



Subtherapeutic INR in a Patient on Warfarin Therapy after Discontinuation of Lomustine

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Author's contribution

The sole author designed, analyzed, interpreted and prepared the manuscript.

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Case Study

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ABSTRACT

Aims: To report a case of a potential drug interaction between warfarin and lomustine that may have led to a subtherapeutic International Normalized Ratio (INR) and to inform health care providers of a need for more frequent INR monitoring in this patient population.

Presentation of Case: A 64 year-old Caucasian male previously stable on warfarin presented to an anticoagulation clinic with a subtherapeutic International Normalized Ratio (INR) of 1.6 after discontinuation of a six-month course of lomustine for glioblastoma three weeks prior. The patient had been on a stable warfarin dose of 42.5 milligrams (mg) weekly while using lomustine therapy for 6 months. After an 11.8% increase in the weekly dose of warfarin, the patient returned to a therapeutic INR.

Discussion: Common drug interaction resources such as Micromedex®, Lexicomp® and Facts and Comparisons® do not consistently list an interaction with warfarin and lomustine. The mechanism of a lomustine and warfarin drug interaction is theorized to be related to decreased liver cytochrome P450 (CYP)-mediated enzyme activities as well as CYP 3A4 enzyme inhibition observed in previous studies. Due to the described effects of lomustine on the CYP enzyme activities and the possibility for pharmacokinetic interactions with a highly CYP metabolized drug

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like warfarin, there is a potential for prolonged warfarin activity when combined with lomustine therapy. For patients taking both medications, more frequent INR monitoring may be advised more than drug interaction references suggest. An objective causality assessment revealed that the interaction was probable (Drug Interaction Probability Scale: 6-7).

Conclusion: The interaction between lomustine and warfarin likely decreased the INR in this patient case report due to a reversal of decreased liver CYP 450-mediated enzyme activities and pharmacokinetic effects upon warfarin. Common drug-interaction references do not consistently list an interaction with warfarin and lomustine. Increased frequency of INR monitoring may be advised for patients taking both of these medications more than drug interaction references suggest.

Keywords: Drug interaction; warfarin; lomustine; cardiology; pharmacology; drug metabolism; oncology.

1. INTRODUCTION

The purpose of this case report and literature analysis is to describe a potential drug interaction between warfarin and lomustine that may have led to a subtherapeutic International Normalized Ratio (INR) and to inform health care providers of a need for more frequent INR monitoring in this patient population. Lomustine is an agent indicated for the treatment of breast carcinoma, Hodgkin's disease (secondary therapy in combination with other therapies), intracranial tumor, lung cancer and malignant melanoma. Lomustine is a cell-cycle nonspecific antineoplastic agent whose antitumor activity is related to its monohydroxylated metabolites following oral administration [1].

Warfarin has been a cornerstone of oral anticoagulant therapy for thromboembolism prophylaxis in patients with atrial fibrillation, heart valve replacement, deep venous thromboembolism or pulmonary embolism [2]. Oral chemotherapy such as lomustine is rapidly becoming a popular dosage formulation for cancer treatment. For patients with oncology comorbidities such as deep venous thrombosis or pulmonary embolism secondary to chemotherapy or tumor activation, coadministration of lomustine and warfarin becomes a more common occurrence.

2. PRESENTATION OF CASE

A 64 year-old Caucasian male had been anticoagulated on warfarin therapy following a deep vein thrombosis and pulmonary embolism one week after total resection of a left frontal glioblastoma three years prior to initiation of lomustine. After initiation of lomustine, the patient required a dose decrease of warfarin two weeks after concomitant therapy. The patient

maintained a warfarin weekly dose of 42.5 mg with therapeutic INRs from October 2015 through early April 2016. The patient presented to the anticoagulation clinic on 4/26/16 with an INR of 1.6. The patient's INR the month prior to discontinuation of lomustine was 2.8 (3/28/16). Three weeks prior to his anticoagulation clinic appointment in late April, the patient had discontinued his 6 month therapy of lomustine 200 mg every 6 weeks. The patient was interviewed by the anticoagulation pharmacist and denied any other change in prescription medication, over-the-counter medication or supplements, exercise, alcohol use, cigarette/tobacco use, vitamin K intake, supplements, higher protein intake, V8® juice intake, green tea intake, or recent illness etc. Unchanged daily medications included: metoprolol 25 mg twice daily, spironolactone 25 mg, cholecalciferol 1000 mg, albuterol inhaler as needed, vitamin B complex, zafirlukast 20 mg twice daily, multivitamin, atorvastatin 20 mg, ondansetron 8 mg every 8 hours as needed, lisinopril 20 mg and warfarin 5 mg (42.5 mg weekly dose). The patient's INR 9 days after an 11.8% warfarin dose increase from 42.5 mg to 47.5 mg per week was therapeutic at 2.4 (goal 2-3) without any noted changes by the patient.

