CHAPTER 4

Treatment for Survival Prior to Death and Interpretation of Postmortem Toxicologic Findings

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The protocol for postmortem examination in the medical examiner's or coroner's office should provide for a minimum toxicologic examination in every death. Specimens to be collected for toxicologic evaluation should include: (a) gastric contents with notation of the total volume, (b) heart blood, (c) urine, (d) bile, and (e) selected tissues, such as liver, lung, and kidney.

The minimum toxicologic examination should provide for qualitative screening with quantitation when the qualitative procedures are positive. Minimum routine screening procedures should include a test for volatile organics and screening procedures for detection of a variety of groups of drugs. Circumstances of death may dictate a more elaborate protocol or suggest specific substances or groups of substances that should be assessed.[1] The only significance that routinely can be attached to positive toxicologic findings is that a detected substance is present. It is extremely rare that causal significance can be attributed to a substance on the basis of analytical data alone. More commonly, the results of toxicologic findings must be interpreted with consideration given to investigations of the scene, activities of the decedent immediately prior to death, first aid or treatment efforts provided by laymen or by medical personnel, and long-term drug use history. These investigations may result in the cause of death being attributed to a substance which is not detectable at postmortem examination. Substances detected may be found to have been administered medicinally and to have no causative role whatsoever. Concentrations of drugs for which tolerance develops may be so high as to be considered an unequivocal cause of death in a pharmacologically naive individual, while they may have played no role whatsoever in a chronic drug user.

The purpose of this discussion is to direct attention to the circumstances which influence the interpretation of toxicologic findings at postmortem examination.

CIRCUMSTANCES INFLUENCING INTERPRETATION

Statistical parameters, such as "the lethal dose 50 percent" or "the lethal concentration 50 percent," permit the determination of the relative toxicity of a substance for various species or for subgroups within a single species. The relative toxicity of various substances may be compared using these concepts. They are, however, not applicable to single individuals within a population except for approximation of the order of magnitude of susceptibility of the individual to the substance under consideration.

When discussions of susceptibility are limited to single individuals, statistical concepts lose validity. It becomes necessary to examine the factors that influence variation in susceptibility of individuals within the population. While many of these variables have not been defined, some have been the subject of investigation.

Individual differences in susceptibility to toxic substances are determined in part by genetic factors. Differences in enzymatic armamentaria which determine efficacy of

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[1]For further discussion of topics treated here, see also chapter 3, "Postmortem Examination," and chapter 5, "Forensic Toxicology in Death Investigation."

detoxification are slow and fast acetylation, glucose-6-phosphate dehydrogenase deficiencies, acetylcholinesterase deficiencies, and metabolic correlates with the hemoglobinopathies, such as sickle cell disease. Defects in amino acid metabolism also may alter susceptibility to some toxic substances. The occurrence of these genetically determined variations in metabolism may place the individual significantly outside the normal curve of susceptibility, influencing interpretation of postmortem findings.

An individual may be made more susceptible to some substances by preexisting pathology. Susceptibility to carbon monoxide may be increased by coexisting pathological processes limiting exchange of oxygen in the lung or in a target organ, such as brain or heart. Acquired end-organ susceptibility is illustrated by chronic exposure to anticholinesterase insecticides. Reduction of cholinesterase levels results in significant increase in response to administration of succinyl choline. Impairment of liver function increases the relative susceptibility to substances dependent upon hepatic enzymes for detoxification. Significantly impaired renal function increases susceptibility to substances normally excreted by the kidney in a pharmacologically active form.

Tolerance may develop to make an individual less susceptible to the lethal effects of certain drugs. Dispositional tolerance is exemplified by hepatic microsomal enzyme induction. Experience with a toxic substance over a period of time may result in increasing the rate of detoxification by increasing the activity of enzymes that effect the biotransformation of the substance to a nontoxic metabolite. Dispositional tolerance does not increase the concentration of toxic substance that can be tolerated at the target end organ. Comparison of a tolerant individual with a pharmacologically naive individual after a similar survival interval shows lower tissue concentrations of the substance in the tolerant individual. "End-organ tolerance" describes the adaptive procedure by which the target organ becomes less responsive to the pharmacologic effect of the substance. Development of end-organ tolerance permits an individual to survive tissue concentrations of a drug which would unequivocally be fatal for the pharmacologically naive individual.

