J Forensic Sci, Apr. 1974, Vol. 19, No. 2

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Role of Toxicology in Suicide Evaluation

Defining the Population

It is a well-known and often stated fact that the typical suicide case is a white male, married, and between the ages of 45 and 60 years. Any forensic toxicologist who has taken the trouble to inquire as to the age, sex, and race of the suicide cases on which he is conducting toxicological tests, would probably have the impression that a typical suicide would fall into a category other than that stated above. In Virginia, certainly, it has been our experience that most suicides by ingestion of a toxic substance were committed by females, rather than males, marital status being uncertain, but the age probably lower than that for the general suicide population. Not until 1972 when the publication of the Vital Statistics of the United States for 1968 [*1*] became available, was it possible to look critically at the nature of the suicide population, particularly those due to ingestion of solid and liquid substances. For the first time in that year, a breakdown by age and sex was made, which enabled correlations to be made with suicides in general, suicides by ingestion of solid and liquid substances, suicides by ingestion of drugs, or suicides by exposure to carbon monoxide.

From these data, it became evident that the male to female ratio of the suicide population in general for 1968 in the United States was 2.6 to 1. If suicides from all poisonous substances were considered, the male to female ratio was about equally divided, namely, 1 to 1. If only those suicides by drug overdosage were considered, the male to female ratio became 1 to 2, while if suicides by carbon monoxide alone were considered, the male to female ratio returned back to the 2 to 1 proportion (see Fig. 1).

Distribution of these cases as a function of age and sex could not be compared in quite the same way as the comparison based on sex alone. This was due to the fact that the age distribution statistics were not broken down sufficiently to isolate those due to drugs alone. Nevertheless, when one looks at the figures for suicides by ingestion of solid or liquid substances, the predominance of the females in this comparison is evident, while the age distribution is approximately a decade younger in this group than in the total suicide population. Those suicides due to carbon monoxide alone show a sex and age profile very similar to the total suicide population (see Fig. 2).

I shall not attempt to probe into the meaning of these statistics but will, rather, leave this for the psychiatrists to evaluate. Nevertheless, to quote one authority who has studied this problem in some detail, "men tend to use more precipitous, more action-involved, more lethal agents and methods than women" [*2*].

Presented at the 25th Annual Meeting of the American Academy of Forensic Sciences, Las Vegas, Nev., 22 Feb. 1973. Received for publication 23 Feb. 1973; revised manuscript received 7 Aug. 1973; accepted for publication 13 Sept. 1973.

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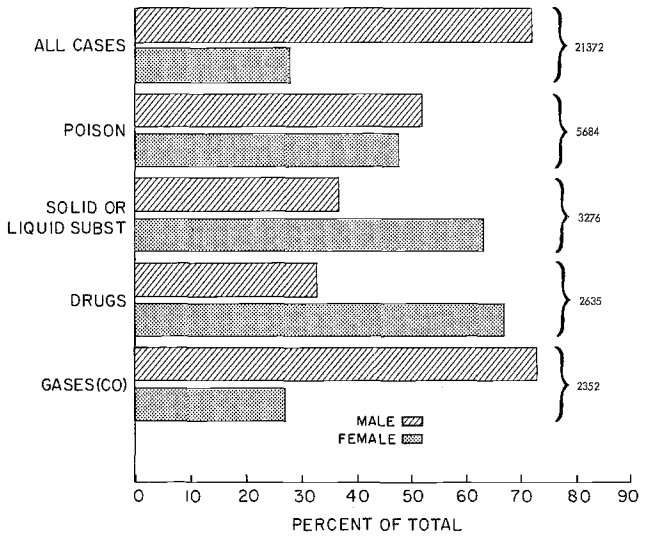

FIG. 1—*Sex profiles of suicides in the United States in 1968, compared by cause. Bracketed figures indicate total cases reported in each category.*