3. DISCUSSION

Anticoagulation therapy in oncology patients is not an uncommon occurrence. Approximately 1 in 200 oncology patients will develop a venous thromboembolism each year. A cancer or tumor can increase the risk for thromboembolism by leading to tissue damage, an inflammatory response or secreted hormone that may activate the coagulation system [3]. The warfarin-anticoagulated patient described in the case report experienced a subtherapeutic INR after a recent discontinuation of lomustine therapy.

Table 1. Medication therapy and INR timeline

INR date	INR	Weekly warfarin dose	Patient changes
9/29/15	2.2	45 mg	None
10/27/2015	3.3	45 mg	Lomustine initiated 10/14/15
11/24/15	1.9	42.5 mg	None
12/22/15	1.8	42.5 mg	None
1/18/16	3.3	45 mg	None
2/8/16	2.2	42.5 mg	None
2/29/16	2.4	42.5 mg	None
3/28/16	2.8	42.5 mg	None
4/26/16	1.6	42.5 mg	Lomustine discontinued after 4/3/16
5/5/16	2.4	47.5 mg	None
6/9/16	3.0	47.5 mg	None

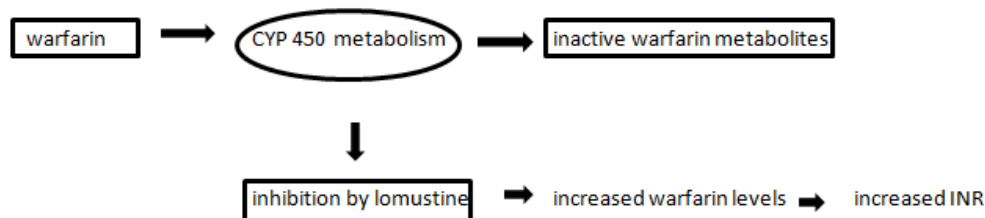
The patient had been taking a stable weekly warfarin dose of 42.5 milligrams (mg) for the previous 6 months of lomustine therapy. Prolonged decrease in cytochrome (CYP) 450-mediated enzyme activity [4] and inhibition of CYP 3A4 enzyme [5] is documented in the literature with lomustine therapy. Warfarin is a highly CYP metabolized drug notorious for CYP 450-mediated drug interactions [1]. A review of three common drug interaction search engines (Micromedex®, Facts and Comparisons®, and Lexicomp®) yielded no drug interaction between lomustine and warfarin [1,6,7]. Micromedex®, Facts and Comparisons®, and Lexicomp® are common drug interaction software programs used by health care professionals to check for drug interactions. To the best of the author's knowledge, there are no case reports documenting the interaction solely between lomustine and warfarin.

There is a randomized trial that compared hemorrhagic toxicity of methotrexate, doxorubicin, cyclophosphamide and lomustine (MACC) plus warfarin therapy with mitomycin, etoposide, cisplatin, and hexamethylmelamine (MEPH) plus warfarin therapy in small-cell lung cancer patients. Hemorrhagic toxicity was increased in the lomustine (MACC) plus warfarin therapy group with 4% of hemorrhages being life-threatening and 2% resulting in fatal

hemorrhages. The combination MACC therapy contains other chemotherapy agents known to increase the INR, but the MEPH treatment group also had known interacting drugs with warfarin [8].

According to the following literature about lomustine, there are two proposed theories for lomustine's effect on warfarin therapy: 1. Prolonged decrease in liver CYP P450-mediated enzyme activity in lomustine treated rats [4] 2. Weak competitive inhibition of CYP 3A4 by lomustine [5]. Due to the described effects of lomustine on inhibition of CYP enzyme metabolism, there is a potential for an increase in warfarin metabolism when lomustine is discontinued while stable on warfarin therapy. Therefore, discontinuing lomustine would have the reverse effect and decrease warfarin therapy effectiveness as shown by a subtherapeutic INR.

Researchers have observed prolonged decreases in liver CYP 450-mediated enzyme activities in adult male rats given single intraperitoneal doses of lomustine 30 mg/kg. The change in activity was evidenced by a reduction of known CYP enzyme-mediated hydroxylation of cyclophosphamide and ifosfamide activity (30-60% decrease after 7-27 days of lomustine exposure) [4].

**Fig. 1. Proposed mechanism of warfarin and lomustine interaction**

Warfarin is metabolized by the following CYP enzymes: CYP2C9, 2C19, 2C8, 2C18, 1A2, and 3A4. Warfarin is a racemic mixture of R- and S-enantiomers that are metabolized differently by the CYP enzyme system. The S-enantiomer, which is metabolized by the CYP2C9 enzyme, is two to five times more potent than the R-enantiomer. The R-enantiomer does have a longer terminal elimination half-life compared to the S-enantiomer (up to twice as long) [2]. Weak competitive inhibition of CYP 3A4 by lomustine may inhibit the metabolism of the R-enantiomer of warfarin and thus increase the concentration of warfarin. Similarly, increased warfarin effect has been observed by erythromycin inhibition of the CYP 3A4 enzyme [9]. Therefore, when a patient is on a stable dose of warfarin while using lomustine and the lomustine is discontinued, this may cause a decrease in warfarin concentration or anticoagulation effectiveness as measured by the INR.