Interpretation of the toxicologic findings in postmortem examination requires consideration of the genetic variable in susceptibility, appraisal of preexisting pathology, and assessment of the pharmacologic experience of the decedent.

TREATMENT PRIOR TO DEATH

The phrase "treatment prior to death" is used to describe occurrences during the interval between exposure and death. This includes first aid given by laymen as well as treatment administered by the medical community. Implicit is a survival interval between the exposure and the occurrence of death. During this interval, the pharmacodynamics of redistribution or disposition influence the interpretation of the chemical findings at postmortem examination.

Attempts at first aid may include the mechanical induction of vomiting with consequent aspiration asphyxia resulting in death unrelated to the concentration of toxic substances present in the body. Efforts to induce vomiting with sodium chloride are not uncommon, and where vomiting has failed to occur, death from hypernatremia has occurred in the presence of drugs of no toxicologic significance. Utilization of street treatment folklore may result in intravenous injections of milk or intravenous injections of table salt. Other drugs that may be used in a treatment effort include administration of amphetamines for barbiturate overdose and administration of chlorpromazine for amphetamine overdose.

Once a patient finds his way to medical care, interpretation of subsequent postmortem findings may become very complicated. Administration of supportive care for pulmonary or cardiovascular failure may result in survival after the time that the original offending substance has been cleared from the body, with death due to injury incurred while the toxic substance was present. The performance of gastric lavage alters the interpretation of postmortem examination of gastric contents and may add the complications of

aspiration asphyxia or aspiration pneumonitis of chemical or of infectious origin. In the treatment effort a variety of other drugs such as central nervous system and respiratory stimulants and pressor amines may be administered. Not only do these substances complicate interpretation of postmortem findings, but they may contribute to the lethality of the situation by adding the hazard of overdose with these therapeutic agents. Other possible complications that may occur during the treatment process include protracted hyperventilation; overcompensation of acid/base disturbances; dehydration and overhydration in attempts at forced diuresis; obstruction of a main stem bronchus causing collapse of the lung, arteriovenous shunting, and hypoxemia; and rupture of an emphysematous bleb with tension pneumothorax. Monitoring of central venous pressure by way of a subclavian puncture has an attendant hazard of hemothorax from the subclavian puncture. Also, retroperitoneal hemorrhage secondary to extracorporeal dialysis has occurred.

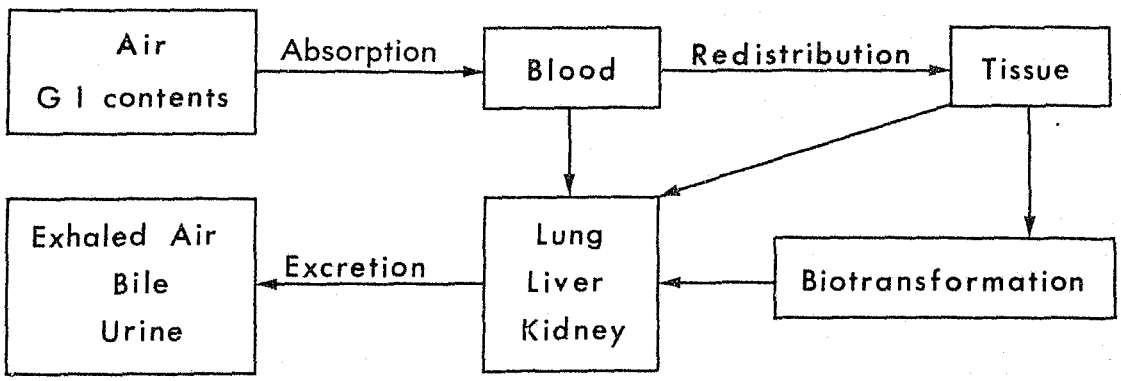
The investigation of treatment prior to death and careful review of any clinical records assist in the interpretation of postmortem toxicologic findings. Treatment may permit a survival interval sufficient to remove the originally involved substances from the body, may add one or more drugs not involved in the primary toxic episode, and may add a variety of complicating circumstances, any of which could be contributing factors in delayed death.

