Original Article

Utilization of Oral Anticoagulation in a Teaching Hospital in Nigeria

Anakwue RC, Ocheni S[1], Madu AJ[1]

Departments of Medicine, Pharmacology and Therapeutics and [1]Hematology and Immunology, College of Medicine, University of Nigeria, Enugu Campus, Enugu, Nigeria

Address for correspondence:
Dr. Anazoeze Jude Madu,
Department of Hematology and Immunology, College of Medicine, University of Nigeria, Enugu Campus, Enugu, Nigeria.
E-mail: anazoeze@yahoo.com

Abstract

Background: Anticoagulation is an essential lifesaving management practice indicated for arterial, venous and intracardiac thromboembolism. **Aim:** This study was undertaken to examine the utilization of anticoagulation services in University of Nigeria Teaching Hospital, Enugu (UNTH) Nigeria. **Materials and Methods:** This retrospective study involved assessing data from folders of subjects on anticoagulation and monitoring in UNTH, Enugu. Patients' profile, risk factors, diagnosis, indication for oral anticoagulation, anticoagulant used; target, monitoring, outcome and complications of anticoagulation were recorded. **Results:** A total of 26 patients over a period of 5 years were on anticoagulation and laboratory monitoring done in UNTH. The mean age of the patients was 53.4 years and more females than males were on anticoagulation and monitoring (F14:M12). The most common indications for anticoagulation include deep venous thrombosis/pulmonary embolism, congestive heart failure with atrial fibrillation and mitral valve disease with atrial fibrillation. Desired clinical outcome was achieved in eight patients 8/26 (30.8%). Minor bleeding was the only complication reported in three patients 3/26 (11.5%). **Conclusion:** The absence of diagnostic tools and anticoagulation monitoring clinics and the apprehension of adverse effects have combined to make this lifesaving treatment inaccessible to many patients in Nigeria.

Keywords: Anticoagulation, Barriers, Nigeria, Utilization

Introduction

Anticoagulation is an essential lifesaving management practice indicated for arterial, venous and intracardiac thrombo-embolism. However, there are two major issues associated with its use: One that is related to under-anticoagulation with attendant clinical thromboembolism and the other over-anticoagulation with complications, particularly bleeding. The use of anticoagulants must follow recommended guidelines; otherwise, it is fraught with increased morbidity and mortality. When anticoagulation is used appropriately, it is an effective and safe practice.[1,2]

The clinical consequences of thrombosis in the arteries and heart chambers include acute and chronic ischemic heart disease, arrhythmia, sudden death, ischemic cerebrovascular disease, peripheral artery disease and renovascular hypertension. Venous thrombosis in the deep veins may lead to pulmonary embolism.[3]

Anticoagulants prevent the formation of thrombi. Thrombi can form in the veins, artery, or intracardium and cause complication through local obstruction, distant embolism in the distal microcirculation and consumption of hemostatic material.[3]

Anticoagulants are divided into oral and parenteral agents. The later is used when rapid anticoagulation is required, because the former requires several days before achieving optimal antithrombotic effect. The oral drugs are the most widely used anticoagulants.[3]

Warfarin, a racemic mixture of levorotatory S-warfarin and levorotatory R-warfarin is the most currently clinically used oral anticoagulant. Warfarin acts by inhibiting the synthesis of vitamin K-dependent clotting factors, which include factors II, VII, IX, and X, and the anticoagulant proteins C and S. Vitamin K is an essential cofactor for the post ribosomal synthesis of the vitamin K-dependent clotting factors.

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Vitamin K promotes the biosynthesis of γ-carboxyglutamic acid residues in the proteins that are essential for biological activity. Warfarin is thought to interfere with clotting factor synthesis by inhibition of the C1 subunit of vitamin K epoxide reductase enzyme complex, thereby reducing the regeneration of vitamin K1 epoxide. This makes warfarin useful in the prevention and treatment of thromboembolic disorders. The therapeutic range of warfarin is defined by international normalized range (INR).[3]

The clinical usefulness of warfarin is affected by factors that increase the INR (pharmacokinetic: Amiodarone, cimetidine, metronidazole, trimethoprim-sulfamethoxazole; pharmacodynamic: Aspirin, cephalosporin, liver disease, hyperthyroidism) and those that decrease INR (pharmacokinetic: Barbiturates, carbamazepine, rifampin; pharmacodynamic: Diuretics, vitamin k, hypothyroidism).[4] Reversal of warfarin action is by stopping the drug, administration of vitamin k and fresh-frozen plasma rich in coagulation factors.[5]

Physicians in the developing countries where resources are scarce, face peculiar problems when using anticoagulants. Anticoagulation requires good diagnostic facilities, appropriate monitoring tools and adequate anticoagulation management infrastructure. These are not easily available in developing countries like Nigeria. Anticoagulation services provide anticoagulants, monitor their use, outcome and complications.[6] A critical part of anticoagulation service is the personnel who must be adequately trained. Their training includes a thorough knowledge of anticoagulants including new and emerging drugs. It should be emphasized that laboratory services is at the core of effective and efficient anticoagulant service.

