

Potentially Unsafe Herb-drug Interactions Between a Commercial Product of Noni Juice and Phenytoin- A Case Report

Yu-Chan Kang¹, Ming-Hong Chen², Shung-Lon Lai³

Abstract-

Purpose: To report the unsafe herb-drug interactions between a commercial product of noni juice and phenytoin in a human case.

Case Report: A 49-year-old-male has been treated with phenytoin for epilepsy for more than ten years. In spite of his medication adherence, persistent sub-therapeutic phenytoin levels, which were sometimes from low to undetectable, with the result of having poor seizure control were noted as the noni fruit juice was co-administered daily. The possible mechanism is speculated to be due to noni juice-induced cytochrome P-450 2C9 metabolism of phenytoin. Owing to many beneficial effects of noni juice, the patient was unwilling to accept our advice to quit taking it. Clobazam treatment was added, and with gradually reducing the amount of juice drunk over six months, the patient's epilepsy has been well controlled. Now only auras along with sometimes minor partial seizures occur, but no major attack has been reported for more than one year.

Conclusion: Phenytoin had been commonly used for seizure control worldwide and nearly half of patients with epilepsy had received complementary and alternative medicine in Taiwan. Thus, this report is significantly important for clinicians to be aware of the interaction between antiepileptic drugs and some herbs like noni juice. Moreover, as far as we know, this is a rare human case that is reported to disclose this unfavorable herb-drug interaction.

Key Words: Herb-drug interaction, *Morinda citrifolia*, noni juice, phenytoin

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INTRODUCTION

Herbal and natural products from folk medicine have been used as complimentary medicines alongside conventional drugs for centuries in every culture through-

out the world, as they have always been considered to be natural and safe. However, some of them may interact with conventional drugs, and such interactions will be more clinically meaningful to drugs with narrow therapeutic ranges, like phenytoin. Here we report a

From the ¹Division of Clinical Pharmacy Service; ²Departments of Pharmacy; ³Neurology, Chang Gung Memorial Hospital-Kaohsiung Medical Center, Chang Gung University College of Medicine, Kaohsiung, Taiwan.

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Correspondence to: Shung-Lon Lai, MD. Department of Neurology, Kaohsiung Chang Gung Memorial Hospital, No. 123, Ta-Pei Road, Niao-Sung District, Kaohsiung city, 83342, Taiwan. E-mail: shunglon@gmail.com

human case of a drug-herb interaction between phenytoin and noni juice, an herbal remedy which is made from the fruit of the *Morinda citrifolia* L. (noni) and reported to have a broad range of therapeutic effects⁽¹⁾. A 49-year-old-male was treated with phenytoin for epilepsy. Persistent sub-therapeutic phenytoin levels, which were sometimes from low to undetectable, with the result of having poor seizure control were noted as the noni fruit juice was co-administered daily. This case report was approved by the Institutional Review Board of Chang Gung Memorial Hospital; the signed informed consent from the patient was obtained before submitting.

CASE REPORT

A 49-year-old-male without a family history had partial seizures with a secondarily generalization since he was 27 years old. Focal high intensity lesion in the T2 and diffuse-weighted image was noted in his brain magnetic resonance imaging (MRI). He refused operation for the lesion, and decided to receive medical therapy. The follow-up MRI showed no interval change for several outpatient visits. The initial antiepileptic drug prescribed was phenytoin with therapeutic drug concentration monitoring. In our hospital, the plasma level of total phenytoin concentration is routinely measured by using the Abbott fluorescence polarization immunoassay (FPIA). Poor seizure control, due to sub-therapeutic levels of phenytoin, at times being low to even undetectable was detected in the patient, and medication non-adherence has always been considered the major cause. After the dose of phenytoin sodium 100 mg/capsule was added to 6-7 capsules per day, the drug level could reach up to 18~19 mg/L. Lamotrigine 400 mg/day was also added to the prescription because he still had seizures despite the therapeutic phenytoin levels. Subsequently, the frequency of his seizures was substantially reduced from multiple daily seizures to one seizure every few months under the phenytoin sodium 600-700 mg/day plus lamotrigine 400 mg/day therapies. He was followed up at our neurology outpatient department monthly and under the regimen for more than two years without any drug intoxication.

A special accident drew our attention that there might be possible drug and food interaction in this case, after he had severe pleural effusions and was admitted to a

local hospital for almost one month. During that period, even though he received the same dose of 600 mg/day treatment, the level of phenytoin fell into the very low sub-therapeutic range, <10 mg/L or undetectable, again. However, a few days after his discharge, he was found ataxia and presented to the emergency department of that local hospital. The level of phenytoin measured at that time reached 37 mg/L. Because they could not find the reason, the patient was suggested to go back to our neurology outpatient department for further survey. We assessed his medication compliance first. His medications are administered by his wife, who insisted on her husband's good adherence to the medication regimen as before. Besides, there was no other associated medication which may pharmacologically interact with phenytoin. Then, we inquired about his daily foods, and according to his wife's statement, no special eating habit change except for the daily consumption of noni juice was reported. The noni fruit juice he took is a commercial product with brand name of Tahitian Noni® Original Bioactive Beverage™. It is flavored with blueberry and grape juice. The manufacturer dosing recommendations is 60 ml twice a day, but no maximum daily dose is specified. He started to drink it since 10 years ago, and was used to drink about 90 ml every morning. However, for his health, 80-90 ml twice a day and sometimes up to 100 ml twice a day were fed by his wife when he was in extremely debilitated conditions during the hospital stays. After his discharge, he stopped drinking noni juice for several days due to not having any remaining at home. Based on the above description, the noni juice was highly suspected to be the factor that altered the serum concentration of phenytoin.

