



The relationship between Mitragynine blood concentrations and death in Thailand

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Abstract

Kratom (*Mitragyna speciosa* Korth) is a plant that is indigenous to Thailand and leads to addiction. In Thailand, every part of the Kratom plant is classified as a Penal Drug in a Category-5 Narcotic under the Narcotics Act B.E. 2522 (1979). Mitragynine and its derivatives are a type of alkaloids from the Kratom plant that have pharmacotoxicological effects. Blood samples of the deceased whose urine screening with Toxyper™ was positive for Mitragynine ($N = 34$) and blood samples of persons suspected of Kratom abuse ($N = 7$) were obtained from the Institute of Forensic Medicine under the Royal Thai Police Headquarters from January 2017 to December 2017. The purpose of this research is to study the Mitragynine blood levels in Thai people. The average blood Mitragynine concentration of all 41 samples (categorized into 7 groups) was 197.71 ± 338.16 ng/ml (ranged 2.98 - 1,554.23). Group A ($N = 15$), a group of people whose the autopsy results were not able to determine the exact cause of death, indicated the average blood Mitragynine concentrations of 332.96 ± 495.27 ng/ml, while the average blood Mitragynine concentration of Group B ($N = 12$), fatal accident victims, was 114.99 ± 145.19 ng/ml. Moreover, Group C ($N = 2$) with homicidal cases reported the blood Mitragynine concentration at 347.84 ± 205.47 ng/ml, Group D ($N = 1$) with a suicide case reported at 60.40 ng/ml, Group E ($N = 1$) in which a person died from cancer reported at 2.98 ng/ml, Group F ($N = 3$) in which people died from cardiovascular disorders reported at 232.60 ± 333.10 ng/ml, and Group G ($N = 7$) who were suspected of Kratom abuse reported at 39.29 ± 32.29 ng/ml. High blood Mitragynine concentrations can also cause death. This is the first study in Thailand investigating the level of Mitragynine in blood samples of the deceased and the accused.

Keywords: Mitragynine, Kratom, blood, deceased

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1. Introduction

Kratom (*Mitragyna speciosa* Korth) is a plant that is indigenous to Thailand and leads to addiction. In Thailand, all parts of the Kratom plant are classified as a Penal Drug in a Category-5 Narcotic under the Narcotics Act B.E. 2522 (1979); therefore, consuming any parts of Kratom is still prohibited in Thailand.

Historically, Thai people used Kratom in two ways: chewing the leaves for their stimulating effects on the nerves to work harder, and consuming the '4 × 100' (pronounced: sii koon roi) considered as a type of addiction as entertainment. The '4 × 100' is a boiled Kratom juice cocktail containing antihistamines and sleeping pills or psychotropic drugs, and the narcotic drug is often added. However, this 4 × 100 cocktail puts the addicts at risk of death easily owing to the overdose of poly-drugs.

Mitragynine and its derivatives are types of alkaloids from the Kratom plant that have pharmacotoxicological effects. To elaborate, any persons who

consume any parts of the Kratom plant can be found positive for Mitragynine or its derivatives in human biological specimens such as blood or urine.

In the past, most of the Thai Kratom users, who died unnaturally and were sent to the autopsy at the Institute of Forensic Medicine under the Police General Hospital, were involved in '4 × 100' abuse. The first publication concerning the fatal 4 × 100 was reported by Tungtanuwat and Lawanprasert, demonstrating that Mitragynine and many substances (i.e. Caffeine, Diphenhydramine, Alprazolam, Nortriptyline, Methadone, Tramadol and Methamphetamine) were found in the biological specimens of the deceased but no quantitative analysis data of Mitragynine content was reported [1]. The possible explanation may be due to the lack of reference standards, thus making the toxicological data of Mitragynine affecting the death of this case disappear.

In addition, Kronstrand et al. conducted a pilot research study on quantitative analysis of Mitragynine in the deceased [2]. In their study, nine cases of unintentional fatal intoxications with Mitragynine and

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O-desmethyltramadol from the herbal blend Krypton, whose blood Mitragynine concentration postmortem ranging from 200 – 1,800 ng/mg. They concluded that the synergistic effect of the potent mu-receptor agonist of O-desmethyltramadol and Mitragynine contributed to the unintentional death of the nine cases presented. Subsequently, research on the content of Mitragynine has continuously been published. No previous studies, however, have been conducted among Thai people who consume a lot of the Kratom plant; consequently, the quantitative information of Mitragynine among Thai drug abusers is scant. To fill the gap, therefore, this study has been established.