The aim of this study was to examine the utilization of oral anticoagulation in a low resource country, like Nigeria. The study was to find out the clinical indications of anticoagulation, drug dosing, treatment outcome and complications of the use of oral anticoagulants.

Materials and Methods

This retrospective investigation involved assessing data from folders of subjects on anticoagulation and monitoring in the University of Nigeria Teaching Hospital Enugu (UNTH) over a 5 year period (2005–2010). Patients' profile, risk factors, diagnosis, indication for anticoagulation, anticoagulant used; target, monitoring, outcome and complications of anticoagulation were recorded. Patients who were on prophylactic anticoagulation or who were on low molecular weight heparin and so did not require routine monitoring or patients monitored outside the teaching hospital were excluded from this survey. Anticoagulation monitoring was with INR. Recommended therapeutic ranges of INR are 2.0-3.0 for most disease indications, and 2.0-3.5 with cardiac valve prostheses.[1,2]

Target INR was defined by the attainment of therapeutic ranges of oral anticoagulants in keeping with the guidelines.[1,2] Desired clinical outcome was defined by the attainment of prophylactic or therapeutic goals of oral anticoagulation.

Ethical clearance was obtained from the UNTH Health Research and Ethics review committee.

Results

A total of 26 patients over a period of 5 years were on oral anticoagulation and laboratory monitoring done in UNTH. The mean age of the patients was 53.4 years (range 13–84 years) and more females were on anticoagulation and monitoring (female: male - 14:12). The oral anticoagulant used was warfarin. The most common indications for anticoagulation were deep venous thrombosis/pulmonary embolism 14/26 (53.8%), congestive heart failure with atrial fibrillation 3/26 (11.5%) and mitral valve disease with atrial fibrillation 3/26 (11.5%). Anticoagulation INR was achieved in 10 patients 10/26 (38.5%). Desired clinical outcome was achieved in eight patients 8/26 (30.8%). Bleeding complications were seen in three patients 3/26 (11.5%) [Tables 1 and 2]. Only minor bleeding was recorded, and the dose of oral anticoagulant was reduced temporarily to restore the INR to normal ranges. No other adverse reaction was reported.

Discussion

The low number of patients recruited for this study is likely due to under-utilization of oral anticoagulants and the increasing use of low molecular weight heparin in anticoagulation in our center. Anticoagulation service, target and desired outcome are still not optimum in our center as shown in this study. In Nigeria, anticoagulation services are managed by hematologists who are very few in number.

Table 1: Clinical indications of anticoagulation

Clinical indications	Number of patients (%)
Deep venous thrombosis/pulmonary embolism	14/26 (53.8)
Congestive cardiac failure with atrial fibrillation	3/26 (11.5)
Mitral valve disease with atrial fibrillation	3/26 (11.5)
Hypertension with atrial fibrillation	2/26 (7.7)
Cardiovascular disease (thromboembolic stroke)	2/26 (7.7)
Heart valve replacement	2/26 (7.7)

Table 2: Anticoagulant drug dosing, treatment outcome and complications

Characteristics	Yes (%)	No (%)
Target INR achieved?	10/26 (38.5)	16/26 (61.5)
Desired clinical outcome achieved?	8/26 (30.8)	18/26 (69.2)
Minor bleeding complications found	3/26 (11.5)	23/26 (88.5)

INR: International normalized range

There are no dedicated anticoagulation monitoring clinics in Nigeria, but South Africa and Kenya now have monitoring clinics in some of their centers.

Anticoagulation clinics (ACCs) in South Africa are managed by specialist physicians together with other doctors and in some clinics by physicians supported by nurses.[7] In Kenya, there are pharmacist's controlled ACCs. Dedicated ACCs tend to have a better outcome.[8]

The absence of dedicated anticoagulation clinics, lead physicians in Nigeria to observe long waiting periods to get results of anticoagulation monitoring, and this tends to keep them over guarded to avoid excessive anticoagulation. Hopefully, the South African venous thrombo-embolism prophylactic and treatment guidelines will provide the framework for other regions to put together their plan for improved anticoagulation practices.[7]

In this study, the most common indications for anticoagulation were deep venous thrombosis/pulmonary embolism, congestive heart failure with atrial fibrillation and hypertension with atrial fibrillation in that order, while in South Africa, the most common indication for anticoagulation in two centers were atrial fibrillation, followed by mixed valve disease and valve replacement. Hypertension was adduced as the cause of high prevalence of atrial fibrillation - associated anticoagulation in South Africa. In Kenya, the most common indication for anticoagulation was deep venous thrombosis and pulmonary embolism followed by rheumatic valvular disease and valve replacement. Valve replacement was not a common cause of anticoagulation in this study because of the suspension of open heart surgeries in our center. This pattern is similar to other centers in Nigeria.