To test our hypothesis, we requested the patient tentatively to stop taking noni juice for one period, restart with his usual daily consumption at the next period. The results were as we expected. During the "stop period" with phenytoin 600 mg/day therapy, the level of phenytoin raised to 25.34 mg/L after noni juice was stopped for one week. Even after the dose was adjusted to 500 mg/day, the level of phenytoin continued to rise to 33.26 mg/L 11 days later. However, during the "resumption" period, the drug level dropped to 17.82 mg/L two weeks later under the same dose of phenytoin 500 mg/day. A dizzy sensation, the inability to walk, and ataxia occurred at the stop period and multiple seizures attacked the patient upon

starting the use of noni juice at the resumption period. The concomitant medications were lamotrigene 400 mg/day and lorazepam 3 mg prn if any major seizure occurs. The test, coupled with the event the patient experienced at the local hospital, further confirmed our speculation. We therefore advised the patient to quit taking noni juice. However, due to the many beneficial effects of noni juice, the patient was only willing to reduce the amount rather than stop drinking it. We started to add clobazam to control his seizure attacks, and with gradually reducing the amount of juice drunk over six months, the patient's epilepsy has been well controlled. Now only auras along with sometimes minor absence seizures occur, but no major attack has been reported for more than one year.

DISCUSSION

Phenytoin had been commonly used for seizure control worldwide. In addition to interact with many drugs, phenytoin is also known to have interactions with folic acid⁽²⁾, alcohol⁽³⁾, and enteral feeding formulations⁽⁴⁾. However, a human case of herb-drug interaction between noni juice and phenytoin, to our knowledge, had been rarely reported.

Noni juice is derived from the fruit of *Morinda citrifolia* L., family *Rubiaceae*, commonly known as noni, which has been used in Polynesia for over 2000 years for food, medicine, and the dyeing of traditional clothes. The plant is a small evergreen tree or shrub, native to South Asia, and currently grows throughout the tropics⁽¹⁾. The use of noni has recently grown tremendously in North America, Western Europe, and elsewhere and its products have also become available in Taiwan in recent years. Noni juice is the most popular product, and claimed to be beneficial for many illnesses, although most scientific evidence is preliminary⁽¹⁾.

Using an *ex vivo* model of human hepatocytes, Santiago K et al found that noni juice is a potential inducer of cytochrome P-450 (CYP450) 3A4, 2C8/2C9, and 2D6⁽⁵⁾. It's worth mentioning that CYP2C9 is the predominant enzyme which catalyzes the 4'-hydroxylation of phenytoin to form 5-(4p-hydroxyphenyl)-5-phenylhydantoin (HPPH), and this conversion accounts for approximate 80% of phenytoin elimination in humans⁽⁶⁾. Since the role of noni juice and phenytoin are the "inducer" and "substrate"

of CYP2C9, respectively, it can explain why decreased serum phenytoin concentrations were observed in our patient after concurrent administration of noni juice. This mechanism of interaction was further confirmed by an *in vivo* animal experiment which showed that rats pretreated with noni juice experienced a decrease in the bioavailability of phenytoin by a 2.81 fold⁽⁷⁾.

A similar herb-drug interaction has also been reported between noni juice and warfarin with acquired warfarin resistance in a 41-year-old female following the concurrent administration of noni juice. A decline in international normalized ratio (INR) was noted despite an increase in the warfarin dosage. The possible mechanism that the author reported was fortified vitamin K in noni juice⁽⁸⁾. However, because warfarin is also a substrate of CYP2C9, which catalyzed about 80 to 85% of the more potent (S)-enantiomer of warfarin to 6- and 7-hydroxy (S)-warfarin, we suspected a similar mechanism of herb-drug interaction as noni juice and phenytoin may play an important role as well⁽⁶⁾.

Nearly half of patients with epilepsy had received complementary and alternative medicine in Taiwan⁽⁹⁾. Clinicians should be aware of this clinically significant interaction, for the serum phenytoin concentration may be substantially reduced to trigger epileptic seizures attack. Therefore, noni juice would not be safe to use while receiving phenytoin therapy, and should be stopped if possible. In addition to the clinical experience obtained from our patient, we speculated the possible mechanism, however, according to the limited *ex vivo* and *in vivo* literature, further research on human is still required to determine this interaction.

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