J Forensic Sci, Jul. 1973, Vol. 18, No. 3

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Quinine Cardiotoxicity: A Mechanism for Sudden Death in Narcotic Addicts

Narcotic abuse has reached alarming proportions in many areas of the United States, carrying with it a pernicious morbidity and a tragic mortality. The latter is estimated to be approximately 0.7 percent of the addict population per annum [*1*]. There were over 1000 such deaths annually in 1969 and 1970 in New York City alone [*2*]. Eighty percent of these fatalities in New York are attributed to "immediate acute reactions" [*2*] following administration (usually intravenous) of narcotics. In Dade County (Metropolitan Miami), Florida, 86 of 87 narcotic-related fatalities, excluding 13 violent deaths in the reported series, "collapsed and died following the injection of a narcotic" [*3*]. The mechanisms of sudden death in this circumstance are complex and have not been elucidated completely. Several possible explanations include narcotic overdosage with respiratory depression, narcotic induced postural hypotension [*4*], hypersensitivity or anaphylactic reaction [*5,6*], idiosyncratic reaction to unspecified material(s) [*1*], adverse response to intravenous injection of colloid or particulate material ("colloidoclastic crisis") [*7*], or adverse reactions to adulterants in narcotic packets which are purchased "on the street".

Quinine is utilized commonly as an adulterant for narcotics. This practice began in New York in the 1930's, an era when malaria was prevalent among addicts, and now is widespread in the United States except for the West Coast [*2,8*]. Quinine depresses myocardial excitability and at one time was used to suppress cardiac arrhythmias prior to its replacement by its more potent isomer quinidine. More recently, it has been suggested that intravenous injections of heroin-quinine mixtures may depress myocardial excitability [*9*]. However, there has been no demonstration that quinine, per se, can cause hyperacute death following intravenous administration.

This communication describes an experimental demonstration of the cardiotoxic effects of rapidly administered, intravenous injections of quinine in an attempt to evaluate further the possibility of a cause and effect relationship between the quinine content of the "street" narcotic and sudden death following its intravenous injection. We do not intend that this paper be construed as an attempt to evaluate definitively quinine's effects upon the heart, and we recognize that no experimental design can simulate all of the variables of human narcotic abuse.

Manuscript received for publication 3 Nov. 1972; revised manuscript received 11 Dec. 1972; accepted for publication 16 Dec. 1972.

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In addition, we propose a classification of narcotic fatalities which provides a logical conceptualization for analysis of post mortem findings and interpretation of mechanisms of death in such instances.

Method

Healthy, young-adult, male Wistar rats, weighing 300–400 gm, were subjected to rapid injections of quinine hydrochloride via a catheter in the external jugular vein. All animals were anesthetized lightly by an intraperitoneal injection of sodium pentobarbital (0.2 ml of a 2 percent solution/100 gm). Heart rate and rhythm were monitored continuously using an ECG polygraph (three standard leads).

Pure quinine hydrochloride (Sigma) was dissolved in 0.8 percent saline to produce a 40 mg/ml solution. The volume of injected fluid did not exceed 0.5 ml, administered in 1.5 to 2.5 s. No rat was used more than once, and all rats were autopsied.

Control rats were injected with an 0.8 percent saline solution adjusted to pH 6.8 (the pH of our experimental quinine solution) with 0.1 *N* hydrochloric acid in order to evaluate the independent effects of rate and volume of intravenous injections.

Results

Ten control injections of 0.8 percent saline adjusted to pH 6.8 in volumes up to 1.0 ml, administered in 1.0 to 2.5 s, caused transient (2–5 s) slowing of heart rate from 400 to 360 beats per minute without disturbance of cardiac rhythm. In sharp contrast, quinine injections produced marked bradyarrhythmias within 2.5 s of injection. With doses as low as 5 mg/kg (2.5 mg/kg/s), these abnormalities persisted for an average of 12–15 minutes. Increases of quinine dosage from 5 to 50 mg/kg (given over a 2 s interval) in 25 rats showed that the higher dosage produced more severe disturbances of rhythm which either persisted longer or terminated in asystole. Doses over 50 mg/kg (25 mg/kg/s) were uniformly fatal. The electrocardiograms of two rats, obtained during and following quinine administration, are shown in Figs. 1 and 2.

