, at the beginning of the 1980s, a decade marked by numerous advances in Medicine, the clinical observation that anticoagulation drastically reduced

Keywords

Heart Valve Diseases / therapy; Warfarin; Anticoagulants / adminstration & dosage.

Mailing Address: Max Grinberg •
Rua Manoel Antonio Pinto, 04 ap. 21A, Paraisópolis, Postal Code 05663-020, São Paulo, SP – Brazil
E-mail: max@cardiol.br, grinberg@incor.usp.br
Manuscript received August 02, 2012, revised manuscript November 16, 2012, accepted November 27, 2012.

DOI: 10.5935/abc.20130097

the thromboembolic event associated with atrial fibrillation was not unanimous. The lack of controlled studies and the fear of hemorrhage determined reluctance to pharmacological prevention. Milliken[11] was cautious on his recommendation: pending controlled trials, the alleged risk-benefit ratio in each patient with chronic atrial fibrillation should be considered to prevent deaths and sequelae from thromboembolism; thus, anticoagulation should not be reserved solely for patients with embolic manifestations. On the same decade, the World Health Organization (WHO) introduced the International Normalized Ratio (INR), and, by its end, warfarin had acquired the following concept: "There are many pitfalls in warfarin therapy, but most can be avoided by close monitoring with a reliable prothrombin time assay and intensive patient counseling; warfarin remains a valuable drug but should be treated with respect"[12].

The scientific production accumulated since then has provided Medicine with daily data and facts and studies, such as the AFASAK (1989)[13], BAATAF (1990)[14], SPAF (1990)[15] and SPINAF (1992)[16], supporting the ethical recommendation on unbalancing the pro/anti natural coagulation in patients with heart valve disease by using warfarin, without counting on a clinical revelation of effect.

The reference point of the relationship between benefit that "would be happening", presumed based on the pharmacological action, and safety that "would be at a proper level", based on the lack of alert signs of hemorrhage, is centered on periodically assessing the INR according to individual results. Thus, the laboratory platform constituted by INR bands provides relative safety to the following objectives of the oral anticoagulation context: a) to lead a new application to stability; b) to preserve the stability achieved; c) to totally eliminate the effect of oral anticoagulation in face of the need for an invasive intervention; and d) to allow assessment of hemorrhage during its use.

Thrombotic or hemorrhagic events during the use of warfarin are usually associated with inadequate INR values, resulting from non-compliance with the fundamental triad of its use (dose-control-interaction with drug, food and procedure). However, the participation of a hidden lesion (female genital, urinary and digestive) is not rare, facilitating bleeding, which manifests at INR values within the target range. Lavitola et al[17] have identified that correspondence in all hemorrhagic episodes associated with INR < 3.5. On the other hand, it is worth noting the existence of a heterogeneous hemorrhagic expression at high INR values, emphasizing the role of individuality.

In this second decade of the 21st century, warfarin occupies the central position in oral anticoagulation, being recommended by national and international guidelines and "certified" according to preventive/safe INR values. As an expression of the Brazilian reality, it is worth noting that the 1,500 prescriptions issued per month at the Valvulopathy Outpatient Clinic of the InCor include warfarin, meaning that one in every two patients (with chronic atrial fibrillation and/or a history of thromboembolic event and/or metallic valve prosthesis) is kept in permanent iatrogenesis – considering its concept of security breach, regardless of consequence. In addition, there is no perspective of change in the universe of oral anticoagulation for heart valve diseases in coming decades. Thus, the uncertainties about the balance between two opposed blood states continue to challenge health care, to stimulate research and to promote knowledge.

Considering the perspective that an occasional pharmacological innovation might become both an alternative to and a substitute for warfarin, we suggest that cardiologists managing the subgroup of patients with heart valve diseases, who require long-term anticoagulation, consider the questions below derived from the experience with the use of warfarin. Even though studies might predict the usefulness and safety of pharmacological innovations to patients with heart valve diseases, the universal experience over more than half a century with the use of warfarin is a strong indication that attention should be given to the unpredictability of phase 4 clinical trials.

1. What is the importance of the patient's individual history? Would several years of lack of thrombohemorrhagic events advise against an eventual substitution?

2. Could the destination of resources to the availability of a new drug be compensated by cost reductions in laboratory control and in hospitalizations due to intercurrences?

