

Evaluation of the Potential Drug Interaction of Melatonin and Warfarin: A Case Series

Noha I. Ashy¹, Krishna V. Shroff²

¹Noha Ashy, PharmD, Department of Clinical Pharmacy, King Abdulaziz University, Jeddah, Saudi Arabia

²Krishna Shroff, PharmD, Pharmacy Department, Massachusetts General Hospital, 55 Fruit St, Boston, MA 02114
noha_ashy@hotmail.com

Abstract: Melatonin has the potential to interact with warfarin for many reasons. According to the Micromedex drug interaction database, melatonin has been associated with bleeding complications and reduced prothrombin time (PT) in four case reports of patients who received both melatonin and warfarin. However, there is no primary literature that supports this finding. The objective of this case series is to evaluate potential drug interactions between melatonin and warfarin. Ten adult patients, who admitted to Massachusetts General Hospital (MGH) (Boston, MA) between April 2011 and April 2012 and were treated with melatonin and warfarin concurrently, were evaluated. MGH is a 950-bed teaching hospital. Those 10 patients had changes in INR and PT. They are selected because they were not on any other medications that have major interactions with warfarin, did not receive other anticoagulants, chemotherapy, as needed or 1 dose of melatonin during their hospital stay. The Drug Interaction Probability Scale (DIPS) was used to evaluate the potential drug interaction, and the following outcomes were recorded for each patient: bleeding events, INR, PT, albumin, and LFTs. The 10 patients were 54 years old or older and the duration of concurrent administration of both medications ranged from 2 to 10 days. Melatonin dose was stable in all 10 patients while warfarin dose had changed (increased/ decreased) in some patients. Both INR and PT increased in most patients during concurrent administration of melatonin with warfarin and no bleeding events have been noted. By calculating DIPS score for each patient, we found that 6 patients experienced possible drug interaction, 2 had probable drug interaction, and 2 had doubtful drug interaction. LFTs and albumin were normal in most patients. In conclusion, concurrent use of melatonin and warfarin may result in INR and PT changes and affects coagulation activity. Monitoring INR and PT regularly is suggested when both medications are administered concurrently.

[Ashy N, Shroff K. **Evaluation of the Potential Drug Interaction of Melatonin and Warfarin: A Case Series.** *Life Sci J* 2016;13(6):46-51]. ISSN: 1097-8135 (Print) / ISSN: 2372-613X (Online). <http://www.lifesciencesite.com>. 6. doi: [10.7537/marslsj13061606](https://doi.org/10.7537/marslsj13061606).

Key words: melatonin, warfarin, interaction, bleeding, INR, PT

1. Introduction

Melatonin (N-acetyl-5-methoxytryptamine) is an endogenous neurohormone secreted by the pineal gland during the dark hours of the day-night cycle (Dollins, 1994) (Tzischinsky, 1994).¹⁻² It binds to MT1 and MT2 melatonin receptors in the suprachiasmatic nucleus of the hypothalamus, which contributes to its sleep-promoting and sleep/wake rhythm regulating effects (Srinivasan, 2009).³ Exogenous melatonin is commonly used to treat sleep disorders or insomnia related to jet lag or shift-work cycle.⁴

Endogenous melatonin may also produce anti-thrombotic, antioxidant and anti-inflammatory activity, which could favorably influence coronary artery disease (CAD) (Carrillo-Vico, 2005), (Claustrat, 2005) (Dahm, 2006).⁵⁻⁷ In vitro studies showed that melatonin can cause inhibition of platelet aggregation (Del Zar, 1990) (Kornblihtt, 1993).⁸⁻⁹ Additionally, a placebo-controlled study in healthy young men showed a dose-response relationship between melatonin plasma concentration and coagulation activity (Wirtz, 2008).¹⁰ Melatonin

administration is associated with lower levels of the coagulation measures FVIII: C and fibrinogen. In other word, higher melatonin plasma concentration can predict lower plasma levels of coagulation measures.¹⁰

