A SIX YEAR DRUG UTILIZATION STUDY IN A TERTIARY HEALTHCARE SYSTEM: EMERGENCE OF NEWER ORAL ANTICOAGULANTS

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ABSTRACT

BACKGROUND

Vitamin K antagonists like warfarin have been used extensively for various medical and surgical conditions. Their use is often associated with bleeding as an adverse effect. Novel oral anticoagulants like dabigatran, rivaroxaban, apixaban achieve anticoagulation with relatively less risk of bleeding and the availability of reversal agents.

The present study aims to study the drug consumption pattern of oral anticoagulants and analyses the change in pattern of prescription.

MATERIALS AND METHODS

The consumption pattern of oral anticoagulants was analysed from the prescriptions over a period of six years from 2013 to 2018 in a busy tertiary care centre.

RESULTS

The analysis of 12,05,000 prescriptions reveal that the use of warfarin dropped from 45.64% in 2013 to 7.17% in 2018. Similarly, there was a gradual rise in the use of NOAC from 3.14% in 2013 to 73.72% in 2018.

CONCLUSION

Novel oral anticoagulants like dabigatran, rivaroxaban, apixaban are gradually emerging as the preferred anticoagulants, along with a steady decline in the prescription of warfarin.

KEYWORDS

Drug Utilization Study, Warfarin, Novel Oral Anticoagulants.

HOW TO CITE THIS ARTICLE: Tejus A, Pradhan S, Mathur AG, et al. A six year drug utilization study in a tertiary healthcare system: emergence of newer oral anticoagulants. J. Evid. Based Med. Healthc. 2019; 6(9), 676-679. DOI: 10.18410/jebmh/2019/141

BACKGROUND

Oral anticoagulants are often indicated for the prophylaxis or treatment of venous thromboembolism (VTE) including deep vein thrombosis (DVT) and pulmonary embolism (PE);[1] Atrial fibrillation;[2] Cardioversion;[3] Valvular heart disease;[4] Acute coronary syndrome;[5] cardiomyopathy[6] and rarely peripheral vascular disease.[7,8,9,10] Vitamin K antagonist (VKA) - warfarin has ruled this field for more than half century since its approval in 1954.[11] Later, other vitamin K antagonist (VKA) such as phenprocoumon or acenocoumarol (nicoumalone) that differ mainly in their half-life were developed and introduced for clinical use.[10]

The drawbacks attached with warfarin were frequent requirement of monitoring of International Normalized Ratio (INR) between 2-3, slow onset of action- with actions peaking after 3-6days, narrowness of therapeutic index with frequent interaction with food & medications and a long half-life of 20-60 hrs.[10,11] The above-mentioned factors often produce bleeding as adverse effect, which could be potentially fatal. The recommended measures to control bleeding includes Prothrombin complex concentrate (PCC) containing factor II, IV, IX and X; Vitamin K; fresh frozen plasma which can successfully reverse the coagulation induced by warfarin.[11] The mere existence of this risk, demands the need of newer oral anticoagulants, which could replace warfarin with limited risk of bleeding.[10,11]

The first oral direct thrombin inhibitor, dabigatran etexilate was approved to lower the risk of stroke in patients of non-valvular atrial fibrillation (2010) and for treatment of venous thromboembolism. The main advantage tagged to it is the non- requirement of INR control, reduced food and drug interaction ultimately leading to reduced risk of bleeding.[12] The other group is of direct factor Xa inhibitors, Rivaroxaban (2011), Apixaban (2012), edoxaban (2014) and betrixaban (2017).[13,14] All are collectively called as Novel oral anticoagulants (NOACs).

Although these new drugs achieve anticoagulation with relatively less risk of bleeding (but no statistically significant

Financial or Other, Competing Interest: None.
Submission 20-02-2019, Peer Review 21-02-2019,
Acceptance 26-02-2019, Published 02-03-2019.
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DOI: 10.18410/jebmh/2019/141

difference with warfarin), there has been hesitancy in prescription of these agents by physicians against clinically established and cheaper warfarin. One of the main reasons is the absence of effective reversal agents which may be lifesaving if serious bleeding occurs inevitably.[14,15]

The constant search for reversal agents lead to the discovery of potential reversal agent's idarucizumab, andexanet alfa and ciraparantag (PER977). Idarucizumab is a humanized monoclonal antibody which binds to Dabigatran with high affinity and acts as a specific antagonist for Dabigatran induced anticoagulation. FDA has designated it as a breakthrough therapy in June 2014.[15] Andexanet alfa is a recombinant protein from human factor X for the reversal of anticoagulation induced by direct factor Xa inhibitors.[15,16] Ciraparantag (PER977) is a small synthetic, water soluble molecule having activity against both older anticoagulants (heparin, LMWHs) and the newer anticoagulants (Dabigatran, apixaban, rivaroxaban and edoxaban).[16,17]

This topic assumes great significance as the available of reversal agents could potentially dethrone warfarin and establish the newer thrombin and factor Xa inhibitors as the oral anticoagulants of choice. Hence, the present study was planned to explore the drug utilization pattern of newer oral anticoagulants in a tertiary healthcare system.