PHARMACODYNAMICS OF HOST-SUBSTANCE RELATIONSHIPS

Understanding the pharmacodynamics occurring with exposure to a toxic substance is essential to interpretation of postmortem findings. Figure 1 presents a schematic model of the major events in absorption, redistribution, biotransformation, and excretion of toxic substances in the body. The substances are absorbed through mucous membranes of the lung or the gastrointestinal tract into the systemic circulation. Water-soluble substances may be excreted directly by the kidney. Lipid-soluble substances may be excreted by the liver through the bile. Gases may reenter the lung and be exhaled. Lipid-soluble substances accumulate in fat depots from which they are gradually released to be excreted or to be further metabolized. Within the various tissues biotransformation may occur, resulting in a derivative which is less toxic or more water soluble and more easily excreted by the kidney. In some instances, biotransformation may result in products that are as toxic or more toxic than the original compound. Quantitative data on blood levels of methaqualone and its metabolites, for example, sug-

FIGURE 1

PHARMACODYNAMICS OF HOST-SUBSTANCE RELATIONSHIPS



gest, in the author's experience, that the degree of central nervous system depression following acute overdose correlates better with the blood levels of a metabolite than it does with the blood concentration of methaqualone.

Prior to death, all the processes illustrated in figure 1 are actively occurring. With the advent of death, the arrest of circulation, and the subsequent occurrence of tissue death, these processes are arrested to yield the toxicologic findings at postmortem examination.

For interpretation of postmortem findings, the simplest situation prevails when there has been a continuous excess of a toxic substance available for absorption up until the moment of death. The postmortem toxicologic examination then reveals blood and tissue concentrations that were present at the time some vital function was fatally impaired.

Once the toxic substance becomes limiting, the events diagramed in figure 1 no longer are driven by continuing absorption. When absorption ceases, blood levels become a function of the rate of redistribution and metabolism. When redistribution is controlled primarily by physical factors such as storage in lipid depots where the substance has no pharmacologic activity, the rapid decrease in blood levels may have no relation to toxicity. During this redistribution phase, the value of quantitative assessment of substances in the blood is substantially reduced. When nonreversible toxic injury occurs in the presence of a toxic substance that subsequently is removed from the body by continuing metabolic processes, death may occur with no detectable drug in the body.

It is important to determine whether the processes in figure 1 were driven by a continuous excess of the toxic substance up until the moment of death or whether the toxic substance, for any reason, became limiting prior to the occurrence of death.

Carbon Monoxide

Because of the simplicity of host-substance interactions, carbon monoxide provides a useful example to explore principles discussed above. Carbon monoxide is absorbed across the respiratory mucosa and excreted across the respiratory mucosa. There is no significant biotransformation. Tolerance to carbon monoxide is not increased significantly by previous experience with the substance. The pathophysiology of carbon monoxide consists of carboxyhemoglobin formation producing an oxygen transport deficiency tissue anoxia. When respiration ceases, no further change in carboxyhemoglobin concentration occurs.

Continuous exposure of a healthy young adult to an excess of carbon monoxide results in accumulation of carboxyhemoglobin to a concentration in the order of 60 percent saturation or higher. At these levels, cerebral anoxia results in respiratory arrest with no further change in carboxyhemoglobin concentration. Postmortem examination reveals carboxyhemoglobin concentrations in excess of 60 percent with no other toxicologic findings.