The assessment of a potential drug interaction was performed using the Drug Interaction Probability Scale (DIPS) [10]. For this case report, the objective causality scoring system evaluated the following: a potential previous credible report of the interaction in humans, consistency with known CYP interactions of lomustine and similar metabolism of warfarin, a reasonable time frame of the interaction, remission of the interaction upon dechallenge of lomustine, lack of rechallenge with lomustine, whether any reasonable alternative causes were present, laboratory work (INR) being consistent with the interaction, and confirmation of objective evidence consistent with the effects of warfarin. The DIPS score of six to seven revealed that the interaction was probable. The DIPS score could be as much as seven if considering the randomized trial with combination therapy containing lomustine and warfarin resulting in increased hemorrhagic toxicity. A score of five to eight is a probable interaction and eight or greater is a highly probable interaction.

4. CONCLUSION

This case report suggests the interaction between lomustine and warfarin likely decreased the patient's INR to a subtherapeutic level upon lomustine discontinuation due to pharmacokinetic effects of lomustine on the CYP 450 enzyme system. The mechanism of lomustine interaction is theorized to be due to decreased liver CYP 450-mediated enzyme activities as well as weak competitive inhibition of CYP 3A4 metabolism.

Common drug interaction resources do not consistently list an interaction with warfarin and extended-release lomustine.

For patients taking both of these medications, increased frequency of INR monitoring may be advised more than typical drug interaction references suggest. Weekly INR monitoring would be recommended upon initiation or discontinuation of lomustine in a patient concurrently taking warfarin. For patients initiating lomustine when currently on warfarin therapy, the clinician should recommend weekly INR monitoring as well as review signs and symptoms of bleeding with the patient (see Table 2). For patients discontinuing lomustine when currently on warfarin therapy, the clinician should also recommend weekly INR monitoring as well as review signs and symptoms of thromboembolism with the patient (see Table 3). If the patient experiences any symptoms of bleeding or thromboembolism, they should be instructed to contact their health care provider immediately.

Table 2. Signs and symptoms of bleeding

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- Nose bleeds
 - Bleeding from gums
 - Black/red or tarry stools
 - Red or rust-colored urine
 - Increased bruising
-

Table 3. Signs and symptoms of thromboembolism

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- Sharp back or chest pain
 - Redness/swelling or pain of a limb or calf muscle
 - Shortness of breath
 - Arm numbness
 - Severe headache
 - Difficulty speaking
-

CONSENT

The author declares that written informed consent was obtained from the patient for release of medical information for education and research purposes. The patient was not identified in this case report according to standard hospital HIPPA policies.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Author has declared that no competing interests exist.

REFERENCES

1. Micromedex on-line drug interaction for lomustine, warfarin. Available:<http://www.thomsonhc.com/home/dispatch> (Accessed May 12, 2016)
2. Ageno W, Gallus AS, Hylek E, et al. Oral anticoagulant therapy. Chest. 2012; 141(2 Suppl):e44S-88S. DOI: 10.1378/chest.11-2292
3. National blood clot alliance. Blood clot FAQs-cancer and blood clots. Available:<https://www.stoptheclot.org/cancer-and-blood-clots.htm> Updated Fall 2015. (Accessed May 13, 2016)
4. Chang TK, Chen H, Waxman DJ. 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea (CCNU) modulates rat liver microsomal cyclophosphamide and ifosfamide activation by suppressing cytochrome P450 2C11 messenger RNA levels. Drug Metabolism and Disposition. 1994;22(5): 673-9.
5. Segal EM, Flood MR, Mancini RS, et al. Oral chemotherapy food and drug interactions: A comprehensive review of the literature. Journal of Oncology Practice. 2014;10(4):e255-68. DOI: 10.1200/JOP.2013.001183
6. Facts and comparisons on-line E facts for lomustine, warfarin. Available:<http://www.factsandcomparisons.com> (Accessed May 12, 2016)
7. Lexicomp on-line drug interaction for lomustine, warfarin. Available:<http://www.lexi.com> (Accessed May 12, 2016)
8. Chahinian AP, Probert KJ, Ware JH, et al. A randomized trial of anticoagulation with warfarin and of alternating chemotherapy in extensive small-cell lung cancer by the cancer and leukemia group B. Journal of Clinical Oncology. 1989;7(8):993-1002.
9. Westphal JF. Macrolide – induced clinically relevant drug interactions with cytochrome P-450A (CYP) 3A4: An update focused on clarithromycin, azithromycin and dirithromycin. Br J Clin Pharmacol. 2000; 50(4):285–295. DOI: 10.1046/j.1365-2125.2000.00261.x
10. Horn JR, Hansten PD, Lingtak-Neander C. Proposal for a new tool to evaluate drug interaction cases. Annals of Pharmacotherapy. 2007;41:674-680. DOI: 10.1345/aph.1H423

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