Comparative Analysis of Pathological and Toxicological Features of Opiate Overdose and Non-Overdose Fatalities

Narin Soravisut MD*,
Pranithan Rattanasalee MD*, Anongphan Junkuy MS*,
Subharat Thampitak BS*, Pongruk Sribanditmongkol MD, PhD*

** Department of Forensic Medicine, Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand*

Objective: *To compare pathological and toxicological features between opiate overdose and non-opiate overdose fatalities examined in the Department of Forensic Medicine, Chiang Mai University, Thailand.*
Material and Method: *A retrospective study of 142 cases, diagnosed as opiate-related deaths between 1996 and 2008 was conducted. Demographic data, pathological findings and toxicological results were retrieved from autopsy records.*
Results: *Within these 142 opiate-related deaths, 102 cases were classified as opiate overdose fatalities by Forensic Medicine doctors. More than 95% of cases were male. About 80% were aged 20 to 39 years. Forty-eight percent were Thai, 13% were British and 11% were American. The most common places of death were residential areas and hotels. Pulmonary edema and needle marks were more common in opiate overdose cases than in non-opiate overdose cases. Toxicological findings showed that 61% of opiate overdose cases and 34% of non-opiate overdose cases were positive for blood morphine. Morphine was detected in about 95% of urine samples in both groups. About 62% of opiate overdose cases and 31% of non-opiate overdose cases had positive blood alcohol.*
Conclusion: *The average incidence of opiate-related death was about 1% of autopsy cases. More than two thirds of the deaths were opiate overdose cases. After the year 2003, more foreigners suffered from opiate overdose fatalities than Thais. The fatalities were confined to an area frequented by tourists. Pulmonary edema and needle puncture marks were more frequently observed in opiate overdose cases. The number of cases of morphine detection in serum from the opiate overdose group was significantly higher than in the non-opiate overdose group. There was no significant difference in urine morphine detection between both groups. Other substances detected in these victims were alcohol, benzodiazepines, methamphetamine, methylenedioxymethamphetamine and methadone. Alcohol was found significantly higher in opiate overdose fatality than in non-opiate overdose deaths.*

Keywords: *Heroin, Opioid, Opiate, Intoxication, Drug abuse, Overdose*

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In the past, heroin abuse was a prominent problem in Thailand and other Southeast Asian countries[1]. The problem of heroin abuse has declined with the emergence of other drugs, especially methamphetamine in Thailand[2]. The data from the Office of Narcotics Control Board of Thailand showed that cases of heroin seized in northern Thailand decreased in the period from 1996 to 2006[3]. Heroin production around the border between Myanmar, Laos, and Thailand was also reported to have declined by about 70%[4].

Chiang Mai, the second largest city in Thailand, is located near the area known as the "Golden Triangle". In cases of sudden and unexpected death in the city of Chiang Mai, the decedents are transferred to the Department of Forensic Medicine, Chiang Mai University, for medicolegal investigation, especially if intoxicated is suspected. Despite the decline in heroin abuse cases in northern Thailand, the authors still observe opiate-related deaths and from our observation, many foreigners are involved. Therefore, the authors have conducted a retrospective study to compare pathological and toxicological features between opiate overdose and non-opiate overdose fatalities examined in the Department of Forensic

Correspondence to:
Sribanditmongkol P, Department of Forensic Medicine, Faculty of Medicine, Chiang Mai University, Chiang Mai 50200, Thailand.
Phone: 053-945-431-4, Mobile: 081-980-4545, Fax: 053-945-435
E-mail: psriband@yahoo.com, psriband@med.cmu.ac.th

Medicine, Chiang Mai University, Thailand between 1996 and 2008.

Material and Method

The present study was approved by The Research Ethics Committee on Human Research, Faculty of Medicine, Chiang Mai University (Study number 08AUG110839).

A retrospective study of autopsy reports from the Department of Forensic Medicine, Faculty of Medicine, Chiang Mai University was conducted. Autopsy cases in which forensic pathologists concluded that the cause of death was opiate overdose and/or the cases in which heroin metabolites were present in toxicological investigation between January 1996 and December 2008 were reviewed. Demographic data, pathological findings and toxicological results were recorded from autopsy and toxicological reports.

In the present study, "opiate overdose" cases are those in which the forensic pathologist responsible indicated heroin overdose as the cause of death in the official autopsy reports. The pathologists gathered all related information including heroin or syringe at scene, police information and autopsy results before their conclusion. "Non-opiate overdose" cases refer to autopsy cases in which heroin metabolites were detected in biological specimens, yet other cause of death was indicated.