2. Materials and Methods

Blood samples from the deceased whose urine screening with Toxtyper™ was positive for Mitragynine ($N = 34$) and blood samples of persons suspected of Kratom abuse ($N = 7$) were obtained from the Institute of Forensic Medicine, Police General Hospital under the Royal Thai Police Headquarters from January 2017 to December 2017. Standard Mitragynine solution (100 $\mu\text{g/mL}$ in methanol) was purchased from Cerilliant®. After blood was processed with SPE (Solid-Phase Extraction) extraction, the eluent will be sent to measure with LC-MS/MS (LC: Ultimate3000™, MS: TSQ Quantiva™) from Thermo Scientific®. The study was approved by the Ethics Committee on Human Experimentation of Police General Hospital. Also, the SPSS version 17 was used for statistical analysis.

3. Results

When classified by autopsy reports, 34 blood samples of the deceased can be divided into 6 groups. The first group (Group A) is a group in which the autopsy report cannot be clearly identified, because no significant pathology has been found to cause death. After checking with the police, body indicated that he died without knowing the cause. There are 15 cases in this group with all males and the average age of 36.00 ± 14.31 (aged 18 - 59 years old). The second group (Group B) include those who died from traffic accidents. There are 12 cases in this group with all males and the average age of 20.75 ± 4.55 (aged 15 - 29 years old). The most common pathology reports include skull rupture, brain trauma, lung injury, laceration, bruising, spleen and renal laceration, as a result of the impact of significant force. The deceased in the third group (Group C) died from the assault or a homicide case. This group consisted of 2 cases with all males and the average age of 25.00 ± 8.49 (aged 19 - 31 years old). One was stabbed with a knife, and the other was attacked with firearms. The deceased in the fourth group (Group D) died from suffocation. The rope marks were found on the neck of the deceased, their

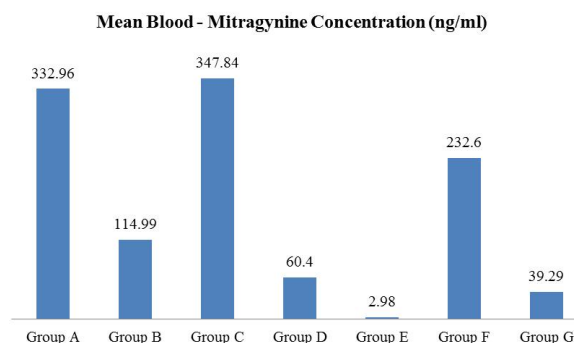


Figure 1: Mean Blood-Mitragynine Concentration (ng/ml).

death was considered as suicide by hanging. There is 1 male aged 21 years old. The deceased in the fifth group (Group E) died from cancer. This group consisted of 1 case, an 83-year-old female whose blood was found positive for Mitragynine and THC-COOH from the Kratom and Marijuana plants. The deceased in the sixth group (Group F) died from cardiovascular disorders. This group comprised 3 cases with all males and the average age of 30.67 ± 14.50 (aged 16, 31 and 45 years old). The last group (Group G) is a group of persons suspected of Kratom abuse. This group comprised 7 cases with all males.

The results of the Mitragynine blood concentrations in the blood specimens showed that all 41 samples (Table 1, Figure 1) had the average concentration of Mitragynine in the blood at 197.71 ± 338.16 ng/ml (ranged 2.98-1,554.23). The groups were sorted in descending order as follows: Group C > Group A > Group F > Group B > Group D > Group G > Group E.

Moreover, Group A, a group in which the autopsy report cannot be clearly identified the cause of death was a large population of this study ($N = 15$) and yielded a high average blood-Mitragynine value (332.96 ± 495.27 ng/ml) with the lowest value of 12.42 and the highest value of 1,554.23 ng/ml. On the contrary, it revealed that one case was detected low blood-Mitragynine level (72.63 ng/ml) but detected narcotic drugs and other drugs up to six items, i.e. Methamphetamine, Morphine, Codeine, Diphenhydramine, Tramadol and Fluoxetine.

In Group B, the group in which the deceased died from a traffic accident, it found that 10 out of 12 cases were using Kratom as recreational cocktail called the '4 × 100', antihistamines such as Diphenhydramine, Cetirizine and Chlorpheniramine, opioid derivatives such as Dextromethorphan and Tramadol, and drugs such as Ketamine, Methamphetamine and Marijuana were found in their blood tests.

In Group C, there were two Homicide cases. First, the 19-year-old man who was found to have died of stabbing was found that his blood-Mitragynine level was 202.55 ng/ml, and Ketamine and Clonazepam

Table 1. Blood-Mitragynine concentration in the Thai deceased.

Group		A	B	C	D	E	F	G	Total
N		15	12	2	1	1	3	7	41
Mitragynine	Mean	332.96	114.99	347.84	60.40	2.98	232.60	39.29	197.71
Concentration	SD	495.27	145.19	205.47	-	-	333.10	32.29	338.16
(ng/ml)	Min	12.42	7.34	202.55	-	-	38.55	5.69	2.98
	Max	1,554.23	453.71	493.13	-	-	617.22	94.57	1,554.23

were detected in his blood specimen. The second man who died from being shot was found that his blood - Mitragynine level was 493.13 ng/ml with Methamphetamine detected in blood.

