

Impact of Drug Interaction on Time in Therapeutic Range of Patients Receiving Oral Anticoagulation Therapy

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ABSTRACT

Objectives: Drug-drug interactions (DDIs) are a significant consideration in Anticoagulation management. The objective of this study was to identify DDIs with Vitamin K Antagonists (VKAs) and to assess the effect of DDIs on Time in Therapeutic range (TTR) (percentage of time a patient's INR is within the desired treatment range). **Methods:** An Observational study carried over a period of 6 months. Patients taking VKAs are included in this study. Patient data were collected from patient records and hospital information system. TTR calculation was done using the Rosendaal method. Drug interaction was checked using the Drug interaction checker (Micromedex) and online Lexi Interact. Criticality index was calculated using "Failure Modes, Effects and Criticality Analysis" (FMECA) method. Association between DDIs and TTR were assessed. **Results:** Fifty four DDIs were identified in a total of 150 patients (mean age 55.47 years, 56.66% women). Twenty one drugs were potentially interacting with VKAs. Four drugs have a criticality index of ≥ 10 are considered as high risk for interacting with VKAs. The mean TTR was $33.12 \pm 26.06\%$, 20 patients (13.33%) were under good control and 130 patients (86.67%) were under poor control. Out of fifty four DDIs, Fifty one DDIs (94%) are in poor control population. Drug interaction and clinical events such as bleeding and thromboembolism were significantly associated ($p=0.01$). Drug interaction ($p=0.02$) was a significant predictor of poor control of TTR. **Conclusion:** DDI is one of the major factors that alter the percentage number of days the patients were in the desired INR range (TTR).

Key words: Vitamin K Antagonist, Drug interaction, Clinical events, Criticality index, Time in Therapeutic Range.

INTRODUCTION

Vitamin K antagonists (VKA) such as Warfarin and Acenocoumarol have been the mainstay of oral anticoagulant therapy for the past 60 years and it is most commonly used to treat or prevent thrombosis in patients with venous thromboembolism, atrial fibrillation and prosthetic heart valves.¹ Patients receiving oral anticoagulation should maintain International Normalized Ratio (INR) with a target range of 2-3. Abnormal INR values will lead to complications such as Bleeding and Thromboembolic events. Anticoagulation control is assessed by Time in Therapeutic Range (TTR). TTR is the percentage of time a patient's INR is within the desired treatment range.^{2,3}

The numerous Drug-Drug Interactions (DDIs) involving VKA influence TTR remarkably. DDIs cause variability in

anticoagulation and leads to severe side effects. DDIs are a significant consideration in anticoagulation management. VKAs interact with various other drugs pharmacokinetically by affecting the metabolism of other drugs, pharmacodynamically by either increasing or decreasing the effect of other drugs and Unknown mechanism.⁴

DDIs with VKAs have been documented earlier but its importance in clinical practice is not determined. This study focuses on the consequences of DDIs on TTR in patients receiving Oral anticoagulation therapy (OAC).

MATERIALS AND METHODS

Research design

The Observational study was carried over a period of 6 months in the department of Cardiology in a tertiary care hospital,

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Coimbatore, India. This study was carried out after approval (approval number – 18/026) from Institutional Human Ethical Committee (IHEC).

Patients receiving OAC were included in the study and those who are not on regular follow up and hepatic dysfunction were excluded. Patient data like Demographics, Medication history and INR values were collected from Hospital Information System and Patient interview. Using the INR values collected, TTR was calculated for each patient using Roosendaal method which was performed with the assistance of template produced and made freely available by INR Pro.⁵ This method calculates TTR by using actual values and frequency of INR measurements. The calculation tool was validated by the Institutional Human Ethics Committee (IHEC). Patients were categorized as good control ($\geq 65\%$) and poor control ($< 65\%$) based on TTR. DDIs of VKAs with other drugs were checked using Drug Interaction Checker (Micromedex) and the online version of Lexi interact. Criticality Index was calculated using “Failure Modes, Effects and Criticality Analysis” (FMECA) method to identify which drug is high risk potential in interaction with VKAs and TTR.²

Statistical analysis

Independent *t* test was used to find the association of TTR (Poor control population and Good control population) with clinical events and DDIs.