Carbon monoxide exposure frequently induces nausea with subsequent vomiting. The presence of gastric contents in the respiratory tract suggests aspiration asphyxia as a contributing factor to the hypoxia and death might ensue with a carboxyhemoglobin concentration of 40-60 percent.

Susceptibility to carbon monoxide-induced hypoxia is increased by the presence of any defect in oxygen transport at the tissue level such as myocardial or cerebral arteriosclerosis. Such preexisting disease would increase the degree of impairment from any level of carboxyhemoglobin saturation and might result in a postmortem finding of 30-60 percent carboxyhemoglobin concentration, depending upon the severity of preexisting myocardial or cerebral injury.

Had the decedent been a black with sickle cell disease, then increased sensitivity to the effects of carbon monoxide would be anticipated. The factors involved would be anemia with a decrease in total oxygen transport capability and the precipitation of sickling with consequent microcapillary obstruction contributing to tissue anoxia.

In all the above examples, continuous excess of carbon monoxide until the time of death was presumed. Had the site investigation revealed the decedent had been removed from exposure prior to death, then the pharmacodynamics of excess substance no longer would prevail, and interpretation becomes considerably more difficult. With removal

from exposure to carbon monoxide, the blood would be in negative equilibrium with the environment with carbon monoxide being excreted via the lungs. The longer the survival interval after removal from exposure, the lower will be the concentration of carbon monoxide found in the blood at postmortem examination. Persisting spontaneous ventilation or provision of passive respiratory support with 100 percent oxygen could result in dissipation of all carbon monoxide from the body prior to the occurrence of death. In such an instance, the postmortem toxicologic examination might reveal carboxyhemoglobin concentrations down to zero. In contrast, a chain smoker whose death was due to traumatic injury could manifest 10 percent carboxyhemoglobin saturation, though carbon monoxide played no role whatever as a cause of death.

In the relatively simple example of carbon monoxide, it is shown that the substance may be present at postmortem toxicologic examination without any causative role. Where a causative relation exists, the interpretation of postmortem findings may be influenced by the genetic pattern, by preexisting disease, by intercurrent complications, by postexposure survival, and by treatment between exposure and death.

Barbiturates

The barbiturates are selected as an example because they are commonly available, widely used drugs; they are encountered frequently in the toxicologic postmortem examination, and they illustrate most of the pharmacodynamic relationships illustrated in figure 1. The primary lethal effect of the barbiturates is anoxia as a result of respiratory arrest following central nervous system depression. Phenobarbital is omitted from this discussion because its pharmacodynamics are very different from the short- and intermediate-acting barbiturates.

Barbiturates taken orally in excess so that absorption is the rate-limiting factor result in coma in 1-6 hours depending upon the presence of food in the gastrointestinal tract. Simultaneous ingestion of alcohol facilitates absorption of the barbiturates because of the increased solubility of barbiturates in alcohol. Single doses of barbiturates may be expected to achieve peak levels in the blood in approximately 2 hours.

After reaching the blood, a very small fraction of the barbiturates is excreted by the kidney unchanged. The major proportion is redistributed to the tissues with a large share going initially to lipid depots. Biotransformation occurs primarily in the liver where the barbiturates are metabolized to inactive derivatives that are excreted by the kidney.

Quantitative determination of barbiturates in the blood is of the greatest value when the barbiturates have been taken in excess and absorption has been continuous up until death has occurred. With secobarbital, concentrations in the order of 2-4 mg/100 ml should be anticipated. Since death is due to anoxia secondary to respiratory depression, the occurrence of respiratory compromise induced by vomiting and aspiration will result in death at slightly lower blood levels. Preexisting disease such as hepatic cirrhosis with reduction in the rate at which barbiturates are metabolized to nontoxic derivatives will not significantly influence the quantitative relationships in the blood so long as the dose administered was in large excess. Preexisting disease which reduces oxygen transport, such as anemia, acute or chronic pulmonary disease, and arteriosclerosis, will reduce the blood level required to account for death. Acquired end-organ tolerance resulting from long-term excessive use of the barbiturates increases the blood level required to cause apnea. Acquired dispositional tolerance by way of hepatic microsomal enzyme induction does not influence the quantitative relationship between blood level and apnea. Conditions which change the rate of absorption of barbiturates from the gastrointestinal tract do not alter the quantitative relationship between blood level and apnea but decrease the time necessary to achieve a fatal concentration. The absence of food, the presence of adequate fluid volume in the gastrointestinal tract, or the simultaneous ingestion of alcohol, all increase the rate at which the barbiturates are absorbed. The simultaneous ingestion of other substances having sedative/hypnotic properties decreases the blood level of barbiturates required to induce apnea. Alcohol ingested simultaneously increases the rate of