Laboratory test

The laboratory conducted substance analysis upon request from forensic pathologists. An immunoassay was used for morphine screening in urine. The cutoff level was 300 ng/mL. If the immunoassay was positive, a thin layer chromatography (TLC) was performed for confirmation and the level of morphine was quantitated with automated high performance liquid chromatography (REMEDi®). For TLC, 50 ml of blood or 20 ml of urine samples were hydrolyzed by adding hydrochloric acid and then heated for 30 min. The hydrolyzed sample was filtrated and the pH was adjusted to pH ~9 by adding sodium hydroxide. Subsequently, the sample was subjected to chloroform extraction. The TLC system was performed in ethyl acetate:MeOH:NH4OH (85:10:5) mixture. The sensitivity of morphine detection by TLC is 500 ng/ml in urine and 1,500 ng/ml in blood. To quantitate serum morphine level with REMEDi®, 10 ml of serum were applied with 5 ml of 1 M K_2CO_3 pH ~9 and the solution was briefly mixed. The mixture was extracted with 50 ml of Hexane: ethylacetate (7:3). The solvent layer was evaporated until dryness under N_2 gas. The residue was dissolved in 1 ml of ultrapure water before injected into REMEDi® system. The sensitivity of serum morphine by REMEDi® is about 100 ng/ml.

Statistical analysis

Descriptive analysis was used. Comparison between both groups was conducted using Chi-square test and p-value less than 0.05 was considered significant difference.

Results

The highest incidence of opiate-related deaths was found in the year 2001 (1.72%). The lowest incidence was 0.25% of autopsy cases in the year 2003 (Fig. 1). The average number of opiate-related deaths during the study period was 11 per annum and the range was from three to 17 cases. The highest number of cases was in 2001 (Fig. 2). The total number of

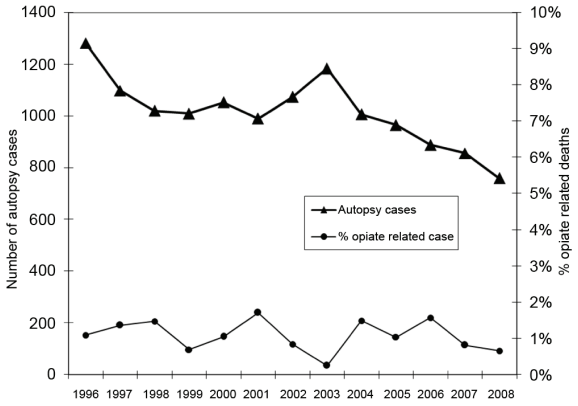

Fig. 1 Number of autopsy cases and percent of opiate-related deaths examined in the Department of Forensic Medicine, Chiang Mai University during 1996-2008

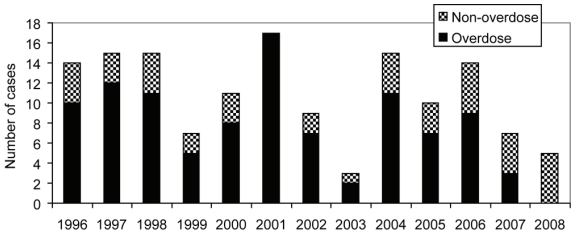

Fig. 2 Number of opiate overdose and non-opiate overdose cases examined in the Department of Forensic Medicine, Chiang Mai University during 1996-2008

opiate-related deaths between 1996 and 2008 was 142. One hundred and two cases were described as opiate overdose cases (71.8%) and 40 cases as non-opiate overdose cases (28.1%). The majority of opiate-related victims were male. There were 97 male cases (95.1%) and five female cases (4.9%) in the opiate overdose group. The highest number of cases was found in 2001 (17 cases) (Fig. 2). In the non-opiate overdose group, 36 cases (90%) were male and four cases (10%) were female. The mean (± SD) age of the opiate overdose group was 32.45 (± 11.8) years, with the range of 17 to 86 years. The predominant age group was 20 to 39 years (Fig. 3). In the non-opiate overdose group, the mean (± SD) was 40.41 (± 13.7) years.