According to the Micromedex (drug interaction) database, concurrent use of melatonin and warfarin may result in an increased risk of bleeding¹¹. Thus, Micromedex recommends avoiding concomitant use of melatonin and warfarin and if both medications are taken concomitantly, it is necessary to frequently monitor a patient's international normalized ratio (INR), prothrombin time (PT), and signs and symptoms of excessive bleeding. Also, if the patient is taking a consistent dose of melatonin of a consistent and standardized brand, it is recommended to adjust the warfarin dose. This recommendation is based on the fact that melatonin has been associated with bleeding complications and reduced PT in four case reports of patients who received both melatonin and warfarin (Herxheimer, 2002).¹² Case 1 was for an 84-year-old male who took warfarin while using melatonin for 8 days. As a result, he had purpura, eye

hemorrhage, and reduced PT. Case 2 was for a 51-year-old female who took melatonin with warfarin for 5 days. She had a nose bleed and a decrease in PT. Case 3 was a 48-year-old male, who took 10 milligrams of melatonin with warfarin and had a decrease in PT. Case 4 was a 72-year-old female who took melatonin with warfarin for an unspecified period of time and had a decrease in PT. Two other cases of patients who took melatonin and warfarin and had an altered PT were reported with no other information (Herxheimer, 2002).¹² However, there is no primary literature that supports this finding.

An explanation for this interaction is that melatonin is metabolized by Cytochromes P450 hepatic microsomal enzymes (CYPs), including primarily CYP2C19 and CYP1A families (particularly CYP1A2) and possibly CYP2C9 (Yeleswaram, 1999) (Faber, 2005).¹³⁻¹⁴ Melatonin appears to inhibit CYP1A2 (Scott, 2002)¹⁵ and induce CYP3A. Theoretically, when melatonin is administered concomitantly with drugs metabolized by these enzymes, this might inhibit the metabolism of these drugs, resulting in increased serum levels. Warfarin is metabolized primarily by CYP2C9 (primary isoenzyme), CYP2C19, CYP2C8, CYP2C18, CYP1A2, and CYP3A4, to inactive metabolites.¹⁶ Warfarin (R-enantiomer) is metabolized by CYP1A2 while (S-enantiomer) is metabolized by CYP2C9. However, S-enantiomer has been determined to have the major pharmacological activities of racemic warfarin (Kaminsky, 1997)¹⁷. Given this basis for the interaction, our aim is to evaluate the potential interaction between melatonin and warfarin in a clinical setting.

2. Material and Methods

Ten patients who received melatonin and warfarin concurrently when admitted to Massachusetts General Hospital (MGH) between April 2011 and April 2012 were evaluated after we got approval from the institutional review board (IRB) of MGH. These

patients had changes in INR and PT while receiving both medications. We selected these 10 patients because they were not on any other medications that have major interactions with warfarin. These patients also did not receive other anticoagulants, chemotherapy, as needed or just 1 dose of melatonin during their hospital stay.

Over each patient's hospital stay, we observed each patient's complete medication list, the occurrence of bleeding events, such as nose bleeds, intraocular hemorrhages, and gum bleeds, and the following laboratory values: routine coagulation measures, including INR and PT, hemoglobin (Hb), albumin, and liver function tests (LFTs), including aspartate aminotransferase (AST) and alanine transaminase (ALT).

The Drug Interaction Probability Scale (DIPS) was utilized to evaluate the potential drug interaction between melatonin and warfarin for each patient (Horn, 2007).¹⁸ DIPS was developed to provide a guide for practitioners to evaluate drug interaction causation in specific patients. By calculating the total DIPS score, each patient was classified into one of four interaction categories: highly probable, probable, possible, or doubtful. For each patient, we used patient's medical information in medical records during hospital stay to answer the scale questions. Also, previous case reports were used as background information for this potential interaction to answer some of the scale questions.

3. Results

Ten patients were included in this case series with ages ranging from 45 to 97 years old (table-1). Each patient was admitted for different reason. None of the patients experienced coagulopathy, blood dyscrasias, hepatic impairment or surgery while receiving melatonin and warfarin concurrently during their hospital stay. Albumin and LFTs were normal in most patients except patient #1 and patient #6 (table-2).

