You cannot always warfawin: a case of significant INR fluctuation with brand to generic conversion of warfarin

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ABSTRACT

Background: Warfarin is affected by many variables such as diet, alcohol, and medications; however, it is unclear if brand to generic conversion may also play a role. This case reports a patient with fluctuating international normalized ratio (INR) while being switched from brand to generic temporarily.

Case Presentation: A 60-year-old obese white male taking brand name Jantoven© (warfarin) at home for 9 years at a consistent dose for atrial fibrillation was in hospital for treatment of cellulitis. He was switched to generic warfarin at his home dose on admission. While in hospital, he required dose escalation to three times his home dose to achieve a therapeutic INR.

Conclusion: Generic warfarin may have different effects on INR when compared to brand name Jantoven©. More research is warranted to determine if differences may truly exist and potential ways to address the issue. Until then, providers should be cognizant of interchanging the two products to monitor for INR variation.

Keywords: Jantoven, warfarin, inpatient, atrial fibrillation, substitution, INR.

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Background

Warfarin has been widely used for various medical conditions that require anticoagulation, dating back to 1954 [1]. There are multiple conditions it is used for, including stroke prevention in atrial fibrillation and venous thromboembolism [2,3]. International normalized ratio (INR) monitoring is indicated to ensure safety and efficacy [4]. While some confounders such as diet, alcohol and medications are known to affect INR, it is unclear if brand to generic conversions may also affect INR, although they are considered interchangeable [5]. This case examines a patient who experienced significant INR fluctuations during hospitalization. The patient was taking brand name Jantoven® at home which was substituted with generic warfarin while in hospital.

Case Presentation

A 60-year-old obese white male presented to the emergency department (ED) with an erythematous and swollen left lower extremity since the previous day. He was admitted to the hospital for treatment of cellulitis. His past medical history included hypertension, atrial fibrillation, and obstructive sleep apnea. His home medications included potassium chloride, bumetanide, amlodipine, benazepril, and brand name Jantoven® (warfarin) for 8 years. He was given levofloxacin and vancomycin in the ED but was switched to vancomycin, ceftriaxone, and clindamycin upon admission. Infectious diseases were consulted to adjust and monitor antibiotic therapy and the same therapy was continued. Pharmacy was consulted to manage the patient's warfarin for atrial fibrillation, with a goal INR of 2-3. At home, the patient took brand name Jantoven® 2 mg orally on Sun/Tues/Wed/Thurs/Sat and 1 mg on Mon/Fri (12 mg weekly) - this dosing regimen was consistent for 7 years. His INR was 1.7 on admission and his home dose was resumed. Over the course of treatment, the patient's INR eventually fell to 1.1 on day 9 of admission. The doses were steadily increased to a peak of 6 mg daily. All pertinent confounders for a warfarin patient were thoroughly investigated with no significant findings. Antibiotic therapy was adjusted during admission to ultimately include daptomycin and cefepime. The patient remained in hospital for 17 days with the INR becoming therapeutic on day 16 of admission. At discharge, the patient's INR was 2.4 and he was receiving oral warfarin 6 mg daily. Knowing that he would be taking brand name Jantoven® as an outpatient, he was discharged on his previous home regimen (12 mg weekly) and his INR 1 week after discharge was 2.8. Upon further investigation into his medical record, it was revealed that the patient had started generic warfarin when he was admitted

Table 1. *Details of anticoagulation during inpatient stay.*

Day of Admission	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
INR	1.7	1.6	1.6	1.8	1.8	2.0	2.0	1.4	1.2	1.1	1.1	1.3	1.4	1.6	1.7	1.9	2.2	2.4
Dose		2mg		1mg	3mg	2mg		3mg		5mg					6mg			

This table represents INR fluctuation with subsequent warfarin dosing during the patients course of stay.