In Group D, a 21 years old male died from suicide by hanging was detected Mitragynine only, indicating that he used the Kratom plant for the sake of increasing work efficiency.

In Group E, an elderly woman who died from stage IV cancer was found that her blood indicated low concentrations of Mitragynine and THC-COOH, an active ingredient of the Kratom and marijuana.

In group F, there was one interesting case, a 31-year-old man whose autopsy report stated that he died of a severe myocardial infarction. The toxicology report showed that his blood indicated the low level of blood-Mitragynine (38.55 ng/ml) but detected two narcotic drugs (Methamphetamine and Methadone) and five other drugs (i.e. Hydroxyzine, Chlorpheniramine, Tramadol, Diphenhydramine and Clonazepam) that were commonly used to add in the 4 × 100 Kratom cocktails.

4. Discussion

From the overall results, it was found that Mitragynine concentrations in the blood of Kratom abusers range from 2.98 to 1,554.23 ng/ml with the mean of 200 ng/ml which is probably the normal value in the regular addicts. This result is consistent with the clinical study in Thailand of Trakulsrichai et al., the researchers conducted a study on the pharmacokinetics of Mitragynine in 10 male subjects using Kratom tea, demonstrating that the highest C_{max} 105 ng/ml were found in the subjects taking the highest loading dose of 23 mg and the lowest C_{max} 18.5 ng/ml were found in the subjects taking the lowest loading dose of 6.25 mg [3]. In their study, they explained that the dose used in their study was 9 times lower than it was actually used in Malaysia.

Group A and Group F have similar characteristics. Since the average age of the deceased is similar and the deceased died without traces of bruise wounds or severe injury, both groups have a wide range of Mitragynine concentrations (see Table 1) and many samples have a higher level of concentrations. For some cases that took in poly-drug use, when compared with other data, it is compatible with fatal accidental drug overdose. The results are in accordance

with the studies by Holler et al. and Neerman et al., Holler et al. reported one case of death involving Propylhexedrine and Mitragynine intake and his blood-Mitragynine was 390 ng/ml [4]. From their study, the authors suggested that the cause of death was ruled propylhexedrine toxicity and Mitragynine may have contributed as well but no published data for drug concentrations was reported. Neerman et al. published an autopsy report of a 17 year old white man who had a recorded history of heroin abuse and chronic back pain and reportedly self medicated with Kratom [5]. His toxicological analysis reported Mitragynine (600 ng/ml) and four drugs (i.e. Dextromethorphan, Diphenhydramine, Temazepam and 7-Aminoclonazepam) were found in his blood sample. Given the facts of the case, the Medical Examiner certified the cause of death as “possible Kratom toxicity”.

When considering the data from Group A, it showed that there were 3 cases having blood-Mitragynine values at a very high concentration (992.85, 1235.72 and 1554.23 ng/ml). In line with the study by Karinen et al., they reported one fatal case with high blood-Mitragynine (1,060 ng/ml) and concluded that the cause of death was intoxication with mitragynine [6]. Moreover, the study by McIntyre et al. found that the blood-Mitragynine corroborates this study. McIntyre et al. published one case report of a 24-year-old man whose medical history was significant for alcohol abuse and depression [7]. The postmortem blood analysis found Mitragynine in peripheral blood (230 ng/ml) and central blood (190 ng/ml) with the addition of Venlafaxine, Diphenhydramine, and Mirtazapine (in therapeutic range).

If only Mitragynine was detected in Group D, it may be concluded that they used Kratom for the sake of increasing work efficiency. In the case of detecting Mitragynine with THC-COOH in the elderly or cancer patients in Group E), it is possible that they used herbal medicines to reduce suffering and unbearable conditions from terminal cancer. In the last three years, the addictive plant law has become more lenient and Thai people are paying much attention to the use of these two medicinal addictive plants to improve the quality of life in terminal cancer patients. The fact that the suspected persons (Group G) had lower blood-Mitragynine concentration than Groups B and C may be explained that this group of the alive person has a less risky and sensational lifestyle compared with both death groups that held a higher Mitragynine concen-

tration.

5. Conclusion

On account of scant research, this study is the first study on the level of Mitragynine in blood samples of the deceased and the accused in Thailand. Mitragynine contents in each group are different. The deceased from traffic accidents or murder often had a high amount of Mitragynine in the blood when compared to the group that consumed herbal medicine to treat illnesses. The deceased from the group of people who died without knowing the cause and of those that died but found pathological conditions on the heart tended to experience a high amount of Mitragynine and might die from an overdose. Moreover, high concentrations of Mitragynine in the blood can also cause death.

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