Table- 1: Baseline characteristics (n= 10)

Age (years)	54 – 97 (median= 75 years old)
Gender	Male= 7 Female= 3
Melatonin dose ^a:	
Patients on melatonin dose of 5mg/day	9
Patients on melatonin dose of 10mg/day	1

^a The usual recommended dose for insomnia: 0.3-5 mg at bedtime has been used (Brusco, 1999) (Haimov, 1995).¹⁹⁻²⁰ Up to 10mg/ day orally may be used.²¹ For jet lag, 0.5-8 mg at bedtime is commonly administered on the arrival day at the destination which can be continued for 2-5 days (Paul, 2010) (Paul, 2004).²²⁻²³ It was found that doses > 5 mg do not seem to be more effective than 5 mg doses (Herxheimer, 2002).¹²

By calculating DIPS score for each patient, we found that 6 patients experienced possible drug interactions, 2 had probable drug interactions, and 2 had doubtful drug interactions.

Table- 2. Laboratory results for the 10 patients:

	Patient #									
	#1	#2	#3	#4	#5	#6	#7	#8	#9	#10
AST (U/L)	18	NA	32	21	23	85	18	NA	NA	37
ALT (U/L)	16	NA	25	13	14	71 (H)	17	NA	NA	34
Albumin (g/dl)	2.1 (L)	NA	3.4	3.0	3.0	3.2 (L)	3.4	3.5	NA	3.6

AST: aspartate aminotransferase (reference range= 10 to 34 U/L), **ALT:** (reference range=10-40 U/L for male and 7 to 35 U/L for female), **albumin (reference range= 3.4 to 5.4 g/dl)** (Hutchison, 2011).²⁴

L: low value, H: high value, NA: not available.

The following characteristics describe the 6 patients who had possible drug interactions. Their ages ranged from 65 to 79 years old (median= 75 years old), and their duration of concurrent administration of melatonin and warfarin was between 2 and 10 days (table-3). They were all on a stable dose of melatonin, while 4 of the patients had their warfarin dose changed. The 2 patients who were on stable dose of warfarin had an increase in INR and PT; the 3 patients who had an increase in warfarin dose had an increase in INR and PT; and the 1 patient who had a decrease in warfarin dose also had an increase in INR and PT (table-3). The latter (patient#2) was on ciprofloxacin, which has a major interaction with warfarin (Bianco, 1992) (Baillargeon, 2012)²⁵⁻²⁶ according to Micromedex²⁷; however, it was discontinued prior to the patient being observed for this report for melatonin and warfarin administration concurrently. No bleeding events were noted in this group.

The following characteristics describe the 2 patients who had probable interaction. Their ages were 91 and 97 years old (median= 94 years old), and their duration of concurrent administration of melatonin and warfarin was 2 days. Both patients were on a stable dose of melatonin but had their warfarin doses increased. They had an increase in INR and PT, but no bleeding events were observed (table-3). One of the patients received 1 dose of levofloxacin, which had a major interaction with warfarin (Baillargeon, 2012) (Ravnan, 2001)^{26,28} according to Micromedex²⁷, two days before starting melatonin (patient #7) (table-3). The other patient had a surgery and hemorrhagic stroke on a previous admission (patient #8) (table-3).

The remaining 2 patients who had doubtful interactions were both 54 years old. Their duration of concurrent administration of melatonin and warfarin was 2 and 3 days. Both patients were on stable doses of melatonin. One patient was on a stable dose of warfarin and the other patient had a decrease in warfarin dose. However, both patients had a decrease in INR and PT for unknown reasons, and no bleeding events were observed (table-3).