Aims and Objectives

To study the consumption pattern of oral anticoagulants in a tertiary healthcare system over a period of 6 years and assess the change in trend of utilization of newer oral anticoagulants.

MATERIALS AND METHODS

The study assessed the consumption pattern of all oral anticoagulants in a tertiary care teaching hospital following a model of healthcare delivery which is sponsored institutionally. After approval from institutional ethics committee, the consumption pattern of all the oral anticoagulants namely warfarin, nicoumalone, dabigatran, rivaroxaban, apixaban and edoxaban was assessed over a period of six years from 2013 to 2018. The rationale of selecting this time zone is based on the approval of first reversal agent (Idarucizumab) for the newer oral anticoagulant dabigatran in 2014. Hence, the study of consumption pattern over these years may provide a change in pattern of the utilization of anticoagulants.

The consumption pattern was obtained using the data from the software installed at the dispensary to check the daily drug utilization from the prescriptions issued and also from medical stores database to document the stocks received by the hospital medical store. The data was cross checked from the registers which were maintained simultaneously. All the doses of the anticoagulants warfarin (1, 2 & 4 mg), Nicoumalone (1, 2 & 4 mg), dabigatran (110 & 150 mg), apixaban (2.5 & 5 mg), rivaroxaban (10 & 20 mg) & edoxaban were treated as one to obtain the overall consumption pattern.

RESULTS

A total of 1205000 prescriptions in a busy tertiary care center were analysed to see the consumption of oral anticoagulants. In the year 2013, Nicoumalone (51.22%) and warfarin (45.64%) constituted the majority of the oral anticoagulant prescribed by the hospital. The only NOAC prescribed was dabigatran, constituting just 3.14% of the total prescription of oral anticoagulants. (Table 1 & 2, Figure 1)

In 2014, the situation was no different with again nicoumalone topping the chart with 50.73% of total oral anticoagulants prescribed, followed by warfarin (44.26%). The NOACs were still a minority with dabigatran (4.82%) and a new entrant rivaroxaban constituting only 0.19% of total oral anticoagulants prescribed from the hospital. (Table 1 & 2, Figure 1).

In 2015 for the first time nicoumalone (44.07%) fell below 50% of total oral anticoagulants prescribed, followed by warfarin (35.58%). There was an upswing in prescribed NOACs with dabigatran (13.39%), apixaban (9.48%) & rivaroxaban (0.48%). This was the first time a NOAC accounted for more than 10% of the prescribed oral anticoagulants. (Table 1 & 2, Figure 1)

In 2016 there was a similar situation with nicoumalone (30.36%), warfarin (26.89%), dabigatran (29.49%), rivaroxaban (0.77%) & apixaban (12.49%). This was for the first, a NOAC dabigatran was preferred and prescribed more than traditional acenocoumarol. (Table 1 & 2, Figure 1)

In 2017, the complete reversal took place with dabigatran becoming the most prescribed oral anticoagulant accounting for 38.02% of the total anticoagulant prescribed. It was followed by another NOAC apixaban (24.67%), then the traditional anticoagulants nicoumalone (20.55%), warfarin (15.41%) & rivaroxaban constituting 1.35% of the prescribed oral anticoagulants. (Table 1 & 2, Figure 1)

In 2018 the consumption pattern was on similar lines to 2017 with dabigatran the most prescribed (41.4%), followed by apixaban (30.25%), nicoumalone (19.11%), warfarin (7.17%) & rivaroxaban (2.07%). The overall trend clearly point towards a downward trend for warfarin & nicoumalone, with an upward trend in favour of NOACs. (Figure 2)

	2013	2014	2015	2016	2017	2018
Warfarin	90000	82000	68000	62000	30000	13500
Nicoumalone	101000	94000	92000	70000	40000	36000
Dabigatran	6200	8940	27960	68000	74000	78000
Rivaroxaban	0	350	1000	1771	2625	3900
Apixaban	0	0	19800	28800	48000	57000
Edoxaban	0	0	0	0	0	0

Table 1. Consumption Pattern of Oral Anticoagulants

	2013	2014	2015	2016	2017	2018
Warfarin	45.64	44.26	35.58	26.89	15.41	7.17
Nicoumalone	51.22	50.73	44.07	30.36	20.55	19.11
Dabigatran	3.14	4.82	13.39	29.49	38.02	41.4
Rivaroxaban	0	0.19	0.48	0.77	1.35	2.07
Apixaban	0	0	9.48	12.49	24.67	30.25
Edoxaban	0	0	0	0	0	0