In a study of admitted patients in USA, the most common indications for anticoagulant use were venous thromboembolism prophylaxis (67.5% of cases), acute coronary syndrome (13.5% of cases), and venous thromboembolism treatment (11.9% of cases).[9]

The achievement of desired anticoagulation is low in Africa, ranging from 7% to 30% in Kenya, which is comparable to 39% in this study. In South Africa, it is about 32–58%.[9] Reaching optimal target in anticoagulation is directly related to the infrastructure of anticoagulation services available.

Pooled data from USA, China and Canada showed a higher level of achievement of desired anticoagulation compared to data from African centers.[10] Pooled data of randomized controlled trials from these countries showed weighted mean of percent time within the therapeutic range (%TTR) for patients randomized to anticoagulant clinics (ACC) of 59.9% (range of means 56–64%), while data from cohort studies showed weighted mean of %TTR for the four studies report of 63.5% for the intervention groups. This pattern is expected given the quality of anticoagulation services in these countries.[10]

The challenges of anticoagulation stems from dose related adverse effects of the anticoagulants, inadequate monitoring of anticoagulation and inadequate anticoagulation. The most common complication of warfarin is bleeding, which occurs in 6–39% of recipient's annually.[11] Intracranial hemorrhage accounts for approximately 2% of the reported hemorrhagic complications of warfarin therapy and is associated with a mortality rate of 10–68%[12]

In USA, reported anticoagulant-related adverse events among hospitalized patients in 2009 involved mainly minor or major bleeding, which occurred in 36% and 32% of cases, respectively.[9] Interestingly, only 12% (three patients) had bleeding among the anticoagulated patients in this study. This low level of bleeding and other known complications may be because of the sub-optimal level of anticoagulation: Adequate dosing was achieved in only in 54% of the patients [Table 2].

Anticoagulation service in Nigeria is still evolving, and there are challenges associated with it. There is a need for dedicated anticoagulation services with defined roles and mission. Different types of health professional cadres can be trained to work in these centers. There is no doubt that hematologists and cardiologists could play leading or supervisory roles in these centers. The Kenyan and South African example show that nurses and pharmacists can also co-run these centers.

Some of the anticoagulation monitoring tests include activated partial thromboplastin time which can detect abnormalities in the intrinsic and common clotting pathways, the activated clotting time (ACT), which is a point of care (POC) test that can be employed to monitor high-dose heparin during invasive and surgical procedures. The ACT therapeutic range will depend on the specific procedure or surgery being performed. The INR is the gold standard for monitoring patients on warfarin.[13]

There is a need to increasingly use the bedside or POC monitoring in anticoagulation services in Nigeria. This will complement the central laboratory anticoagulation monitoring that is routine. Clinicians should however be acquainted with the benefits and the limitations of POC monitoring.

The accuracy of POC INR testing compared with standard measurement in a hospital laboratory is variable.[14-17]

Despite this variability, POC measurement results in the same clinical decision in 66–78% of cases when compared with decisions based on the results from a hospital-based laboratory.[18] POC testing has furthermore proven to be

Box 1: Components of an ideal anticoagulation service

Determine the appropriate clinical indications for anticoagulant treatment
Choose the best drug in relation to clinical patient profile
Evaluate any potential pharmacological interference, in particular in the elderly
Control drug adherence, that for AVKs is guaranteed through laboratory test
Define a follow-up program
Define educational programs to increase adherence
Manage patients undergoing surgical interventions or invasive procedures
Manage patients with bleeding and thrombotic complications, during anticoagulant treatment
Manage patients during inter-current diseases
Choose the best laboratory test for each molecule to support clinical and therapeutic activities
Anti-Vitamin K agents are probably not ideal

AVK: Anti-Vitamin K

an effective monitoring modality with resulting beneficial clinical outcomes.[19,20] This testing provides clinicians with immediate results, allowing for same-day medication adjustments and direct communication between physician and patient regarding management.[20]

Box 1 outlines some of the components of an ideal anticoagulation service.

Conclusion

Anticoagulant therapies in many countries are under-prescribed resulting in high mortality on medical and surgical patients.[8] The absence of diagnostic tools and anticoagulation monitoring services and the apprehension of adverse effects have combined to make this lifesaving treatment inaccessible to many patients in Nigeria and in many low resource countries.