4. Discussions

In this report, the concurrent administration of melatonin and warfarin was associated with an increase in INR and PT in 8 patients; however, no bleeding or clotting events were documented in any of the 10 patients. Some previous case reports have shown that melatonin is associated with decreased PT with no evidence of clotting; however, in these cases some bleeding complications were noted (Kornblihtt, 1993).⁹

There are several explanations for the increase in INR and PT observed in the 10 patients in this report. All 10 patients were on a stable dose of melatonin, but not all were on a stable dose of warfarin. We found that an increase in the warfarin dose (patients# 3, 4, 5, 7, and 8) (table-3) and a decrease in warfarin dose associated with an increase in INR and PT (Patient# 2) (table-3). However, two of the patients were on a stable dose of warfarin during the whole days of observation for interaction evaluation (patient #1 and 6) (table-3), while 1 patient was on a stable dose for a few days (patient# 4) (table-3). All of these patients had an increase in INR and PT, which may be related to melatonin or other medications that may have an interaction with warfarin; however, not all the patients were on medications that have an interaction with warfarin or increase the risk of bleeding.

Some of our 10 patients had been receiving melatonin for longer period of time than the period that we actually analyzed but we only analyzed the period when they were not receiving medications that have major interactions with warfarin, according to Micromedex (drug interaction) database²⁷. Also, some of the 10 patients started taking warfarin before started taking melatonin, which has an effect on INR, depending on whether the patient had reached the steady state of warfarin. In other words, the duration of concurrent administration in this report may not reflect the actual duration of concurrent administration in some patients (table-3). The administration duration of melatonin and warfarin may have had an effect on the potential interaction and on the INR and PT change. The 10 patients were only followed for a few days and these interactions may manifest themselves

after longer-term of concurrent use. In this report, the duration of concurrent administration of both medications ranged between 2 to 10 days (table-3), while in the previous 4 case reports (Herxheimer, 2002)¹², both drugs were administered concurrently for 5 to 8 days. Also, the 10 patients in this report

were 54 years old or older, while the patients in the case reports were 48 years old or older (Herxheimer, 2002)¹². Most of the 10 patients were elderly; therefore, future studies should include patients with a wider age range.

Table- 3. Enrolled patients characteristics and INR trend (n=10)

Pt	Gender	Age (years)	Melatonin dose (mg/day)	Duration of therapy (days) ^a	DIP Score ^b	INR and PT Trend ^c									
						1.6	1.4	1.7	1.7	2.0	1.8	1.8	1.9	2.1	
1	male	76	5	8	4possible	1.6	1.4	1.7	1.7	2.0	1.8	1.8	1.9	2.1	
					PT →	18	16.5	18.9	19.7	21.9	20.3	20.0	21.1	23.3	
2	male	65	5	2	4possible	2.4 ^d	2.9								
					PT →	25.6	30.4								
3	male	79	5	3	4possible	2.2	2.7	2.6							
					PT →	24.5	29.2	28.1							
4	female	75	10	10	4possible	1.1	1.1	1.1	1.3	1.4	1.4	1.4	1.5	1.8	2.0
					PT →	13.2	12.9	13.8	14.9	16.0	16.0	16.5	17.1	20.0	22.5
5	male	75	5	3	4possible	1.7	1.9	1.8							
					PT →	19.7	21.1	20.3							
6	male	65	5	2	4possible	3.5	3.6								
					PT →	36.2	36.9								
7	female	91	5	2	5probable	1.9 ^e	2.0								
					PT →	21.6	21.8								
8	male	97	5	2	5probable	2.0	2.1								
					PT →	21.8	23.4								
9	female	54	5	2	-2doubtful	1.8	1.3								
					PT →	20.0	15.8								
10	male	54	5	3	0doubtful	10.8	3.7	1.5	1.1						
					PT →	137.2	37.9	17.6	13.6						

INR: [International normalized ratio](#), PT: prothrombin time

^aThe duration of concurrent administration of melatonin with warfarin excluding the period of receiving a medication that has a major interaction with warfarin

^bWe calculated DIPS score using (1; Appendix.1 on Ann Pharmacother 2007;41:674-80)¹⁸

^cWhile concurrent administration of melatonin with warfarin, INR and PT have been checked on daily basis in all included patients.

^dCiprofloxacin was discontinued 1 day before we started assessing INR and PT values.

^eOne dose of levofloxacin was given and discontinued 2 days before we started assessing INR and PT values.

