Toxicological Criterion of the Heroin Poisoning

Shigeev S.

Department of Forensic Medicine Faculty of Medicine People's Friendship University of Russia

Summary

The paper presents toxicological characteristics of 198 cases of acute parenteral heroin intoxication, analyzes the clinically encountered range of blood and urinary concentrations of its metabolites. The principal causes of death are elucidated in victims of heroin poisoning at the hospital stage. Where there is a relationship of death probability to the detection of morphine in the victims' biological fluids is considered; its blood and urinary concentrations are determined, which undoubtedly suggests the occurrence of poisoning-related death. It has been established that death from poisoning by heroin may occur in the whole range of its detectable concentrations. There is no doubt that the blood morphine concentrations of at least 2.0 μg/ml should be considered to be fatal.
Key words: morphine – morphine concentration – heroin poisoning

Souhrn

Toxikologická kritéria při otravě heroinem

Práce uvádí toxikologické charakteristiky 198 případů akutní parenterální intoxikace heroinem, analyzuje klinicky získaný rozsah hladin jeho metabolitů v krvi a v moči. Jsou objasněny hlavní příčiny smrti u hospitalizovaných obětí otravy heroinem. Je určen vztah pravděpodobnosti úmrtí při zjištění morfinu v tělních tekutinách obětí, byly stanoveny jeho koncentrace v krvi a v moči, které nepochybně ukazují na to, že nastane smrt způsobená otravou. Bylo stanoveno, že smrt způsobená otravou heroinem může nastat v celém rozmezí jeho detekovatelných hladin. Není pochyb o tom, že koncentrace morfinu v krvi vyšší než 2,0 μg/ml by měla být považována za fatální.

Klíčová slova: morfin – koncentrace morfinu – otrava heroinem

Soud Lék., 52, 2007, No. 1, p. 17–20

Introduction

Poisoning by narcotic agents is high on the list of acute fatal intoxications. Opiates and their semisynthetic analogues with actions similar to those of opiates (opioids) are one of the most commonly used narcotics [4, 7]. In recent years, heroin poisoning is most frequently dealt with [3, 5]. Their hazard to human health is determined by not only high narcogenicity and toxicity, but also by the high probability of accidental or malicious poisoning.

The literature on the study of different aspects of poisoning by narcotics, mainly chronic intoxications, is extensive; papers dealing with acute, including fatal, poisonings are encountered more rarely. There is virtually no literature dedicated to the evaluation of the severity of intoxication and the interpretation of the results of forensic chemical examinations.

Materials and Methods

Case records of 198 inpatients treated in the intensive care units of city hospitals for acute parenteral heroin poisoning were studied 125 medicolegal reports (63.1% of the 198 inpatients) of deceased inpatients were analyzed from the records available in the Bureau of Forensic Medicine, Moscow Department of Health. Clinically, death occurred in the toxicogenic phase of acute poisoning in 55 (44.0%) victims and in the somatogenic phase (due to poisoning-associated complications) in 70 (56.0%).

In all cases, heroin poisoning was verified by their case histories, clinical manifestations, and life-time estimation of heroin metabolic products in blood (100%) and urine (53.0%) (105/198) (LC/MS method, a GCMS-QP5050 device (Japan)), then by the determination of urinary morphine in the victims who had been treated in

the inpatient setting where they died (49.2%, 32/65).

When describing the central distribution trends, the median (Me), maximum (max), and minimum (min) values were estimated, by presenting the results as Me (min-max). By establishing whether a correlation existed between the parameters, the Spearman rank correlation coefficient (r_s) was used. The correlation coefficient ≥ 0.3 (95% CI) was considered significant. The criteria for quantitative toxicity – lethal doses (LD_{25}, LD_{50}, LD_{75}, and LD_{100}) – were calculated by the least squares estimator using the probit analysis. Here we used logit-regression belonging to the nonlinear estimation methods when a response was taken as only two values (0 – "alive" or 1 – "dead"). In our study, the method was based on the assumption that there was a functional relationship between the dependent and independent variables, which we attempted to establish. The findings were used to determine the probability of death probability in a different concentration range. The major feature of assessing the risk of death in victims from this or that blood and urinary morphine concentrations is that strictly dosed concentrations cannot be guided, but one has to be based on the baseline blood and urine levels of metabolites, which naturally agrees well with the real situation of life when a medical man has to keep in mind not only experimental evidence, but also the dose actually entering the organs and tissues in specific victims particularly when the exact amount of an ingested narcotic agent remains unknown.

Results

All examined intoxications were regarded as accidents in users of toxic substances. There were not any available data suggesting narcotic-induced murder or suicide.

Acute poisoning came to a good close (recovery) in 36.9% cases (73/198) and ended with death in 63.1% (125/198) (Fig. 1). Most victims were males (83.8%, 166/198) aged 21-30 years.

The median (Me) of occurrence of heroin-related death at the hospital stage was 96 hours; 25 to 75% of victims died in the range of 24 to 288 hours.