It is interesting to note that the age-sex comparison shown by the national statistics for 1968 is similar to studies which have been done on attempted suicides or "unsuccessful" suicides seen in hospitals. Several studies of these types of cases have been conducted indicating a male to female ratio of 1 to 2 [*2,3*] or 1 to 3.3 [*4*], with the median age being between 25 and 35 years. Because of the higher incidence of females to males in the attempted suicide group Hirsh has also stated, "women appear to employ methods of suiciding which involve an important factor—time—allowing for rescue and resuscitation" [*5*]. This is further reinforced by the fact that estimates of unsuccessful to successful suicides range from 2 to 1 up to almost 8 to 1, with the usually mentioned ratio of 5 to 1 found in the literature [*3*]. It is difficult to state the precise ratio due to the unreliability of the data available. Perhaps the statement by Tuckman [*3*], "attempted suicide is a function of youth and completed suicide a function of age," can be modified for our purposes to: "suicide by drug ingestion is a function of young women and suicide by other means, a function of older men."

Accident versus Suicide

Having unsatisfactorily, but partially, defined the population with which we are dealing in suicides by toxic agents, let us now look more carefully at drug deaths in particular. Here we do not have the benefit of national statistics, since drug deaths are not broken down in sufficient detail for critical comparisons. Table 1 shows the drugs involved in drug related deaths in Virginia for the year 1970. This summary of data was assembled by computer retrieval of all medical examiner and non-medical examiner deaths in Virginia for 1970 by cause of death as written on the death certificate. In addition, all medical examiner cases in which positive drug results were obtained by toxicological analysis were retrieved and each case reviewed, retrospectively, in order to critically evaluate as objectively as possible the cause and manner of death in each case. Those cases in which one or more drugs were clearly responsible for the death are listed in Table 1. Many of these cases were drug combinations, but they are listed according to the drug which was present