3. Did the decrease in the importance of performing the laboratory test periodically reduce the bond between the patient and the physician, and, indirectly, the adhesion to heart valve disease follow-up?

4. Conversely, would reducing the emphasis on the laboratory test eliminate a factor of non-adhesion?

5. Would the perspective of fewer periodic dose adjustments be a positive factor for patient's compliance with oral anticoagulation?

6. Would a fixed dose of oral anticoagulation be a relief or a concern according to your understanding built over the years observing warfarin?

7. Could hemorrhagic episodes with a new drug be controlled promptly?

8. Would the urgency of suspending a new drug due to an emergency procedure be supported, from the theoretical and practical viewpoints, by measures favoring a rapid return to normal coagulation?

9. Could a hidden lesion that facilitates bleeding have any impact?

10. Would the use of oral anticoagulation in the elderly generate less apprehension?

11. Considering the potential for embryopathy, would there be any advantage regarding the use of the drug by women of childbearing age?

12. Would the association with other drugs influencing coagulation become safer?

Author contributions

Conception and design of the research, Writing of the manuscript and Critical revision of the manuscript for intellectual content: Grinberg M.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Sources of Funding

There were no external funding sources for this study.

Study Association

This study is not associated with any post-graduation program.

References

1. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, et al; RE-LY Steering Committee and Investigators. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med. 2009;361(12):1139-51.
2. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, et al; ROCKET AF Investigators. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med. 2011;365(10):883-91.
3. Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M, et al; ARISTOTLE Committees and Investigators. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2011;365(11):981-92.
4. Grinberg M. Entendo & aceito & faço. Estratégia pró-adesão à anticoagulação oral. Arq Bras Cardiol. 2004;82(4):309-12.
5. Harris AW, Levine SA. Cerebral embolism in mitral stenosis. Ann Intern Med. 1941;15(4):637-43.
6. Wright IS. The use of anticoagulants in the treatment of diseases of the heart and blood vessels. Ann Intern Med. 1949;30(1):80-91.
7. Szelely P. Systemic embolism and anticoagulant prophylaxis in rheumatic heart disease. Br Med J. 1964;1(5392):1209-12.
8. Mcdevitt E, Carter SA, Gatje BW, Foley WT, Wright IS. Use of anticoagulants in treatment of cerebral vascular disease: ten-year experience in treatment of thromboembolism. J Am Med Assoc. 1958;166(6):592-7.
9. Shapiro S. Anticoagulant therapy. Surg Clin North Am. 1956 Apr:469-83.
10. Pollock BE. Clinical experience with warfarin (coumadin) sodium, a new anticoagulant. J Am Med Assoc. 1955;159(11):1094-7.
11. Milliken JA. Atrial fibrillation and embolism. Can Med Assoc J. 1983;128(12):1370-2.
12. Scott DK. Control of warfarin therapy. Postgrad Med J. 1989;65(767): 611-2.
13. Petersen P, Boysen G, Godtfredsen J, Andersen ED, Andersen B. Placebo-controlled, randomised trial of warfarin and aspirin for prevention of thromboembolic complications in chronic atrial fibrillation. The Copenhagen AFASAK study. Lancet. 1989;1(8631):175-9.
14. Singer DE, Hughes RA, Gress DR, Sheehan MA, Oertel LB, Maraventano SW, et al. The effect of aspirin on the risk of stroke in patients with nonrheumatic atrial fibrillation: The BAATAF Study. Am Heart J. 1992;124(6):1567-73.
15. Stroke Prevention in Atrial Fibrillation Study: final results. Circulation. 1991;84(2):527-39.
16. Ezekowitz MD, Bridgers SL, James KE, Carliner NH, Colling CL, Gornick CC, et al; Veterans Affairs Stroke Prevention in Nonrheumatic Atrial Fibrillation Investigators. Warfarin in the prevention of stroke associated with nonrheumatic atrial fibrillation. N Engl J Med. 1992;327(20):1406-12.
17. Lavitola P de L, Spina GS, Sampaio RO, Tarasoutchi F, Grinberg M. Sangramento durante a anticoagulação oral: alerta sobre um mal maior. Arq Bras Cardiol. 2009;93(2):174-9.