Thai nationals were predominant in both groups (48% in the overdose group and 67% in non-overdose group). About 14% of opiate overdose victims were from continental European countries namely France, Germany, Switzerland, Italy and Sweden. Thirteen percent were from Great Britain and 11% from USA. In non-opiate overdose deaths, 14% of the victims were from the European countries and 13% from USA (Fig. 4). However, when investigated year by year, the authors found that more foreigners died from opiate overdose than Thais in 1999 and 2003 to 2007 (Fig. 5).

The number of overdose deaths was highest in the month of May (21 cases). The location of deaths was mostly residences (40%) and hotels (24%).

Pathological findings

The pathological findings are shown in Table 1. Pulmonary edema and needle marks were detected in the opiate overdose group in significantly higher numbers than in the non-opiate overdose group. Common myocardial lesions noted in autopsy reports were coronary occlusion (11 cases) and myocardial infarction (13 cases). Cause of death in the non-opiate overdose victims was heart disease (7 cases), gunshot (5 cases), traffic injury (5 cases), hanging (4 cases), and other natural diseases (19 cases).

Toxicological findings

Toxicological results from opiate related deaths are demonstrated in Table 2. Blood morphine was detected in 61.8% of opiate overdose cases while only 34.2% of non-opiate overdose cases were morphine positive ($p = 0.002$). On the other hand, there was no significant difference in either the level or the percentage of morphine, 6-MAM, or codeine in urine between both groups.

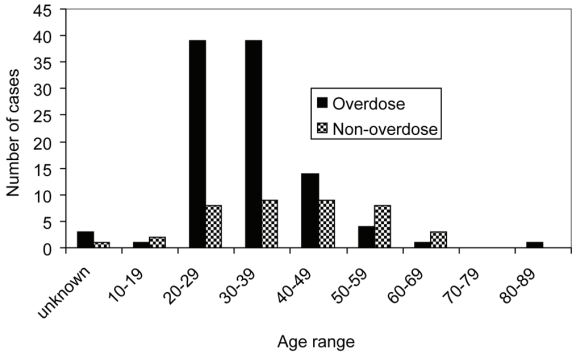

Fig. 3 Age distribution in opiate overdose and non-opiate overdose cases examined in the Department of Forensic Medicine, Chiang Mai University during 1996-2008

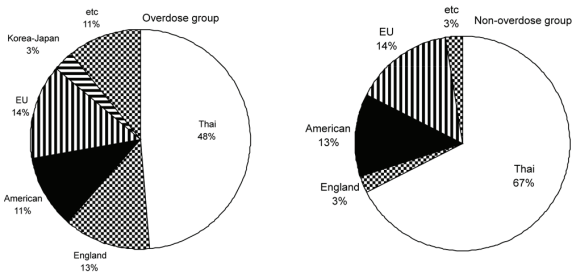

Fig. 4 Nationality of opiate overdose and non-opiate overdose victims examined in the Department of Forensic Medicine, Chiang Mai University during 1996-2008

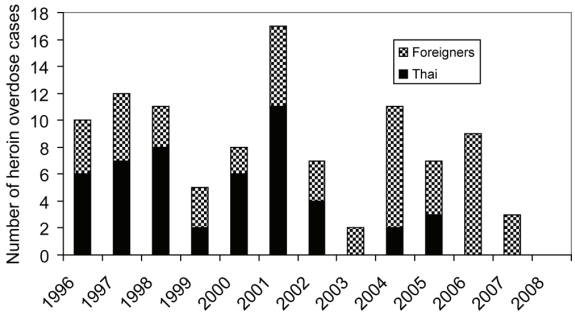

Fig. 5 Comparison of Thai and foreign opiate overdose victims examined in the Department of Forensic Medicine, Chiang Mai University during 1996-2008

Blood alcohol level was measured only in 47 opiate overdose cases and 61.7% of cases were positive, which differed significantly from levels in the non-opiate overdose group ($p = 0.009$) (Table 2).

Table 1. Pathological findings in opiate overdose and non-opiate overdose groups

Pathological findings	Number of opiate overdose cases n = 102 (%)	Number of non-opiate overdose cases n = 40 (%)	Total n = 142 (%)
Pulmonary edema**	71 (69.6)	14 (35)	85 (59.8)
Needle mark*	36 (35.3)	3 (7.5)	39 (27.5)
Myocardial lesion	23 (22.5)	11 (27.5)	34 (23.9)

*, ** $p < 0.01$ and 0.001 compared between opiate overdose and non-opiate overdose groups using Chi-square test

Benzodiazepine was the second most common substance detected in both opiate overdose and non-opiate overdose groups. In some opiate overdose cases, methamphetamine and methylenedioxy-methamphetamine was found in urine. Morphine was detected in other specimens, when available, of overdose cases (Table 3).