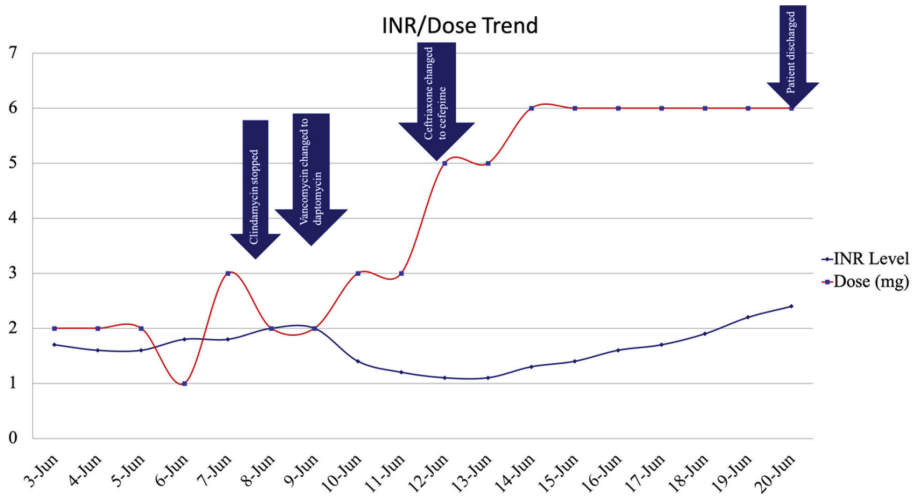

Figure 1. *Adjustments made to antibiotic therapy during inpatient stay. This figure shows the dose fluctuation during the patient's course of stay until discharge. It includes therapy changes, represented by arrows, to show potential causes for dose fluctuation.*

to the hospital in 2010 and diagnosed with atrial fibrillation. During his admission then, he was escalated to 7.5 mg daily, which he was subsequently discharged on. He filled brand name Jantoven® and over the next 3 weeks he consistently had supratherapeutic INRs and eventually reached a dose of 12 mg as a total weekly dose. Since then he has been maintained on brand name Jantoven® with a time in therapeutic range (TTR) of 79% (69 out of 87) over the course of 9 years on a dose of 12-13 mg weekly as an outpatient. All of his INRs, except one that was 3.1, have been within therapeutic goal range of 2-3 since his discharge. Details of his anticoagulation during his inpatient stay are included in Table 1 and adjustments made to antibiotic therapy during admission coinciding with changes in INR are shown in Figure 1.

Discussion

On the last day during his admission, the patient reached a therapeutic INR of 2.4 with a dose of 6 mg daily. This dose is three times his normal home dose. Upon discharge, the patient was instructed to resume his pre-admission dose of brand name Jantoven® (12 mg/week). At his follow-up, with the anticoagulation clinic 1 week after discharge, his INR was in the therapeutic range. The patient was a great historian and was very diligent about taking his warfarin consistently and maintaining a consistent diet and lifestyle, as his TTR suggests. This observation occurred despite vitamin-k rich foods being avoided during the latter part of admission and despite being on antibiotics that could potentially increase INR. Additionally, all causes that could potentially decrease INR were thoroughly investigated without the identification of a source when compared to his home lifestyle. There is little to no data available regarding INR changes with a sedentary lifestyle. Furthermore, a similar observation occurred when the patient first started taking warfarin and switched to Jantoven® 8 years prior, suggesting this was more than just a chance occurrence. As this case suggests, generic warfarin may have a different pharmacokinetic profile and effect on INR compared to brand name Jantoven® in select patients for unknown reasons. Little information currently exists on this potential phenomenon. The two drugs have differences in inactive ingredients such as anhydrous lactate, povidone, lactose monohydrate, and barium oxide; however, it is not known if this can affect INR [2,3]. The Food and Drug Administration (FDA) Orange Book states the generic meets all bioequivalence standards, further posing the question of what caused the INR difference [6]. More research needs to be completed to determine the root of the INR differences as well as potential ways to address the issue. Additionally, more information is needed on whether or not this phenomenon occurs with brand name Coumadin®. The current information available is consistent with the generic meeting all equivalencies. A report completed in 2002 analyzed the substitution of generic warfarin for Coumadin® in an Health Maintenance Organization (HMO) setting and found no significant differences in INR, adverse events, or