Anticoagulation service centers are specialized centers, where well-experienced staff knowledgeable in coagulation mechanisms work to provide anticoagulant treatment and support patients on critical clinical conditions. The ideal Anticoagulant service in Nigeria must design a module to accommodate the peculiar conditions that are found in the country. What will determine the success of any anticoagulation service is a sound pharmacological knowledge of anticoagulant drugs, a coordinated anticoagulation monitoring team and thorough patient education.[21]

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References

1. Keeling D, Baglin T, Tait C, Watson H, Perry D, Baglin C, *et al.* Guidelines on oral anticoagulation with warfarin-Fourth edition. Br J Haematol 2011;154:311-24.
2. A critical appraisal of the use of anticoagulant therapy: Effectiveness, monitoring, and complications. Semin Thromb Hemost 1986;12:1-71.
3. Symposium on thrombosis and antithrombotic therapy – 1986. J Am Coll Cardiol 1986;8 6 Suppl: 1B-167.
4. Hansten PD. Oral anticoagulant drug interactions. In: Drug Interactions. 5th ed., Ch. 2. Philadelphia: Lea and Febiger; 1985. p. 66-114.
5. Levine MN, Hirsh J. Hemorrhagic complications of anticoagulant therapy. Semin Thromb Hemost 1986;12:39-57.
6. Hirsh J, Dalen J, Anderson DR, Poller L, Bussey H, Ansell J, *et al*. Oral anticoagulants: Mechanism of action, clinical effectiveness, and optimal therapeutic range. Chest 2001;119:8S-21.
7. Jacobson BF, Louw S, Mer M, Haas S, Büller HR, Abdul-Carim AT, *et al*. Venous thromboembolism - Prophylactic and therapeutic practice guideline. S Afr Med J 2009;99:467-8, 470-3.8.
8. Pastakia SD, Crisp WI, Schellhase EM. Implementation of a pharmacist managed anticoagulation clinic in Eldoret, Kenya. Southern Med Review 2010; 3:2:20-23.
9. Tiryaki F, Nutescu EA, Hennenfent JA, Karageanes AM, Koesterer LJ, Lambert BL, *et al*. Anticoagulation therapy for hospitalized patients: Patterns of use, compliance with national guidelines, and performance on quality measures. Am J Health Syst Pharm 2011;68:1239-44.
10. Bloomfield HE[1], Krause A, Greer N, Taylor BC, MacDonald R, Rutks I, *et al*. Meta-analysis: Effect of patient self-testing and self-management of long-term anticoagulation on major clinical outcomes. Ann Intern Med. 2011 Apr 5;154:472-82.
11. Levine MN, Raskob G, Landefeld S, Hirsh J. Hemorrhagic complications of anticoagulant treatment. Chest 1995;108 4 Suppl: 276S-90.
12. Landefeld CS, Beyth RJ. Anticoagulant-related bleeding: Clinical epidemiology, prediction, and prevention. Am J Med 1993;95:315-28.
13. Smythe MA, Caffee A. Anticoagulation monitoring. J Pharm Pract 2004;17:317-26
14. Shermock KM, Bragg L, Connor JT, Fink J, Mazzoli G, Kottke-Marchant K. Differences in warfarin dosing decisions based on international normalized ratio measurements with two point-of-care testing devices and a reference laboratory measurement. Pharmacotherapy 2002;22:1397-404.
15. Sunderji R, Gin K, Shalansky K, Carter C, Chambers K, Davies C, *et al*. Clinical impact of point-of-care vs laboratory measurement of anticoagulation. Am J Clin Pathol 2005;123:184-8.
16. McBane RD 2nd, Felty CL, Hartgers ML, Chaudhry R, Beyer LK, Santrach PJ. Importance of device evaluation for point-of-care prothrombin time international normalized ratio testing programs. Mayo Clin Proc 2005;80:181-6.
17. Reiss RA, Haas CE, Griffis DL, Porter B, Tara MA. Point-of-care

versus laboratory monitoring of patients receiving different anticoagulant therapies. Pharmacotherapy 2002;22:677-85.

18. van den Besselaar AM. Accuracy, precision, and quality control for point-of-care testing of oral anticoagulation. J Thromb Thrombolysis 2001;12:35-40.
19. Jackson SL, Peterson GM, House M, Bartlett T. Point-of-care monitoring of anticoagulant therapy by rural community pharmacists: Description of successful outcomes. Aust J Rural Health 2004;12:197-200.
20. Jackson SL, Peterson GM, Vial JH, Jupe DM. Improving the outcomes of anticoagulation: An evaluation of home follow-up of warfarin initiation. J Intern Med 2004;256:137-44.
21. Testa S, Paoletti O, Zimmermann A, Bassi L, Zambelli S, Cancellieri E. The role of anticoagulation clinics in the era of new oral anticoagulants. Thrombosis 2012;2012:835356.

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