Abnormal rhythms consisted initially of sinoatrial node depression, with occasional ventricular or junctional escape beats with aberrant intraventricular conduction. At quinine doses between 10–50 mg/kg (5–25 mg/kg/s) conduction defects were produced at A-V junctional and intraventricular levels. Asystole resulted within seconds of injections at higher doses. In some cases sinoatrial node activity was still present following suppression at lower levels. Thus, quinine produced suppression of impulse formation and conduction at all levels.

Intraperitoneal injections of quinine hydrochloride at doses of 100 mg/kg produced qualitatively similar abnormalities of cardiac rate and rhythm with onset in 8–10 minutes; however, asystole did not occur.

Autopsy, including microscopic examination, showed only cardiac dilatation with marked passive hyperemia of the viscera and pulmonary edema.

Discussion

Secondary narcotic-abuse fatalities include those due to such medical complications as serum hepatitis, bacterial endocarditis, tetanus, pulmonary angiopathy and others as well as all manners of violence. These types of deaths have been reviewed previously in depth [*7,10–13*] and are not considered further here.

We define primary narcotic-abuse fatalities as those which result directly from the pharmacologic (toxic) effects of narcotic alkaloids or adulterants. This classification is

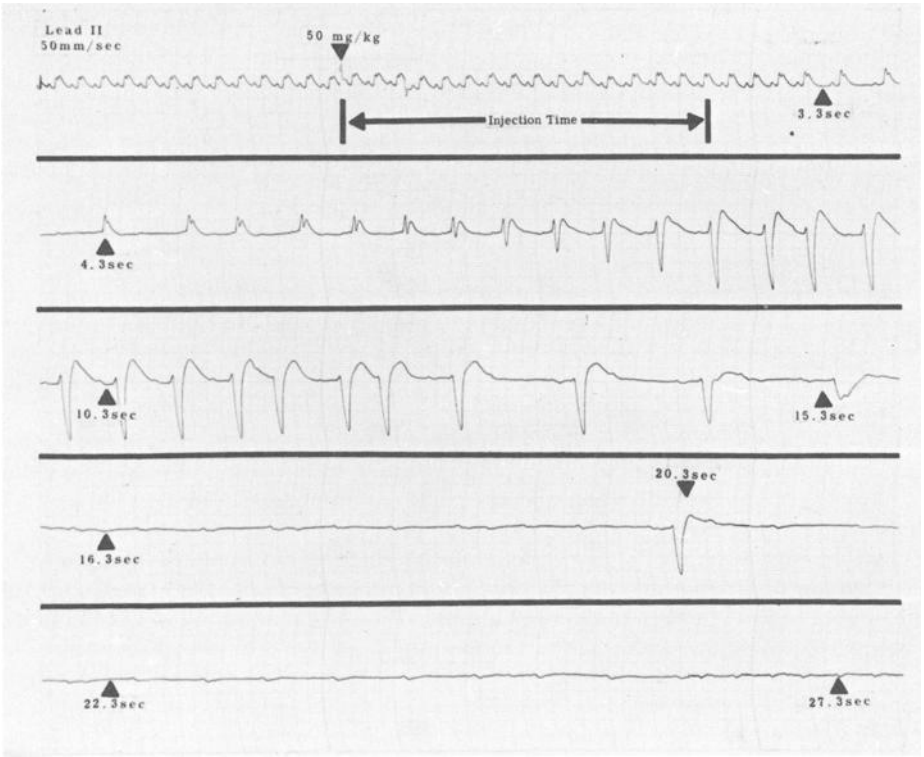

FIG. 1—*Continuous electrocardiographic tracing of a rat following the intravenous administration of 50 mg/kg of quinine hydrochloride over a 2.5 s period as shown. The number of seconds noted refers to elapsed time from initiation of injection.*