Within the first 72 hours, the immediate causes of death were poisoning (44.0%; 55/125) and pneumonia (3.2%; 4/125). In later periods, death was associated with pneumonia (32.8%; 41/125), myocardial dystrophy (5.6%; 7/125), sepsis (5.6%; 7/125), posthypoxic encephalopathy (1.6%; 2/125), and acute renal failure (7.2%; 2/125) developing due to positional injury.

Toxicological studies of blood samples from inpatients (n = 198) for acute poisoning detected morphine (1.5 μg/ml (0.1-4.1 μg/ml)) in all cases (100%), urinary morphine (4.6 μg/ml (0.01-26.0 μg/ml)) was

Table 1. Results of toxicological study of blood and urine from victims of heroin poisoning

Admitted	(n=198)MORPHINE CONCENTRATION (Me (max-min)) (μg/ml)		
	life-time		postmortem
	in blood	in urine	in urine
discharged	0.6 (0.1-0.9) n = 73	0.3 (0.01-0.7) n = 40	-
deceased	2.1 (0.2-4.2) n = 125	11.8 (1.7-26.0) n = 65	4.4 (0.06-12.0) n = 32

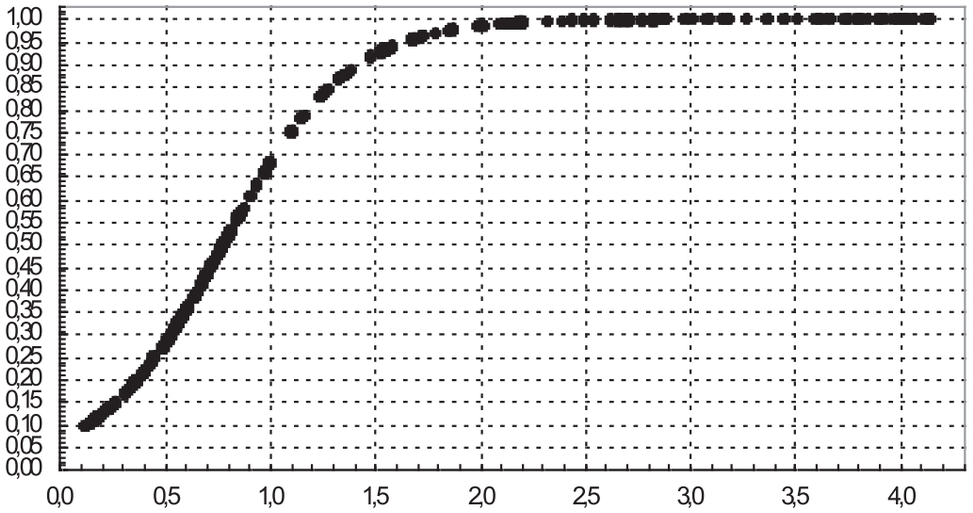

Fig. 1. Death probability (as ordinate in terms of conventional units) against blood morphine concentrations (as abscissa, μg/ml).

also found in 105 victims (53.0% of the 198) (Table 1). At the same time, there was a slight positive correlation between the life-time detection of morphine in blood and urine (r_s = 0.2; p = 0.02).

A forensic chemical study of blood, urine, and viscera from those who had died from intoxication (n = 55) within the first 48 hours after admission revealed morphine only in urine (4.4 µg/ml (0.06–12.0 µg/ml)) just in 58.2% of cases (32/55); the result of the study was negative in 23 cases (41.8%), moreover, any relationship was not found between the life-time detection of blood morphine and the postmortem detection of urinary morphine. Intensive elimination therapy, including that using extracorporeal detoxification in heroin poisoning, did not allow us to trace the time course of changes in the toxicological parameters of blood and urine in later periods of hospitalization and accordingly the occurrence of death.

Discussion

The main conclusion that follows from the analysis of the presented data showing the positive dose-effect dependence is that there is a certain cause-and-effect relation between the action of heroin on the body and the development of a toxic process. Thus, on estimating the death probability from blood or urinary morphine concentrations, the plot represents a distribution curve that is asymmetric about the midpoint, thereby differing from the classical one when there are concentrations that fail to produce a significant effect (the lower asymptom). That is to say that with poisoning by heroin in the whole range of practically encountered blood concentrations of its metabolites, the magnitude of toxic action exceeds the limits of the body's physiological protection and the outcome of poisoning remains uncertain in most cases.

The ascending portion of the curves, the so-called basic response, in the estimation of blood morphine, ranges from 0.1 to 1.4 µg/ml. In the range of these concentrations, the outcome of poisoning is uncertain and the risk of death increases with the higher blood concentrations of a toxic substance; that is to say that the body is in a critical state. It is expedient as an objective criterion to use the median lethal dose of a toxic substance (LD_{50}), which is equal to 0.78 µg/ml, when the critically ill person is evaluated. When the blood morphine concentration is above 2.0 µg/ml (LD_{100}) irrespective of its further increase, the curve of the plot takes up a level position (the upper asymptom), which corresponds to the life-incompatible (irreversible) level of poisoning. The slope of the dose-effect curve, in proximity to the median value (LD_{50}) in particular, characterizes a scatter of the most commonly used concentrations (LD_{25} = 0.44 µg/ml; LD_{75} = 1.1 µg/ml). In addition, the slope shows how great a change in the probability of death due to heroin will be with the altered concentration of its active metabolite morphine: the steep slope suggests that most victims will respond nearly equally in the narrow range of concentrations; the flat slope indicates that there are great differences in the sensitivity to the concentration of the toxic substance.