Discussion

Opiate-related deaths examined in our department were an average 1% of total autopsy cases during 1996-2008.

Opiate overdose cases were more Thais than other nationalities. Tourists from Great Britain, together with other European countries, accounted for 27% of overdose victims (Fig. 4). When yearly figures are examined, the authors observed that the number of foreigners who died was much higher than that of Thais in many years, especially during the last five years, with the exception of the year 2008. One of the reasons many foreigners died of opiate overdose in Thailand may be because the purity of heroin in Thailand was higher than that in the western countries[5].

The location of heroin-related deaths was in the city near the tourist area called "Night Bazaar". Many hotels and guesthouses that accommodate foreign tourists are located in this downtown area. The authors observed that 24% of deaths occurred in hotels, which was noticeably lower than in San Francisco between 1997 and 2000, where 47% of heroin-related deaths were reported to have occurred in hotels[6]. The majority of deaths in the present study occurred in victims' residences (40%).

Pulmonary edema was observed more frequently in opiate overdose cases than in non-opiate overdose cases. This is consistent with a report from the Victorian Institute of Forensic Medicine (VIFM), Australia, that pulmonary edema and congestion were found in 63% of heroin-related deaths[7]. In the present study, only 28% of cases were found to have needle marks while in VIFM, it was found in 65% of autopsy cases. The needle puncture marks could easily be observed on forearms. However, in some cases, the needle marks were found at the hairline of the forehead or the jugular vessel on the side of the neck. In these locations, it may be difficult for medical doctors to identify needle puncture marks. Other routes of heroin administration, not just intravenous, such as inhalation were also considered in cases of opiate-related deaths.

A range of cardiac lesions was recorded in presented autopsy reports. Specifically, the authors identified coronary occlusion, myocardial infarction, cardiomyopathy, and myocarditis. Although it is difficult to prove that these lesions were the consequence of heroin abuse, some other reports have proposed that heroin may induce coronary spasm leading to a variety of lesions in the ventricle and ventricular septum[8].

The percentage of blood morphine detected in the opiate overdose group was significantly higher than that observed in the non-opiate overdose group. However, the percentage of morphine in urine detected was not different in the two groups. In the opiate overdose group, death may have occurred shortly after ingestion so morphine was still measured in blood. In non-opiate overdose cases, morphine had been metabolized and already excreted in urine with less morphine left in the circulation, thus the percentage of blood morphine detection was lower than in the overdose group. Seymour et al reported that morphine was detected in 66% of drug-related deaths in Strathclyde, Scotland[9], which was higher than the percentage of blood morphine detection in the present study. The median blood morphine level measured from 14 opiate overdose cases was 711 ng/ml. The study from Meissner et al showed that cases with serum-free morphine concentration higher than 200 ng/ml displayed fatal outcome[10]. However, serum morphine level may not distinguish between heroin

Table 2. Toxicological results in opiate overdose and non-opiate overdose cases

Substance	Opiate overdose				Non-opiate overdose			p-value
	Number of cases tested	Number of positive (%)	Median	Range	Number of cases tested	Number of positive (%)	Median	Range	
Serum morphine	102	63 (61.8)	711 ng/ml*	164-8,720	38	13 (34.2)	-	-	0.002
Serum 6-MAM	36	7 (19.5)	890 ng/ml	62-1,767	7	0 (0)	-	-	0.062
Serum codeine	36	8 (22.3)	119.5 ng/ml	44-1,472	5	3 (60)	-	-	0.005
Urine morphine	82	78 (95.1)	1,880 ng/ml	198-24,118	36	34 (94.4)	1,389 ng/ml	174-15,647	0.214
Urine 6-MAM	36	23 (63.9)	940 ng/ml	145-7,338	10	6 (60)	1,001 ng/ml	158-2,334	0.949
Urine codeine	36	22 (61.1)	688 ng/ml	204-3,978	9	9 (100)	888 ng/ml	254-4,845	0.647
Alcohol	47	29 (61.7)	139.7 mg%	2-385	16	5 (31.3)	12 mg%	2-305	0.009

p: Compared between opiate overdose and non-opiate overdose groups using Chi-square test
* Only 14 cases had morphine level available
6-MAM = 6-monoacetylmorphine