RESULTS

In a total of 150 patients, the mean TTR was 33.12%. Out of which 20 patients (13.33%) were in good control and 130 patients (86.67%) were in poor control. Clinical events like bleeding and thromboembolic events were high in poor control population (22%). Drug interaction is one of the reasons for abnormal events in patients receiving OAC. Out of 54 DDIs, most of it comes under poor control population (38.4%) which was statistically significant compared to that of good control population ($p=0.04$). When comparing DDIs with Clinical events 34% of Clinical events occurred, out of which 38.4% of DDIs were in poor control population with statistically significant value ($p=0.001$) [Figure 1]. Amiodarone holds the highest percentage of interaction with OAC (31.2%) followed by Sertraline (7.81%), Tramadol (6.25%), Rosuvastatin (6.25%) and various other drugs [Figure 2]. OAC interacts with other drugs by various mechanisms. In this study 35 DDIs comes under Pharmacokinetic interaction, 5 DDIs were Pharmacodynamics interaction and 14 DDIs were due to unknown mechanisms. To know the highest risk potential of each drug that interacts

with OAC, Criticality index was calculated in which Amiodarone was known to have a high risk of interaction with OAC followed by other drugs [Table 1]. Criticality index of >10 (a number which we set arbitrarily) is considered as high risk.

DISCUSSION

Vitamin K Antagonists (VKA) such as Warfarin and Acenocoumarol have been the conventional therapy for the management of various thromboembolic events for decades.^{6,7} Its efficacy is assessed by monitoring International Normalized Ratio (INR) in current clinical practice. Rosendaal *et al.* developed a method called Time in Therapeutic Range (TTR) which assesses the duration of time the patients’ INR is within the desired range in terms of percentage. It is regarded as the golden standard

Table 1: Criticality index for drugs interacting with VKAs.

Drug	Criticality Index*
Amiodarone	300
Sertraline	128
Amitriptylline	16
Rosuvastatin	12
Fluconazole	8

*Criticality index was calculated using FMECA² method. Greater than 10 are considered as high risk interacting drug.

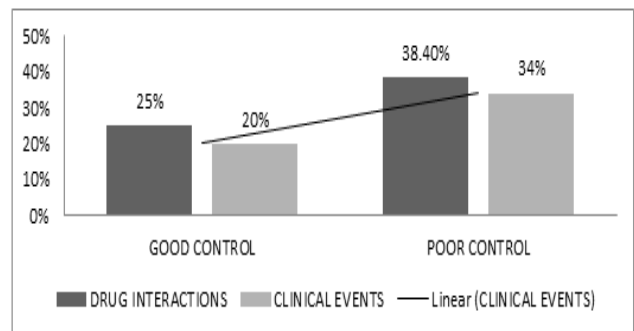


Figure 1: Clinical events in DIs.

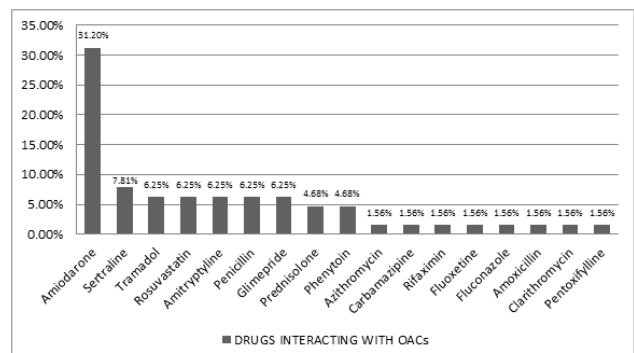


Figure 2: Drugs interacting with OACs.

to assess the quality of anticoagulation therapy.

