Drugs - A Review

PAPE & ASSOCIATES

Specializing in Toxicology

TOXICOLOGY REPORTER

DRUG-RELATED TOPICS

- Revised and Expanded -

Fate of Drugs

Consumption-Absorption-Distribution-Elimination and Case-illustrations

Therapeutic Drug Monitoring

Premortem Drug Testing

Postmortem Drug Testing

Discovery - Review - Retesting

Effects of Drugs

Drugs and Accident or Incident Death Cases

Principles of Case Analysis

Case Consultation

Previous Newsletters

Alcohol-Accident-Death-Testing
Liquor Liability
Review of Laboratory Testing

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Dr. Pape has published more than 50 research papers, scientific abstracts relating to alcohol and drugs, pesticides and toxic chemicals, analytical chemistry, forensic science, and general toxicology. He currently writes the *Toxicology Reporter.*

He has served as a technical and expert consultant to business, labor, and governmental agencies; and he has been qualified as an expert in toxicology and related sciences in Superior and Supreme Courts and Federal Courts.

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Dr. Pape has been qualified to offer expert testimony regarding a wide range of case-related topics relating to clinical, analytical, and forensic toxicology. He has also consulted regarding risk assessment, reliability of laboratory testing, and pre-trial evaluation of expert testimony.

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Pape & Associates Offices:

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This Toxicology Reporter includes expanded content relating to the following topics:

The absorption-distribution-and elimination of drugs

Therapeutic drug monitoring

Quantitative premortem drug test results

Quantitative postmortem drug test results

Chronic drug use *or* acute drug overdose

The amount of the drug most recently consumed

Comparing case evidence with laboratory test results

Death cases: Drug-related questions

Pharmacokinetics
Pharmacodynamics
Extrapolation of drug concentration
Estimates relating to drug use

Discussion of key elements when reviewing a drug-related case or considering an initial phone consultation:

The case-specific civil complaint or criminal charge

The person-of-interest, the incident, and the case-specific issues

The time-course of relevant events

Case specific reports including police, EMS, and emergency medical records and laboratory tests

Relevant medical history

Prescribed medications and other available medications

Physical evidence

Relevant post-event medical records
Autopsy and toxicology test reports

Relevant statements of potential witnesses

Case-relevant expert disclosures or reports

Case status and relevant deadlines

TOXICOLOGY REPORTER

The Fate of Drugs

Drug use

Drug use can be described by terms that include the following:

Acute (recent) use
Chronic (longer-term) use
Therapeutic (medicinal) use
Experimental use
Social-recreational use
Situational use
Compulsive use

Route of entry

Routes of drug use include oral consumption, inhalation, intravenous injection, nasal insufflation, and topical administration. The route of drug use will affect the bioavailability or the portion of the drug dose that is absorbed, the time-course and extent of the absorption and distribution of the drug in body tissues and fluids, the drug concentrations in specific tissues and fluids, and the pharmacodynamic response (i.e. the nature, extent, and time-course of the effects associated with drug use).

Absorption

The absorption of most drugs is a passive process: The drug moves from a location of higher concentration to a location of lower concentration. However, the rate and time-course of absorption are affected by a number of factors. For example: With pills and capsules, the rate-controlling factors affecting drug absorption include the dissolution rate of pills or capsules, gastric emptying time, chemical features such as the ionization of the drug, and drug-related effects. For example, if an oral drug overdose initially results in physiologic effects that decrease gastrointestinal motility and/or gastric emptying time, it can take hours to reach the peak or highest drug concentration in blood.