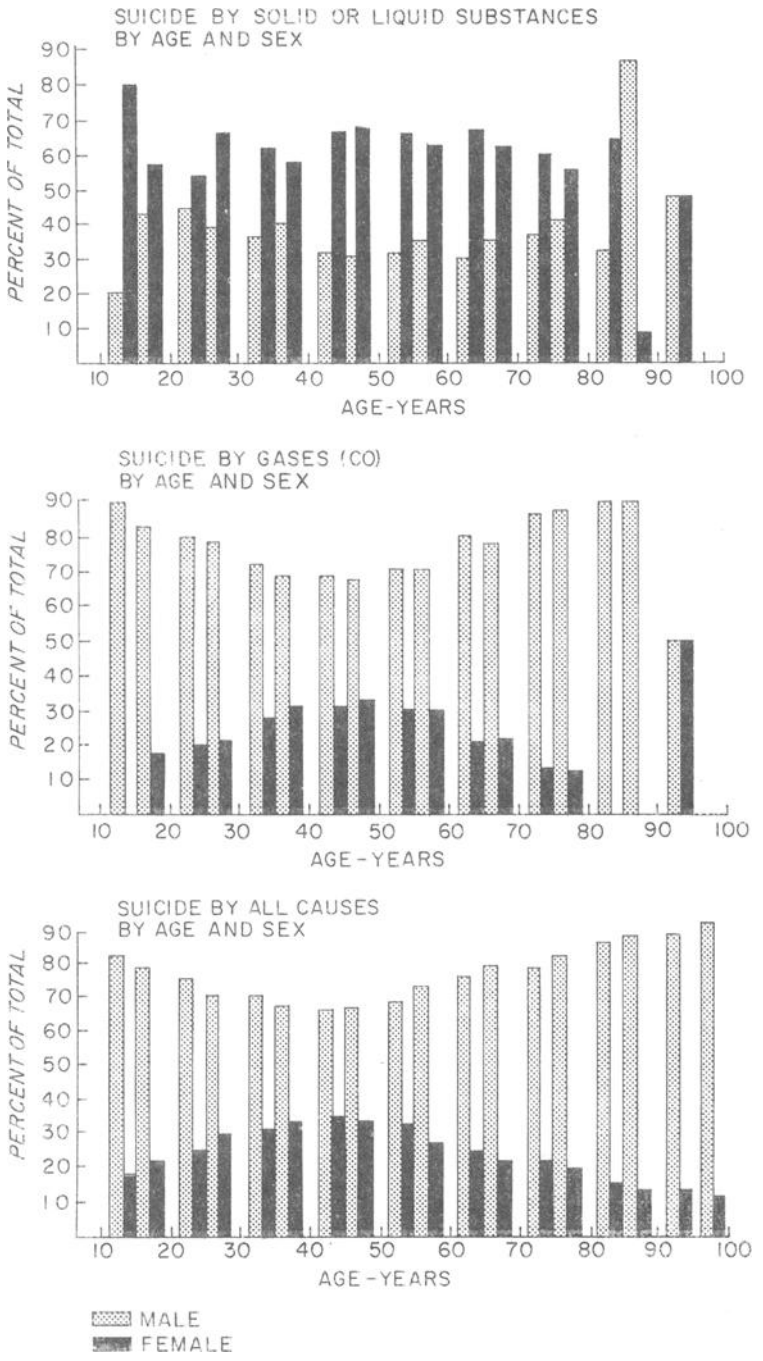

FIG. 2—*Age and sex profiles of suicides in the United States in 1968, compared by cause.*

TABLE 1—*Drug related deaths—Virginia 1970.*

Drug[a]	Manner of Death		
	Suicide	Unknown	Accidental
Barbiturates	33	7	9
Propoxyphene	13	1	4
Heroin (morphine + quinine)	0	0	13
Acute Narcotism (no toxicological findings)	0	1	1
Methadone	0	0	5
Phenothiazines	0	4	3
Glutethimide	4	1	0
Salicylate	4	0	1
Amitriptyline	3	0	0
Meprobamate	2	0	1
Morphine	0	0	2
Chlordiazepoxide	2	0	0
Paraldehyde	0	0	1
Quinine	0	1	0
Ethchlorvynol	1	0	1
Diphenhydramine	1	0	0
Succinyl Choline	0	0	1
Methamphetamine	0	1	0
Atropine	0	0	1
Desipramine	0	0	1
Imipramine	1	0	0
Methaqualone	0	0	1
Furosemide	0	0	1
Chloral Hydrate	0	0	1
Multiple Drug Mixture	2	3	0
Totals	66 (50%)	+ 19 (14.4%)	+ 47 (35.6%) = 132

[a] In case of drug mixtures, the predominant drug is listed.

in excess. As can be seen in the table, 50 percent of these deaths are ruled suicides, while 35.6 percent are ruled accidental. The remaining 14.4 percent are classified as drug deaths, but cannot clearly be categorized as accident or suicide. It is this category, where manner of death is unknown, which I would like to discuss further. It is probable that a concerted effort on the part of toxicologists as well as pathologists could result in clearer decisions as to whether a death was accidental or suicidal.

It is obvious that one contribution of the forensic toxicologist in the study of suicide by drugs, is to aid in the determination of the cause of death. Although in some cases this is not always a simple task (particularly in the case of drug combinations), for most substances methods are available for competent toxicologists who have access to reasonably adequate facilities to detect lethal levels of most common drugs. There is a further contribution which the toxicologist can make, however, but which is frequently ignored. This is to establish the total body burden of the toxic agent involved.

Theories of automatism notwithstanding, the demonstration that a massive dose of a particular drug has been ingested, coupled with a lethal blood level of the drug in question, is a good indication that the ingestion of the drug was not accidental. Thus, an initial impression that a drug death was suicidal in nature can be supported by additional toxicological evidence, when documentation of the suicide is lacking.

The obvious initial step in estimating total body burden of a drug is to determine drug levels in blood, gastric, and bowel contents, and in representative tissue specimens. These

levels, together with the results of tissue distribution studies which have already been done for many drugs, enable a reasonable estimate to be made for the total body burden of the parent drug. Reasonably good methods are now available for most common substances and these methods can be adapted to the analysis of a variety of specimens. Knowing the recovery efficiency of these methods, the total body burden of the parent drug can be readily calculated. Frequently, however, the interval between ingestion and death may be prolonged. In these cases, if the parent drug alone is considered, an erroneously low estimate of the total body burden of the drug may result.