In NICE guidelines TTR percentage of <65% was considered as poor control.⁸ In our study, 86.67% of patients had < 65% TTR and categorized as poor control. The mean TTR in our study was 33.12%. ROCKET AF, a double-blind trial assessed the anticoagulation control with a mean TTR of 36% in India.⁹ From limited data on TTR available in India, we could infer the mean TTR ranges from 30-40%.^{10,11} This shows poor anticoagulation control in India which necessitates the need to elaborate the cause behind the results.

The rationales behind the poor anticoagulation control were appraised as various factors such as age, comorbidities, polypharmacy, socio-economic factors and so on. Out of which drug-drug interactions are one of the most significant factors that can have a remarkable effect on the quality of the therapy. The need to assess the significance of drug interaction with TTR was proposed by Bahram *et al.*² in their study.

In our study, we identified 54 drug interactions among 150 patients. Most of the drug interactions contributed to a poor control of TTR (38.4%) compared to good control population which accounts for a statistical significance of $p = 0.04$. In the light of above findings, the consequence of drug interaction in OAC therapy was revealed. Therefore, the need for monitoring DDI is momentous for the better management and quality of oral anticoagulation.

Another aspect of great importance is regarding DDIs that contribute to clinical events in patients receiving OAC therapy.¹² Drug interactions causing clinical events in poor control populations were significant when compared to good control population ($p = 0.001$) in our study. This reveals the consequences due to DDIs that demands strict monitoring of interactions and subsequent tailoring of the treatment regimen for patients.

Detailing the mechanism behind the interactions is equally important as of identifying DDIs. It is well documented that VKAs interact with other drugs pharmacokinetically by affecting the metabolism of other drugs (38 pharmacokinetic interactions), pharmacodynamically by either increase or decrease the effect of other drugs (5 pharmacodynamic interactions) or by an unknown mechanism (17 interactions).⁴ Understanding about the mechanism helps in customizing the management for patients.

Based on observations, various drugs potentially interact with VKAs. Among the co-prescribed medications

in our study population Amiodarone has the highest risk of interaction with OAC. Amiodarone interacts pharmacokinetically by inhibiting the metabolism of VKA, thereby increasing INR which aggravates bleeding risk.¹ Criticality index was calculated by multiplying three components: Mechanism of drug interaction, Frequency of involvement in a supratherapeutic INR, Frequency of involvement in bleeding events. The criticality index tool which was used to measure the risk of interaction with OAC showed 300 for Amiodarone followed by Sertraline, Tramadol, Rosuvastatin and various other drugs as in [Table 1]. Criticality index of >10 (a number which we set arbitrarily) is considered as high risk.¹³

The study emphasizes the importance of monitoring DDIs in the view of the fact that patients are on polypharmacy due to co-morbid conditions. Maintenance of TTR under good control by appropriately designing treatment regimen to avoid DDIs and provide patient care can keep patients out of clinical events during therapy.

CONCLUSION

DDI is one of the major factors that alter the percentage number of days the patients were in the desired INR range (TTR). Moreover, it contributes to the development of complications. Further implementation of alerts for these drugs would improve the quality of anticoagulation therapy.

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CONFLICT OF INTEREST

The authors declare no other conflict of interest.

ABBREVIATIONS

DDI: Drug-drug interaction; **VKA:** Vitamin K antagonist; **INR:** International normalized ratio; **TTR:** Time in Therapeutic Range; **OAC:** Oral anticoagulation therapy; **IHEC:** Institutional Human Ethics Committee; **FMECA:** Failure Modes, Effects and Criticality Analysis.

SUMMARY

TTR helps in assessing the quality of oral anticoagulation therapy where most of the patients undergoing the therapy fall in poor control. One of the factors associated with this poor control is DDI. The study could effectively

project the evidence for this by showing the statistical significance of DDI with clinical events. Criticality index helps in identifying the drug that has the highest risk in interacting with VKAs. Identifying these interactions and implementing necessary changes will lead to more efficient management of oral anticoagulation therapy.

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