Table 3. Other specimens* in which morphine was analyzed in opiate overdose group

Specimens	Number of cases tested	Number of cases detected	% morphine detection
Nasal swab	20	11	55
Tracheal swab	12	4	33.3
Bile	9	9	100
Liver	5	5	100

* Other specimens were collected from opiate overdose to analyze for morphine

overdose and non-overdose since drug tolerance may play a role[11]. Report from Department of Forensic Medicine, University of New South Wale, Australia showed that there was no significant difference between the median morphine concentrations of the heroin overdose cases and morphine positive homicides cases[12]. 6-MAM, which is a heroin metabolite, was detected in blood in about 20% of overdose victims. This is helpful in indicating acute heroin intoxication since 6-MAM has a shorter half-life than morphine and is an immediate metabolite of heroin. In the non-opiate overdose group, the authors did not detect blood 6-MAM in seven cases tested. Although the authors cannot exclude the possibility that morphine was the administered drug in those cases where 6-MAM was not detected but only morphine, the authors' experience has been that the vast majority of seized opiates in Thailand are in the form of heroin not morphine.

Total morphine in urine was detected in about 95% of the present cases, with no difference between the opiate overdose and non-opiate overdose groups. Morphine in urine is a good index for diagnosis of heroin abuse since it can be detected one to seven days after the last use[13]. However, the level of morphine may not reflect acute poisoning by heroin. The percent of alcohol detection in the blood of the opiate overdose group was 61.7% compared to 31.3% in the non-opiate overdose group. The median blood alcohol level in overdose group was around 140 mg%. The study of Davidson et al showed that alcohol was detected in 46% of heroin-related overdose deaths with the median level of 140 mg% (range 20 to 430 mg%). Many other studies have also demonstrated the presence and important role of alcohol in heroin-related deaths[9,10,14]. Darke et al reported that the heroin overdose cases were more than three times as likely to have blood alcohol present compared to morphine

positive homicide victims[12]. If heroin abusers are unaware of the effect of alcohol, the fatality outcome may be greater.

In opiate overdose cases in which no needle mark was found, nasal and tracheal swabs were collected and submitted for morphine analysis. The results showed that half of the nasal swabs and about one third of the tracheal swabs were positive for morphine. This finding showed that both specimens might be useful to identify the route of administration in smoking or snorting heroin. When serum and urine specimens are not collected, bile and liver can provide alternative sources of samples. In the present study, the authors detected morphine in bile and liver specimens of overdose cases. In about half of the decomposed cases in the present study, morphine tested positive in liver samples (data not shown). As morphine is quite stable, it can be analyzed from tissue even in embalmed cases[15].

Conclusion

The authors reported on opiate-related deaths examined in the Department of Forensic Medicine, Chiang Mai University between 1996 and 2008. The average incidence was about 1% of our autopsy cases. The number of cases was highest in the year 2001 and lowest in the year 2003, when the Thai government declared the "War on Drugs policy". More than two thirds of the deaths were opiate overdose cases. Males aged from 20 to 39 years were the most represented in overdose deaths. After the year 2003, more foreigners suffered from opiate overdose fatalities than Thais. The fatalities were confined to an area frequented by tourists. Pulmonary edema and needle puncture marks were observed more frequently in opiate overdose cases. The number of cases of morphine detection in serum from the opiate overdose group was significantly higher than in the non-opiate overdose group. Other substances detected in these victims were alcohol, benzodiazepines, methamphetamine, methylenedioxy-methamphetamine and methadone. Alcohol was found in about 60% of opiate overdose fatality, which was significantly higher than in non-opiate overdose deaths.

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Potential conflicts of interest

None.

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การตรวจทางนิติพยาธิวิทยาและพิษวิทยาในผู้ที่เสียชีวิตจากสารกลุ่มเฮโรอีนเกินขนาดเปรียบเทียบกับผู้ที่เสียชีวิตจากเหตุอื่นที่มีการใช้เฮโรอีนร่วม

นรินทร์ สรวิสูตร, ประณิธาน รัตนสาลี, อนงพันธ์ จันทร์กุย, ศุภรัตน์ ธรรมพิทักษ์, พงษ์รักษ์ ศรีบัณฑิตมงคล

วัตถุประสงค์: *เพื่อศึกษาเปรียบเทียบผลตรวจทางนิติพยาธิวิทยาและพิษวิทยาในกลุ่มที่เสียชีวิตจากเฮโรอีนเกินขนาดกับกลุ่มที่เสียชีวิตจากเหตุอื่นที่มีการใช้เฮโรอีนร่วม*