management [7]. Another report, a randomized crossover comparison of warfarin products in the treatment of atrial fibrillation, found similar results [8]. This study showed that between two warfarin products, the dose increases and INR changes were similar and were not isolated to one product [8]. Despite these data demonstrating similar effects on a population, this case demonstrates the importance of recognizing individual effects brand substitution may have on patients. An additional article was examined from *New England Journal of Medicine*. This study used a protocol that converted two generic warfarin products for brand name. The study reported no change in rates of INR testing [9]. To note, the above articles mentioned all use brand name Coumadin® and not Jantoven®. Until more data are available investigating this phenomenon, it is important to obtain information about the warfarin formulation a patient is on and closely monitor INR if a substitution is necessary.

List of Abbreviation

INR	International normalized ratio
ED	Emergency department
TTR	Time in therapeutic range
FDA	Food and Drug Administration
HMO	Health Maintenance Organization;

Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this article.

Funding

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Consent for publication

Written consent was obtained from the patient.

Ethical approval

Ethical approval is not required at our institution to publish an anonymous case report.

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References

1. Pirmohamed M. Warfarin: almost 60 years old and still causing problems. Br J Clin Pharmacol. 2006;62(5):509–11. https://doi.org/10.1111/j.1365-2125.2006.02806.x
2. Clinical Pharmacology [Internet]. [cited 2019 Oct]. Available from: https://www.clinicalpharmacology-ip.com/Forms/drugoptions.aspx?cpnum=650&n=Warfarin&t=0&enh=1
3. Warfarin. Micromedex Products [Internet]. [cited 2019 Oct]. Available from : https://www. micromedexsolutions.com/mic romedex2/librarian/CS/ FBD625/ND_PR/evidenc ex pert/ND_P /eviden cexp ert/DU PLICATIO NSHIELDS YNC/DBFC7F/ND_PG/e videncexpert/ND_B/evide ncex pert/ND_AppP roduct/ evi dence xpe rt/ND_T /evide ncexpert/P FActionId/e videncex pert.DoIntegratedSearch ?SearchTe rm=warfarin&UserSearchTerm=warfarin&SearchFilter=filterNone&navitem=-searchALL#
4. International normalised ratio (INR) test. healthdirect. [cited 2019 Nov]. Available from: https://www.healthdirect.gov.au/international-normalised-ratio-INR-test
5. Witt DM, Tillman DJ, Evans CM, Plotkin TV, Sadler MA. Evaluation of the clinical and economic impact of a brand name-to-generic warfarin sodium conversion program. Pharmacotherapy. 2003;23(3):360–8. https://doi.org/10.1592/phco.23.3.360.32103
6. Coumadin: FDA Orange Book: Approved Drug Product List. PharmaCompass.com. [cited 2019 Nov]. Available from: https://www.pharmacompass.com/fda-orange-book/coumadin
7. Milligan PE, Banet GA, Waterman AD, Gatchel SK, Gage BF. Substitution of generic warfarin for coumadin in an HMO setting. Ann Pharmacother. 2002;36(5):764–8. https://doi.org/10.1345/aph.1A327
8. Weibert RT, Yeager BF, Wittkowsky AK, Bussey HI, Wilson DB, Godwin JE, et al. A randomized, crossover comparison of warfarin products in the treatment of chronic atrial fibrillation. Ann Pharmacother. 2000;34(9):981–8. https://doi.org/10.1345/aph.10068
9. Paterson JM, Mamdani M, Juurlink DN, Naglie G, Laupacis A, Stukel TA. Clinical consequences of generic warfarin substitution: an ecological study. JAMA. 2006;296(16):1969–72. https://doi.org/10.1001/jama.296.16.1969-b

Summary of the case

1	**Patient (gender, age)**	Male, 60-year-old
2	**Final diagnosis**	Cellulitis, atrial fibrillation, hypertension, and obstructive sleep apnea
3	**Symptoms**	Erythematous and swollen left lower extremity
4	**Medications**	Generic warfarin
5	**Clinical procedure**	Warfarin 6 mg daily at discharge
6	**Specialty**	Internal medicine, cardiology