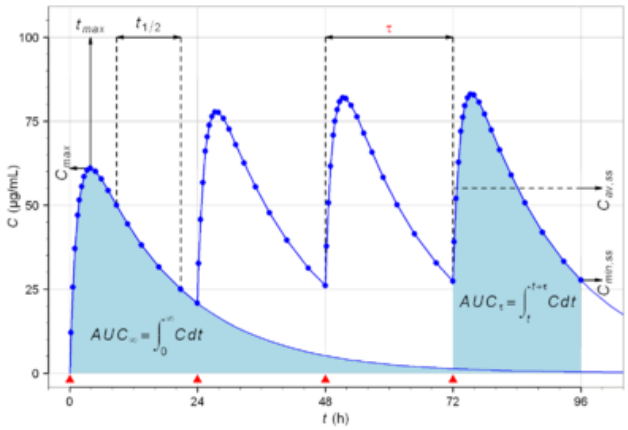
Many drugs are absorbed more slowly while in the stomach compared to the small intestine. When that is the case, the speed with which the stomach is emptied into the small intestine (i.e. the gastric emptying time) affects the overall rate of absorption. In addition to some drug-related effects, the consumption of food can slow (i.e. delay) gastric emptying, increase the time required to reach the peak or highest blood drug concentration (BDC), and reduce the peak BDC. Under some circumstances, it can take more than two hours after last consumption to reach the peak or highest BDC. Some terms which are related to the time course of drug absorption include the following.

Cmax usually refers to the highest BDC following a dose of the drug.

Tmax usually refers to the time it takes for the BDC to reach its peak or highest level following administration.

T-1/2 refers to the time required for the drug concentration to decline to one-half of its prior concentration as a result of metabolism and excretion.

The following graph depicts a typical time-course of drug concentration in blood (BDC) and illustrates some of the relevant pharmacokinetic measurements:



Graphical Simulation: The time-course of BDC over 96 hours following oral administrations every 24 hours. Note: It takes multiples doses of a drug before the rise and fall of the drug concentration curve reach what is called a "steady state".

Distribution, drug ratio, and equilibrium

Distribution refers to the processes involved in the movement of drugs within and between body tissues and fluids (i.e. physiologic compartments). A drug ratio for two or more specimens (e.g. BDC compared to tissue drug concentration) refers to the relative concentration of the drug in two different tissues or fluids at a specific time. When the BDC is rising during an absorptive phase, states of disequilibria occur … these disequilibria are related to the absorption (i.e. movement) of drug from a location of high concentration such as the stomach to an area of lower concentration (e.g. blood), the subsequent distribution of drug to and between body tissues and fluids, and associated changes in both the absolute and relative drug concentrations over time. As a general rule, a state of equilibrium between drug concentrations in tissues and fluids is approached during a post-absorptive period when the drug is no longer being absorbed.

Expected or observed drug concentration ratios have been reported for many classes of drugs (including barbiturates, amphetamines, benzodiazepines, tricyclic antidepressants, and opiates) and for tissues and fluids that include blood, blood serum, blood plasma, cerebrospinal fluid, brain, lung, and liver. A forensic toxicologist can sometimes use postmortem drug ratios to distinguish between an acute overdose and a chronic over-medication.

Theoretical or expected drug concentration ratios are controlled by specimen:specimen differences such as the content of water or fat or protein, while the rates with which these ratios respond to changes in BDCs during the absorptive and post-absorptive state are controlled by diffusion an/d/or distribution processes that include blood flow between and within specific organs or physiologic compartments.

Examples of post-absorptive processes that are indirectly related to the fate and the effects of a drug (i.e. pharmacokinetics and pharmacodynamic response) include the following:

Arterial and venous blood flow moving drug to and between body tissues and fluids

Diffusion of drug across biological blood:tissue barriers affecting the amount (concentration) of drug at the site of action or in other body tissues or fluids

Binding to biological components of blood such as blood cells and/or blood proteins which affects both the amount of drug that is available to enter tissues and the relationship between the concentration of drug in whole blood or blood serum and the expected effect of the drug

Differential solubility or binding of drugs in body tissues and fluids

Test results indicating the apparent blood:tissue concentration ratio can sometimes provide information regarding the route of administration and the time between last drug use and death. Two examples follow.

Abnormally high urine:blood drug and drug metabolite ratios would usually suggest a post-absorptive state.

An abnormally high liver:BDC ratio following a fatal drug oral drug overdose would suggest that death occurred during or shortly after the absorptive phase.