Several caveats apply to our findings. Our findings are based on only 10 cases. Other cases of patients who were on melatonin and warfarin were excluded from our report for a number of reasons, including that the patients were not receiving the medications concurrently, were on medications that have a major interaction with warfarin, or were missing INR values.

Previous potential drug interaction case reports that provided only limited data could also result in a low causation score in DIPS in those 10 patients in this report (Horn, 2007)¹⁸. According to this scale, question #4 was answered with 'Unknown/not applicable' due to a lack of information on the time course of the interaction (onset and/or offset).

DIPS has its own limitations (Horn, 2007).¹⁸ It has been used by only a few evaluators and would benefit from wider exposure and modification by a large number of users. The use of this scale requires a

fairly complete knowledge of the two drugs, and only the previous case reports were used as background information for this potential interaction. Additionally, yes/no responses are limiting and question #9 in DIPS can explain this point (Horn, 2007)¹⁸. Interaction between melatonin and warfarin could be confirmed by a potential increase in INR. Small or large increases in INR will not be reflected if we answer this question with yes. DIPS is an excellent and non-time-consuming scale, but it needs to be modified to overcome its limitations.

For future studies, we recommend conducting a prospective, large, randomized trial with large sample size to overcome this report's limitations and to accurately evaluate the potential interaction between melatonin and warfarin. More safety studies are also needed to evaluate the risk of bleeding from using both drugs concurrently.

Conclusion:

Based on our case series on 10 patients, concurrent use of melatonin and warfarin may result in INR and PT changes and affect coagulation activity. However, this finding needs to be re-evaluated and studied further. We suggest monitoring INR and PT regularly when both medications are administered concurrently.

Acknowledgements:

Noha Ashy had full access to all the data in the article and is responsible for the integrity of the data and the accuracy of the analysis from inception to completion. None of the material in this manuscript has been previously published.

We would also like to thank Barbara Irby (MS, RPh) a PGY-1 Pharmacy residency director at MGH, Dr. Ivo Abraham (PhD) a professor of Pharmacy and Medicine at University of Arizona and Michael Levenson for their comments on an earlier version of the manuscript.

Corresponding Author:

Dr. Noha Ashy
Department of Clinical Pharmacy
King Abdulaziz University
P.O. Box: 80200
Jeddah, Saudi Arabia 21589
E-mail: noha_ashy@hotmail.com