วัสดุและวิธีการ: *เป็นการศึกษาแบบย้อนหลังข้อมูลทางประชากรศาสตร์ ผลตรวจศพทางพยาธิวิทยาและพิษวิทยาในผู้ที่เสียชีวิตที่เกี่ยวข้องกับสารสารเสพติดเฮโรอีนที่ได้รับการตรวจชันสูตรพลิกศพที่ภาควิชานิติเวชศาสตร์ มหาวิทยาลัยเชียงใหม่ ระหว่างปี พ.ศ. 2539-2551*

ผลการศึกษา: *มีการเสียชีวิตที่เกี่ยวข้องกับสารกลุ่มเฮโรอีน 142 ราย เป็นการเสียชีวิตจากการได้รับเฮโรอีนเกินขนาด 102 ราย กว่าร้อยละ 95 เป็นเพศชาย ประมาณร้อยละ 80 อยู่ในช่วงอายุระหว่าง 20-39 ปี ร้อยละ 48 เป็นชาวไทย ร้อยละ 13 เป็นชาวอังกฤษ และร้อยละ 11 เป็นชาวอเมริกัน สถานที่ที่เสียชีวิตบ่อยที่สุดคือที่บ้านและโรงแรม กลุ่มที่เสียชีวิตจากได้รับเฮโรอีนเกินขนาดนี้ ตรวจพบลักษณะปอดบวมน้ำและรอยเข็มฉีดยาได้บ่อยกว่ากลุ่มที่เสียชีวิตจากเหตุอื่นที่มีการใช้เฮโรอีนร่วม ผลการตรวจทางพิษวิทยาพบว่าร้อยละ 61 ของกลุ่มที่เสียชีวิตจากได้รับเฮโรอีนเกินขนาด และร้อยละ 34 ของกลุ่มที่เสียชีวิตจากเหตุอื่นที่มีการใช้เฮโรอีนร่วม มีการตรวจพบมอร์ฟีนในเลือด ขณะที่ประมาณร้อยละ 95 ของทั้งสองกลุ่มสามารถตรวจพบมอร์ฟีนได้ในปัสสาวะ ในกลุ่มที่กลุ่มที่เสียชีวิตจากเฮโรอีนเกินขนาดตรวจพบแอลกอฮอล์ร่วมด้วยร้อยละ 62 ขณะที่กลุ่มที่เสียชีวิตจากเหตุอื่นที่มีการใช้เฮโรอีนร่วม ตรวจพบแอลกอฮอล์ร่วมด้วยเพียงร้อยละ 31 สารอื่น ๆ ที่ตรวจพบร่วมในบางรายได้แก่ สารเบนโซไดอะซีปีน เมทแอมเฟตามีน เมทธิลีนไดออกซีเมทแอมเฟตามีน และเมทธาโดน*

สรุป: *การเสียชีวิตที่เกี่ยวข้องกับสารเสพติดเฮโรอีนเฉลี่ยประมาณร้อยละ 1 ของการตรวจชันสูตรพลิกศพ มากกว่าสองในสามเป็นการเสียชีวิตจากได้รับเฮโรอีนเกินขนาด หลังปี พ.ศ. 2546 มีชาวต่างชาติเสียชีวิต จากเฮโรอีนเกินขนาดมากกว่าคนไทย การเสียชีวิตส่วนใหญ่เกิดขึ้นในบริเวณที่มีนักท่องเที่ยวพักอาศัย จากการตรวจศพทางพยาธิวิทยาพบลักษณะปอดบวมน้ำ และรอยเข็มฉีดยาในกลุ่มที่เสียชีวิตจากเฮโรอีนเกินขนาดได้บ่อยกว่ากลุ่มที่เสียชีวิตจากเหตุอื่นที่มีการใช้เฮโรอีนร่วม ในกลุ่มที่เสียชีวิตจากเฮโรอีนเกินขนาดมีการตรวจพบมอร์ฟีนในเลือดได้บ่อยกว่ากลุ่มที่เสียชีวิตจากเหตุอื่นที่มีการใช้เฮโรอีนร่วมอย่างมีนัยสำคัญ ไม่มีความแตกต่างในการตรวจพบมอร์ฟีนในปัสสาวะทั้งสองกลุ่ม*