absorption and decreases the blood levels required to induce apnea.

When the dose of barbiturates is limiting, or when absorption is interrupted by emptying the stomach or the administration of activated charcoal, the survival may occur during an interval when the blood is not in positive balance with respect to the barbiturates in the gastrointestinal tract. Interpretation of quantitative blood levels of barbiturates is extremely difficult when the blood concentration is decreasing. The concentration observed becomes a function of the rate of metabolism or rate of excretion. Abnormalities of either may increase or decrease the rate at which the barbiturate concentration in the blood is reduced. The ingestion of a single dose of 3,000 mg of secobarbital by a pharmacologically naive individual may result in coma for up to 48 hours or death. In contrast, ingestion of 3,000 mg of barbiturate by an individual who is a chronic heavy user of barbiturates may induce coma for a period of only 8-12 hours. The longer the period of coma, the greater is the influence of secondary complications such as dehydration, aspiration pneumonia, and secondary infections.

Administration of medical care introduces the possibility of complications secondary to diagnostic and treatment procedures as outlined above under the section Carbon Monoxide. The toxicologic examination further is complicated by drugs used therapeutically during the period of medical care.

DETERMINATION OF TOLERANCE TO SEDATIVE DRUGS

Clinical and laboratory assessment of tolerance to sedative drugs among chronic drug users has been possible in the Polydrug Abuse Research and Treatment Program of the Institute of Clinical Toxicology in Houston, Texas.[2] Detoxification of potentially addicted individuals requires determination of the dosage level of sedative drugs from which the individual should be withdrawn. Tolerance is determined by a clinical titration technique.

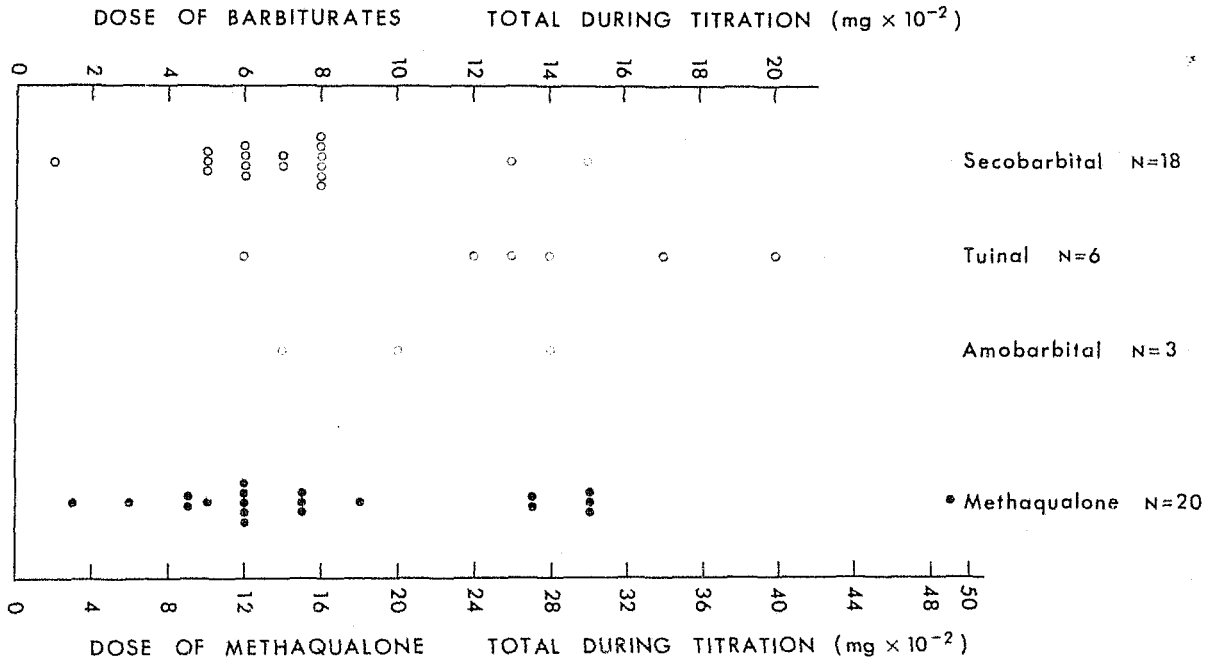
In order to be considered for titration, patients must have a history of sedative drug use consisting of a minimum daily average dose of three times the usual therapeutic amount for a period of time exceeding 3 weeks. Pre-titration assessment includes a complete medical and social history, a physical examination, a psychiatric diagnostic interview, clinical laboratory procedures, including a routine urine, CBC, SMA-12, VDRL, and chest x-ray, and blood and urine analyses for drugs. If there are no significant medical findings, the patient is considered a candidate for titration.