Table 2. Consumption Pattern of Oral Anticoagulants in Percentage

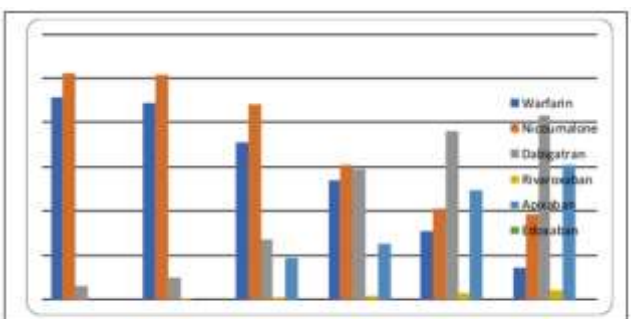

Figure 1. Consumption Pattern of Oral Anticoagulants

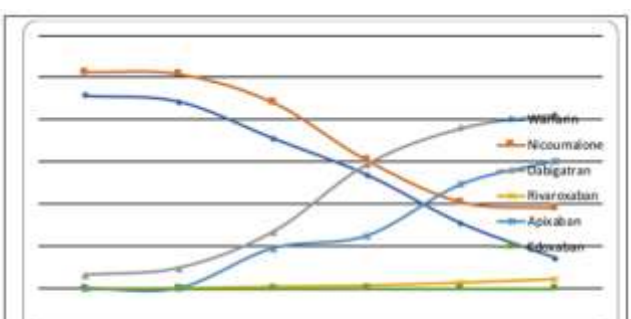

Figure 2. Trends in Consumption Pattern of all Oral Anticoagulants

DISCUSSION

The current study was undertaken to study the overall consumption of oral anticoagulants in a tertiary care centre. Our study clearly brings out a declining in the use of warfarin & nicoumalone and an increasing trend in the use of NOACs rivaroxaban, apixaban and edoxaban. In line with our study, Ziakas et al (2018) in their retrospective, cross-sectional analysis of claims with respect to NOACs presented an overall increase in the use of prescribed oral anticoagulants to 24.4 million with an estimated cost of $ 3.3 billion. They also reported that NOACs amount to 31% of total oral anticoagulant claims.[14]

Weitz JI, et al (2015) in their study of prescription pattern of oral anticoagulants from 2008- 2014 in Canada, have demonstrated a steady decline in the prescription of warfarin as oral anticoagulant from 99% in 2010 to 67% in 2014.[18] This clearly correlates with our study where a similar lower trend in warfarin prescription noted, with warfarin accounting to just 7% & nicoumalone to 20% in comparison to their combined utilization of 97% in 2013.

Loo SY; et al (2017) in their study to assess trends in prescription of NOACs in UK primary care reported an overall increase in rate of prescribed oral anticoagulants. The NOACs initiated has shown an overall increase of 17 fold from 2012 - 2015. The NOACs in 2015 accounted for 56.5% of total oral anticoagulants prescribed. This again support the results of our study.[19]

Hanley CM et al (2015) reviewed four large studies with different populations of patients with AF and concluded that the direct thrombin and factor Xa inhibitors have been shown to have a more favourable bleeding profile and are as efficacious as warfarin. They also stated that although it is difficult to understand why a practitioner would start warfarin in a new patient without a contraindication to a NOAC, switching to a newer agent may not be necessary for the patient in whom the INR has been well controlled with warfarin. They also concluded that although a new era of anticoagulation is emerging, but the decision to use a novel agent versus warfarin must be an individual one.[20]

Ahmad M et al (2015) in his questionnaire based study on Registrar/Consultant showed that all were aware of the 3 NOACs, but less than half could state individual mode of actions (39%). 46% could state NICE approved indications and 48% recognized the need for variant dosing. 83% of respondents correctly answered NOACs do not need monitoring, 74% identified the need for interruption pre procedures/surgery. 81% reported lack of a reversal agent. Only 36% had prescribed a NOAC with only 28% confident to initiate a NOAC.[21]

Loo SY, et al (2017) in their study report that rivaroxaban to be the most commonly prescribed NOACs followed by apixaban and dabigatran.[19] This was in contrast to our study result which brings out dabigatran to be the most commonly used NOAC followed by apixaban and rivaroxaban. Mendoza-Sanchez J, et al (2018) in their multi-criteria decision analysis to assess the benefit, risk & cost of using NOACs in comparison to warfarin in atrial fibrillation concluded that apixaban should be the most preferred anticoagulant followed by dabigatran, warfarin and rivaroxaban.[22]

CONCLUSION

The new oral anticoagulants are indeed a great boon but are underused and easily overshadowed by well-established warfarin. There has been a significant change in market dynamics with the introduction of new reversal agents. Various anticoagulant drug manufacturers are entering into a pact with the companies working on these reversal agents, which carry potential to take over market of warfarin. We should get ready for this game changing dynamics which looks promising at the moment and probably save many lives which can lost due to either excess or under anticoagulation attained with warfarin.

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