Drug Metabolism

It is becoming increasingly important for forensic toxicologists to determine metabolite levels as well as parent drug levels. In this situation technical problems become more severe. Generally, a variety of metabolites may be produced from a single parent drug which may necessitate the use of varying extraction procedures. In addition, the levels of metabolites are generally lower than those of the parent drug, which makes more demands on the sensitivity of the method utilized. Nevertheless, methods are available for identifying metabolites of most drugs, and data relating the proportion of a particular drug appearing as metabolites are being generated in experimental studies in man and animals. Urine and bile are particularly useful specimens for the identification of metabolites, but lung, liver, and kidney specimens are also potential sources for these substances.

This is not a completely new approach, of course, since some drugs which are rapidly metabolized can generally be detected only by identifying specific metabolites. Acetylsalicylic acid, for example, is most commonly measured as its primary metabolite, salicylic acid. Similarly, morphine is the drug generally identified in cases of heroin overdosage, due to the rapidity with which heroin is deacetylated.

Also, in anesthetic deaths due to local anesthetics, it is necessary to identify the hydrolysis products of local anesthetics in order to estimate the total body burden of this drug in the event of a suspected accidental overdosage [*6*]. Thus, the estimation of drug metabolites should not be completely foreign to the forensic toxicologist. The metabolism of other drugs such as the barbiturates, phenothiazine derivatives, and tricyclic drugs in general, have been studied extensively. Yet it is common practice to determine only the parent drug and not report the presence of metabolites.

In this regard, it is of interest that older, colorimetric, or spectrophotometric methods undoubtedly measured the parent drug as well as some of the metabolites. Since the advent of gas-liquid chromatography (GLC), the parent drug can be measured independently of metabolites and this is usually the only substance reported by the toxicologist. This is unfortunate, since GLC can be used as a tool, not only for detecting the unchanged drug, but frequently for measuring the metabolites simultaneously. Methadone is an example which is particularly appropriate, since many workers have found that metabolites of this drug may be present in amounts greater than the tissue levels of the parent drug. It is obvious, I believe, that considerably more research is necessary in this area relating tissue distribution, parent drug, and metabolite levels to quantity of drug ingested. However, the forensic toxicologist enjoys a unique opportunity to contribute valuable data in this field if the necessary tissue specimens, methodology, and facilities are available to him.

Pharmacokinetics

Additionally, the area of pharmacokinetics promises to develop further aids in the estimation of drug dosages. "The purpose of pharmacokinetics is to study the time course

of drug and metabolite concentrations and amounts in various body fluids, tissues, and excreta, and thereby develop suitable mathematical models to describe and interpret absorption, distribution, metabolism, and excretion processes" [7]. The use of one, two, or even three compartment open systems as pharmacokinetic models enables the calculation of a constant K, the overall elimination rate constant. This, in turn, enables the biologic half-life of a drug to be determined. Theoretically, then, such mathematical treatment of the pharmacokinetic aspects of drug metabolism should enable a reasonable approximation of the drug ingested to be calculated from plasma or tissue levels of the drug or its metabolites. Much experimental work remains to be done in this area, but already many drugs have been studied by this means and should clearly aid in the interpretation of drug metabolism studies which would be of great practical benefit in toxicology.

The route of absorption may also be suggested by tissue distribution studies or metabolite identification. Although this is not usually an area of dispute in cases of suicide, it does constitute an additional bonus when these studies are carried out. For example, in the case of propoxyphene when taken by the oral route, liver levels are generally considerably higher than blood levels. After intravenous administration, however, blood levels are higher, generally within the same magnitude as those levels found in the liver. The lung may also be a useful specimen in attempting to resolve the route of administration, in the case of volatile substances which might be taken by inhalation.