On comparing the findings with the data available in the literature on this issue, we can note their agreement in some details with a slight difference in their overall assessment. It is known from the literature that blood morphine concentrations of 0.08–0.15, 0.15-0.5, and 0.05–0.4 µg/ml should be considered therapeutic, toxic, and fatal, respectively [1, 2]. According to these data, the range of lethal concentrations combines and even is outside that of therapeutic and toxic concentrations. Our analysis of a specific clinical material gives grounds to conclude that heroin-related death may occur in the whole range of its detectable concentrations, but there is no doubt that the blood morphine concentration of at least 2.0 µg/ml should be considered fatal. This is also suggested by the data of a life-time study of drivers who may use opiates, in whom blood morphine concentrations are toxicologically revealed as high as 1.5 µg/ml and as high as 0.3 µg/ml in heroin abusers [6].

Conclusions

In our opinion, the foregoing suggests that the positive results of a forensic chemical study cannot be unambiguously interpreted as evidence for fatal heroin poisoning particularly if their metabolites are detectable only in urine even if they are estimated. The absolute requirement for exactly ascertaining the fact of fatal heroin poisoning is to quantitatively determine their metabolites only in blood. Each case of a positive result should be considered only as a proof of the use of opiates not long before death rather than evidence for death from their poisoning.

References

1. **Baselt RC.** *Disposition of Toxic Drugs and Chemicals in Man, 6th ed*. Biomedical Publications, Foster City, CA; 2002.

2. **Druid H, Holmgren P.** A Compilation of Fatal and Control Concentrations of Drugs in Postmortem Femoral Blood. *J Forensic Science*. 1997;42:79–87.
3. **Gerostamoulos J, Staikos V, Drummer OH.** Heroin-related deaths in Victoria: a review of cases for 1997 and 1998. *Drug Alcohol Depend* 2001;61:123–127.
4. **Hall WD, Degenhardt LJ, Lynskey MT.** Opioid overdose mortality in Australia, 1964-1997: birth-cohort trends. *Med J Aust* 1999;171:34-37.
5. **Oxman G, Kowalski S, Drapela L, Gray ES, Fafara S, Lyons H, et al.** Heroin overdose deaths-Multnomah County, Oregon, 1993-1999. *MMWR Morb Mortal Wkly Rep* 2000;49:633–636.
6. **Platt JJ.** *Heroin Addiction: Theory, Research, and Treatment, 2nd edition*, Robert E. Krieger Publishing Company, Malabar, Florida, USA; 1986.
7. **Solet D, Hagan H, Nakagawara J, Plough A, Ball J.** Unintentional opiate overdose deaths-King County, Washington, 1990-1999. *MMWR Morb Mortal Wkly Rep* 2000;49:636–640.

Dr. Sergey V. Shigeev, CSc.
Department of Forensic Medicine
Faculty of Medicine
People's Friendship University of Russia
21-67, Malysheva street, Moscow, Russia

KAZUISTIKY Z MOLEKULÁRNÍ GENETIKY

Jan Lebl, Milan Macek jr., hlavní autoři a pořadatelé

Obsáhlý soubor 70 kazuistik dětských pacientů s monogenními onemocněními, na němž se podílel více než stočlenný autorský kolektiv odborníků z České republiky i ze zahraničí, obsahuje ty nejzajímavější případy z jejich klinické praxe. Autoři se soustředili jak na nejčastější choroby, tak i na onemocnění vzácná, ale z různých pohledů důležitá (buď z etnického hlediska, nebo z hlediska modelových patogenetických aspektů). Sborník je rozčleněn do 15 okruhů, týkajících se jednotlivých onemocnění (hyperglykémie, malý vzrůst, hemostáza, hypertenze, obezita, bolesti břicha, plicní onemocnění, poruchy sluchu, štítná žláza, nadledviny, lipidy, kriticky nemocný novorozenec, neurogenetická onemocnění, vývojové anomálie, srdeční vady), a doplněn bohatou fotodokumentací. Autoři kazuistik uvedené příběhy se svými pacienty osobně prožili; jsou mezi nimi příběhy smutné i příběhy se šťastným koncem, všechny ale přispěly k poznání a poučení.

Vydal Galén v roce 2006, ISBN 80-7262-418-0, formát 155 x 225 mm, brož., 219 str., cena 190 Kč.

Objednávku můžete poslat na adresu: Nakladatelské a tiskové středisko ČLS JEP, Sokolská 31, 120 26 Praha 2, fax 224 266 226, e-mail: nts@cls.cz