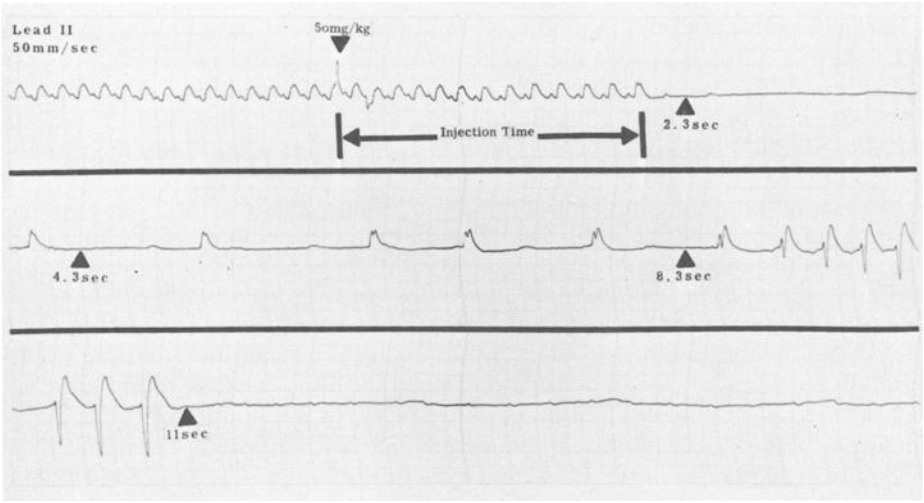

FIG. 2—*Conditions as in Fig. 1 with the injection time of 2.0 s as shown.*

subdivided into (*a*) *hyperacute* or *immediate*, with incapacitation and death within seconds or a few minutes following injection; (*b*) *acute*, with death within one half to a few hours following injection; and (*c*) *subacute* or *delayed*, with death occurring at least several hours following injection. The distinctions between these subdivisions are not always clear-cut, and accurate anamnestic details rarely are provided by the victim's colleagues. In fact, it is common for dead victims to be "dumped" in public places or anonymously deposited at hospital emergency rooms. However, in many instances an evaluation of circumstantial ("scene") and morphologic findings provides reliable data for reconstruction of the fatal incident.

Hyperacute fatalities classically are those in which the victim is observed to "drop dead" immediately following narcotic injection or in which he is found dead with his (makeshift) syringe still inserted in a vein or beneath his body. In addition to the usual cutaneous and visceral pathologic hallmarks of narcotic abuse, autopsy on these individuals generally shows only nonspecific visceral congestion with pulmonary edema. These fulminant deaths demonstrate dramatically how rapidly intravenous narcotism can incapacitate and kill, a phenomenon most logically and readily explicable on the basis of cardiac arrhythmia or standstill rather than respiratory depression. Even instantaneous respiratory arrest, if such occurs, would not be expected to cause immediate incapacitation.

Fatalities characterized by an initial loss of consciousness followed by gradually deepening coma, which may last for brief or prolonged periods, are indicative of the anticipated sequel of an overdose of a drug which produces central nervous system (and respiratory) depression. These victims almost invariably develop bronchopneumonia if the coma lasts longer than a few hours, and the sequence of morphologic pulmonary changes in this circumstance is well documented [*3*,*12*]. In our experience, bronchopneumonia which develops following narcotic overdosage, with or without aspiration of gastric content, is identical with bronchopneumonia due to prolonged unconsciousness of any etiology, whether it be natural disease (for example, intracerebral hemorrhage), some other intoxication (for example, ethyl alcohol), or mechanical trauma (for example, craniocerebral injury).

We know of no reason to assume that hyperacute narcotic fatalities are due to an anaphylactic or hypersensitivity reaction. There is no published documentation either of hypersensitivity induced by the injected substances or of anaphylactic-type, nonfatal reactions in living addicts. Although pathologic findings in human anaphylactic fatalities are said to be nonspecific [*14*], there is no reported instance of laryngeal (aryepiglottic fold) edema in the victim of a narcotic-induced sudden death. Furthermore, clinically observed signs in victims of human anaphylaxis do not characteristically cause immediate incapacitation.

Narcotic packets purchased by drug abusers generally contain 100–200 mg of powder, of which an average of 4–8 mg is heroin. The remainder of the powder consists of variable proportions of one or more diluents such as sugars (lactose, mannitol, dextrose, sucrose) and other drugs (quinine, procaine, cocaine, methapyrilene). Chemical analyses of confiscated narcotic packets in two reported studies have shown quinine concentrations as high as 38.7 percent [*15*] and 40.8 percent [*16*]. Illicit drugs ordinarily are prepared for injection by dissolving them in about 5 ml of tap water in a small receptacle such as a bottle cap or spoon ("cooker"). The resulting solution then is drawn into a standard or improvised (eyedropper) syringe and characteristically self-administered intravenously as rapidly as possible. While the needle is still in place, many addicts aspirate blood into the eyedropper and reinject it. This verifies that the original injection was intravenous and flushes out any remaining narcotic solution.