References

- Dollins AB, Zhdanova IV, Wurtman RJ, Lynch HJ, Deng MH. Effect of inducing nocturnal serum melatonin concentrations in daytime on sleep, mood, body temperature, and performance. *Proc Natl Acad Sci* 1994; 91:1824-1828.
- Tzischinsky O & Lavie P: Melatonin possesses time-dependent hypnotic effects. *Sleep* 1994; 17:638-645.
- Srinivasan VI, Pandi-Perumal SR, Trahkt I, et al. Melatonin and melatonergic drugs on sleep: possible mechanisms of action. *Int J Neurosci*. 2009;119(6):821-46.
- Natural Standard. Melatonin: therapeutic use, June 2016. Available from https://naturalmedicines-therapeuticresearch-com.ezproxy1.library.arizona.edu/databases/food_-herbs-supplements/professional.aspx?productid=940#peopleUseThisFor. Accessed February 10, 2016.
- Carrillo-Vico A, Guerrero JM, Lardone PJ, Reiter RJ. A review of the multiple actions of melatonin on the immune system. *Endocrine* 2005; 27:189-200.
- Claustrat B, Brun J, Chazot G. The basic physiology and pathophysiology of melatonin. *Sleep Med Rev* 2005; 9:11-24.
- Dahm A, Osterud B, Hjeltnes N, Sandset PM, Iversen PO. Opposite circadian rhythms in melatonin and tissue factor pathway inhibitor type 1: does daylight affect coagulation? *J Thromb Haemot* 2006; 4: 1840-1842.
- Del Zar MM, Martinuzzo M, Falcon C, Cardinali DP, Carreras LO, Vacas MI. Inhibition of human platelet aggregation and thromboxane-B2 production by melatonin: evidence for a diurnal variation. *J Clin Endocrinol Metab* 1990; 70:246-251.
- Kornblihtt LI, Finocchiaro L, Molinas FC. Inhibitory effect of melatonin on platelet activation induced by collagen and arachidonic acid. *J Pineal Res* 1993; 14:184-191.
- Wirtz PH, Spillmann M, Bärtschi C, Ehlert U, von Känel R. Oral melatonin reduces blood coagulation activity: a placebo-controlled study in healthy young men. *J Pineal Res*. 2008;44(2):127-33.
- Micromedex® Healthcare Series [Internet database]. Greenwood Village, Colo: Thomson Micromedex. Updated periodically. Drug interaction between melatonin and warfarin. Available from: <http://www.micromedexsolutions.com/micromedex2/librarian/PFDefaultActionId/evidenceexpert.ShowDrugInteractionsResults>.
- Herxheimer A, Petrie KJ: Melatonin for the prevention and treatment of jet lag (Cochrane Review). *Cochrane Database Syst Rev*. 2002;(2):CD001520. In: The Cochrane Library, Issue 2, 2003. Oxford: Update Software, 2002.
- Yeleswaram K, Vachharajani N, Santone K. Involvement of cytochrome P-450 isozymes in melatonin metabolism and clinical implications. *J Pineal Res* 1999;26(3):190-191.
- Faber MS, Jetter A, Fuhr U. Assessment of CYP1A2 activity in clinical practice: why, how, and when? *Basic Clin Pharmacol Toxicol*. 2005;97(3):125-134.
- Scott GN, Elmer GW. Update on natural product-drug interactions. *Am J Health Syst. Pharm* 2-15-2002;59(4):339-347.
- Bristol-Myers Squibb Company. Coumadin (warfarin sodium) oral ts, intravenous injection package insert. Princeton, NJ; 2010.
- Kaminsky LS, Zhang ZY, Human P450 metabolism of warfarin. *Pharmacol Ther* 1997;73: 67- 74.

18. Horn J, Hansten Ph, Chan L. Proposal for a New Tool to Evaluate Drug Interaction Cases. *Ann Pharmacother* 2007;41:674-80.
19. Brusco LI, Fainstein I, Marquez M, Cardinali DP. Effect of melatonin in selected populations of sleep-disturbed patients. *Biol Signals Recept* 1999;8:126-31.
20. Haimov I, Lavie P, Laudon M, et al. Melatonin replacement therapy of elderly insomniacs. *Sleep* 1995;18:598-603.
21. Longevity Health Group Inc. Melatonin oral capsules, ts package insert. Las Vegas, NV, 2011.
22. Paul M.A., Miller, J.C., Gray G.W., Love R.J., Lieberman H.R., and Arendt J. Melatonin treatment for eastward and westward travel preparation. *Psychopharmacology (Berl)* 2010;208(3):377-386.
23. Paul, M. A., Gray, G., Sardana, T. M., and Pigeau, R. A. Melatonin and zopiclone as facilitators of early circadian sleep in operational air transport crews. *Aviat. Space Environ. Med* 2004;75(5):439-443.
24. Hutchison RE, McPherson RA, Schexneider KI. Basic examination of blood and bone marrow. In: McPherson RA, Pincus MR, eds. *Henry's Clinical Diagnosis and Management by Laboratory Methods*. 22nd ed. Philadelphia, Pa: Elsevier Saunders; 2011:chap 30.
25. Bianco TM, Bussey HI, Farnett LE, et al. Potential warfarin-ciprofloxacin interaction in patients receiving long-term anticoagulation. *Pharmacotherapy* 1992; 12:435-439.
26. Baillargeon J, Holmes HM, Lin YL, et al. Concurrent use of warfarin and antibiotics and the risk of bleeding in older adults. *Am J Med* Feb, 2012; 125(2):183-189.
27. Drug interactions. *Micromedex Healthcare Series*. Thomson Micromedex. Retrieved at: www.thomsonhc.com. Accessed 2016 March 1.
28. Ravnan S, Locke C. Levofloxacin and warfarin interaction. *Pharmacotherapy* 2001; 21(7):884-885.

5/21/2016