Differences in metabolism of drugs when absorbed orally, as compared to parenterally administered drugs, have also been observed. Some of these differences may be due to bacteria in the gut metabolizing drugs prior to absorption, or due to changes in the drug as it traverses the wall of the intestine during the active absorption process. It has been shown, for example, that isoproterenol, an important antiasthmatic drug frequently administered by inhalation, achieves a high concentration in the plasma when administered parenterally and that about one third of the administered drug is converted to the 3-0-methyl derivative in the liver, some of which is excreted unchanged and some in a conjugated form. When administered orally, over 90 percent of the drug is conjugated, probably in the gut wall during absorption, and the amount methylated in the liver is much less. Propranolol, a widely used drug to treat cardiac arrhythmias and angina, shows the presence of an active metabolite, 4-hydroxy-propranolol, when administered orally. This metabolite is not seen after parenteral administration of the drug. These observations [8] not only illustrate the fact that the route of administration may be suggested by appropriate tissue distribution or metabolite studies, but that important pharmacological and toxicological differences in effects of drugs can be elicited depending upon the route of administration.

Additional Problems

A situation in which discrimination between accidental and suicidal deaths by estimating total body burden of drug absorbed may not be possible is in the case of drug tolerance. Obviously, an addict whose tolerance has progressed to the point where he is taking quantities of drugs which may well be lethal to a naive subject, can conceivably accidentally overdose. In these situations, attempts to arrive at a decision as to whether a death is accidental or suicidal by the total body burden of drug may lead to erroneous conclusions. Similarly, in the case of multiple drug ingestions, unless one or more components of the drug combination are present in enormous excess, it is frequently difficult to draw conclusions, based on toxicological evidence alone, as to the manner of death. This is particularly true in light of recent observations relating the effects of one drug on the metabolism of another. For example [9], the administration of phenobarbital to adult

patients receiving diphenylhydantoin results in a significant decrease in diphenylhydantoin plasma levels. Conversely, discontinuation of phenobarbital in patients receiving combined therapy with phenobarbital and diphenylhydantoin produces significant increases in diphenylhydantoin plasma levels. These effects are probably due to the fact that phenobarbital enhances the hepatic microsomal enzymes that hydroxylate diphenylhydantoin. The additional observation that diphenylhydantoin administered to epileptic children receiving phenobarbital results in a marked increase of phenobarbital plasma levels has no obvious explanation. Thus, interpretation of toxicological findings in cases of drug combinations involving drug interactions remains a problem and awaits further experimental studies before these drug effects can be evaluated.

The demonstration of nonlethal or therapeutic levels of drugs may also be important in arriving at a decision as to whether a particular death is suicidal or accidental. The correlation of positive alcohol findings with motor vehicle accidents is well-known. In Virginia, for example, about 55 percent of motor vehicle accident deaths showed positive alcohol findings in a recent study. This is similar to what has been reported in other areas. The same study, however, showed that other accidental deaths such as death from fire, drowning, exposure, gunshot wounds, etc, also showed a high correlation with positive alcohol findings. More than 50 percent of these accidental deaths (exclusive of motor vehicle accidents) showed positive alcohol findings [*10*]. Although a similar study was not done correlating drug levels with accidental death, it would be reasonable to expect that some accidental deaths occur due to impairment of judgment, visual acuity, or slowing of reflex times by substances other than alcohol. Thus, the demonstration of nonlethal or therapeutic levels of drugs in deaths where the primary cause is not a toxic agent, may be of assistance in evaluating the circumstances in order to arrive at a decision as to whether a particular death was accidental or suicidal.

Summary

It is evident that the toxicologist has more to offer in questionable suicides or accidental deaths than merely to establish that a lethal level of a specific agent is present. With proper review of the social and medical history of the decedent, pathological and other findings, an analytical approach can be planned which, with proper interpretation, can yield useful information in resolving difficult questions raised in discriminating between accidental and suicidal deaths. Estimation of the total body burden and, indirectly, the total dose ingested, may be important. This would include tissue distribution studies and identification and quantitation of metabolites, as well as of parent drugs. Even sublethal or therapeutic levels of drugs and other chemical substances can be important in resolving suspicious suicide cases. It is obvious that much information is lacking and further research is necessary before some of the more perplexing problems can be resolved. However, new avenues of research are opening and, by being aware of the nature of the problems presently receiving an active research interest, the forensic toxicologist can make important contributions towards the resolution of these problems.

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