The cardiovascular effects of quinine are qualitatively similar to those of its more potent

isomer quinidine [17]. While quinidine is 5–10 times more potent [18], both agents reduce the rate of pacemaker discharge, slow conductivity, and prolong the effective refractory period. When quinidine is given to humans in excessive doses, it can produce conduction defects or ventricular filbrillation; either could be a mechanism of hyperacute death.

There are at least three lines of evidence incriminating quinine cardiotoxicity as a mechanism for hyperacute narcotic fatalities. When a 70 kg addict injects his narcotic solution in two seconds, he receives 0.03 to 0.06 mg/kg/s of heroin and 0.7 to 1.4 mg/kg/s of adulterant. If quinine is 30 percent of the adulterant, this dose (0.2–0.4 mg/kg/s) exceeds by approximately 20 to 40 times the recommended maximum therapeutic rate of intravenous quinine injection of 50 mg/min (approximately 0.01 mg/kg/s) [19]. Since quinine and quinidine both have relatively narrow margins of safety between doses effective in suppressing arrhythmias and toxic or lethal doses, such an excess would be expected to produce fatal arrhythmias.

Secondly, in the rat, we have shown that arrhythmias are produced at rates of intravenous administration above 2.5 mg/kg/s and uniformly fatal arrhythmias occur at doses of 25 mg/kg/s. The LD_{50} for slowly absorbed (subcutaneous) quinine in rats is 790 mg/kg [20]; whereas, in humans, the acute oral fatal dose has been reported to be approximately 100 mg/kg [21]. Thus, it appears that rats are more resistant to the cardiovascular effects of quinine. Consequently, assuming at least a tenfold difference in sensitivity to quinine between rat and man, intravenous administration of 0.2–0.4 mg/kg/s to man would be expected to produce arrhythmias which might be fatal in some instances.

Thirdly, a clinical report [9] documents the occurrence of A-V conduction defects in a heroin addict who had quinine in his urine. When quinine was no longer demonstrable, A-V conduction returned to normal.

With rapid intravenous administration of quinine, depression of myocardial contractility and peripheral vasodilatation may lead to marked hypotension [21]. This may enhance cardiotoxicity by diminishing coronary perfusion, thereby producing myocardial hypoxia and increasing susceptibility of the conduction system to suppressant agents.

We do not know why one injection of an illicit narcotic-quinine mixture, ostensibly similar to other previously injected mixtures, should prove fatal at a particular time. The lethality of the final injection may be related to many variables, such as the content of heroin, quinine, or other adulterants [8,15,16]; rate of injection; interval between injections; physiologic status of the victim at the moment of injection; or altered physiologic response to the injected chemicals.

The evidence indicates that rapidly administered intravenous injections of quinine can cause hyperacute death in rats, and we believe that the quinine moiety in the "street bag" may be responsible for human drug abuse fatalities of this type. Other cardiac suppressants which have been identified in confiscated narcotic packets include procaine [8,15,16] and quinidine [8], further indicating that more attention should be focused on the study of adulterants in evaluation of narcotic fatalities and in emergency management of the "overdose" syndrome.

While a pharmacologic overdose, whether it be due to injection of an unusually large amount of narcotic alkaloid or to loss of tolerance following a period of voluntary or forced abstinence, has obvious lethal potential and probably claims many victims, the lumping together of all drug deaths as "overdoses" is an oversimplification which obscures a complex problem.

Summary

Quinine is used commonly as an adulterant for illicit narcotics. An experimental demonstration of quinine's cardiotoxicity has shown that rats develop bradyarrhythmias and

asystole within seconds following rapid intravenous administration of quinine hydrochloride. Hyperacute death due to intravenous narcotism is defined as immediate collapse followed by death within a few minutes after intravenous injection of an illicit narcotic. Our study incriminates the cardiotoxic properties of quinine as one of the mechanisms which may precipitate such hyperacute deaths.

The assumption that all narcotic deaths are a result of pharmacologic overdosage is an oversimplification which obscures a complex problem. Attention should be focused on the study of adulterants as well as narcotic alkaloids in evaluation of narcotic fatalities and in emergency management of the "overdose" syndrome.

Acknowledgment

The authors gratefully acknowledge the technical assistance of Simon Koletsky, M.D.

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