The purpose of the titration is to achieve a gradually increasing blood level of a sedative drug to reach the clinical manifestations consistent with early intoxication. The titration protocol is discontinued when the patient manifests ataxia, slurred speech, drowsiness, and horizontal and vertical nystagmus. From the beginning of the titration until the clinical end point is reached, an oral dose of sedative drug is administered hourly with assessment and recording of vital signs and other clinical signs and symptoms before the administration of each dose. Titration is initiated at 9:00 a.m. If the patient is free of any signs or symptoms of toxicity, the following dosage schedule is observed: In the first hour, two therapeutic doses are administered. On the second and third hours, a single therapeutic dose is administered. If the patient manifests no signs or symptoms of intoxication, on the fourth hour a dosage of two times the therapeutic dose is resumed and is continued each hour until the predetermined clinical manifestations are observed. Blood is drawn every 2 hours during the administration phase of titration and each hour after the administration of the last dose until the next dose of medication is required. Ordinarily this time interval is of the order of 6-8 hours. A therapeutic dose of short-acting to intermediate-acting barbiturates is 100 mg, and a therapeutic dose of methaqualone is 300 mg.

Table 1 summarizes the data on total dose of sedative drug required to reach clinical end point with the administration of four commonly used sedative drugs: secobarbital, Tuinal (a combination of equal parts of secobarbital and amobarbital), amobarbital, and methaqualone. Data on 18 patients titrated

[2]Supported by the National Institute on Drug Abuse, grant #H81 DA 01466 01S1.

TABLE 1. Total dose of sedative drug required to reach mild toxicity by clinical signs and symptoms



with secobarbital reveal the minimum dose to reach toxicity to be 100 mg, and the maximum dose required to be 1,500 mg. Fifteen of the 18 patients required 500-800 mg to reach the clinical end point. Six patients were titrated with Tuinal. The data shown represent total combined barbiturate in mg, and the range to reach toxicity was 600-2,000 mg. Three patients were titrated on amobarbital, revealing a range of 700-1,400 mg. Twenty patients were titrated with methaqualone, revealing a range of 300-4,950 mg with 17 patients falling within the range of 900-3,000 mg. The data from clinical titration, considering the total amount of drug tolerated, reveal that in a population with a history of chronic drug misuse, the amount of drug tolerated to reach a well-defined state of clinical intoxication varies in the order of tenfold.

The concentration of the drug in blood was determined hourly after the patient reached the clinical end point of toxicity. The highest concentration of the administered drug occurred ordinarily 2-3 hours after the last dose. Table 2 displays the maximum concentration encountered with four drugs: Methaqualone, secobarbital, Tuinal, and amobarbital. These data reveal the variability in blood level among patients who manifest similar degrees of clinical impairment.

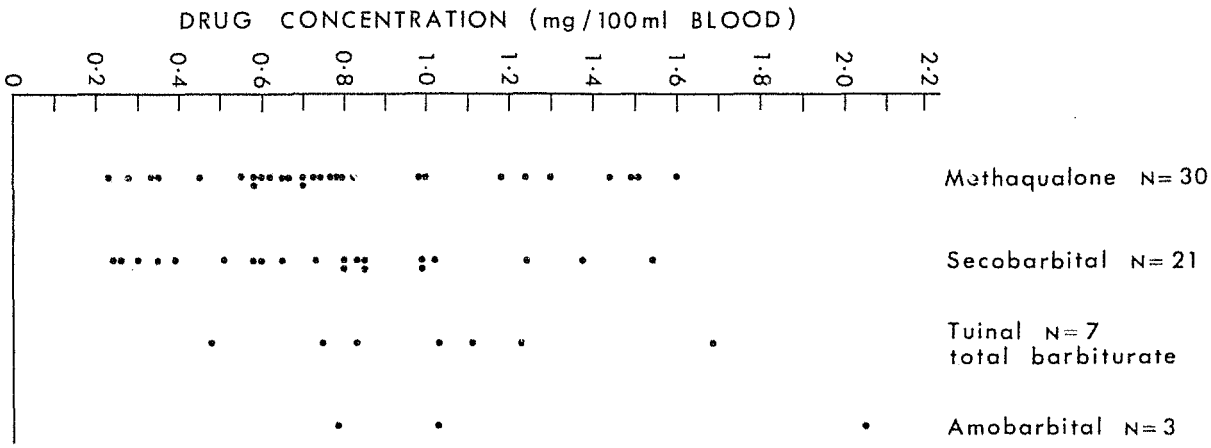
CONCLUSIONS

The only unequivocal conclusion to be drawn from postmortem toxicology examination is that the drugs identified are present in the body. Toxicological data alone are not sufficient to establish the cause of death. Drugs or other toxic substances present may have no etiologic significance. In contrast, a fatal illness may be precipitated by a toxic substance which has been cleared to below the limit of detection at the time death occurs. The investigation required for interpretation of the toxicologic findings should include the following considerations:

1. Was the toxic substance present in excess so that the blood concentration was increasing at the time of death?

2. If the toxic substance was not present in excess and the blood concentration was decreasing at the time of death, what was the

TABLE 2. Peak blood levels found in chronic drug-using patients after titration to mild toxicity with the drug indicated. Clinical findings are ataxia, slurred speech, drowsiness, nystagmus.



(●) = one patient.

duration of time between maximum blood concentration and the time that death occurred?

3. What secondary events occurred, such as aspiration, which would compromise vital function?

4. What disease conditions pre-existed which could increase sensitivity to the effects of the toxic substance?

5. Were multiple substances identified, and what was their relative contribution to the terminal event?

6. What drugs or other toxic substances was the decedent using or exposed to in his current everyday activities including occupational exposure?

7. What chronic drug use or occupational exposure to toxic substances has the decedent sustained?

8. Is the decedent pharmacologically naive or has there been long-term use of the substance(s) involved acutely or other substances to which cross-tolerance might exist?

9. Are the substances involved ones which induce end-organ or dispositional tolerance?

10. If first aid or other treatment was administered prior to death, what diagnostic and therapeutic procedures were performed, what drugs were administered, and what complications might have these procedures or drugs induced?

11. What genetic factors exist that might influence susceptibility to the toxic substance involved?

12. How comprehensive was the postmortem toxicology examination, and what substances or groups of substances might not have been detected?

END