When considering a drug concentration ratio, it is important to include any evidence of a grossly altered physiologic condition (e.g. abnormal kidney function or liver function) that could substantially affect the distribution and/or elimination of a drug.

Elimination – metabolism and excretion

Elimination refers to the processes that directly result in a reduction of drug concentration:

Metabolism due to enzyme-controlled processes resulting in the formation of drug metabolites that are usually less biologically active than the parent drug and more readily excreted from the body

Chemical decomposition that does not involve an enzyme but which usually results in the formation of products that exhibit less biological activity and an increased rate of excretion

Excretion in biological products including urine or extraction by artificial means such as dialysis

Studies have shown that the rate or speed of elimination of a drug is affected by variables that can include age-weight-sex, organ function, and effects related to the use of other drugs. Person-specific factors and variability within a population of similar subjects should be considered.

Effects

Studies relating to the pharmacodynamics and risk assessment of adverse drug-related effects or related consequences have included the following topics:

Acute (shorter-term) v. residual (longer-term) effects

Dose:effect and concentration:effect relationships

For example: What is the relationship between blood drug concentration (BDC) and the occurrence or severity of adverse drug-related effects including effects associated with an increased risk of accident or death?

Physical and behavioral effects and associated risks

For example: Did the consumption of a drug substantially contribute to his decision to commit suicide?

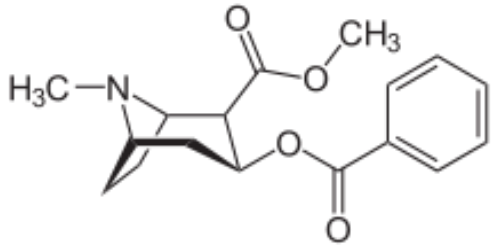
Causation v. contribution v. coincidental factors

For example: Was the pedestrian-MVA related to drug use? How? To what extent? What was the risk?

Degree of certainty or predictability or likelihood

For example: What percentage of adults would exhibit one or more visible or obvious indicia of intoxication at a specified BDC?

Cocaine-related illustration:



Pharmacokinetics describes rates and relationships relating to the absorption, distribution, and elimination of a drug. *Refer to the definition of Cmax, Tmax, and T-1/2 discussed above.*

The *Cmax* for the whole blood or blood serum or plasma cocaine concentration depends on factors that include the subject's physical features, the dose, and the route of administration.

The *Tmax* for the time necessary to reach the highest blood or serum or plasma cocaine concentration (i.e. the Cmax) depends on features that include the route of administration.

The *T-1/2* for the elimination of cocaine usually ranges between 60 and 120 minutes.

Absorption:
Cocaine is abused by routes of administration that include nasal insufflation or snorting of cocaine powder, smoking of *crack* or *free-base* cocaine, or injection of a solution of cocaine powder. Consuming the same net weights of cocaine by means of injection (1), nasal insufflation (2), and free-basing (3), would likely result in the absorption of weights of drug in the order of 1 > 2 > 3, but the acute CNS effects would likely be 3 > 2 > 1 or 3 > 1 > 2.

Example: The consumption of cocaine by mouth results in chemical decomposition in the gastrointestinal tract and the delayed absorption of the available cocaine. These processes as well as substantial hepatic extraction leading to a much higher post-absorptive concentration of cocaine in liver tissue compared to brain tissue result in reduced CNS effects when cocaine is taken by mouth.

Example: The time-course of the absorption of cocaine powder consumed by nasal insufflation is subject to several variables. An example simulation follows:

Nasal Insufflation

Time	Observation	Rate (fraction/min.)
6:00 p.m.	50 mg "snorted"	
6:15	30 mg absorbed	0.60/15 min.
6:30	10 mg absorbed	0.80/30 min.
6:45	5 mg absorbed	0.90/45 min.
7:00	3 mg absorbed	0.96/60 min.
7:15	1 mg absorbed	0.98/75 min.

In this simulation, the rate of absorption is not constant (i.e. zero-order) … it is closer to a first-order process reflecting the amount of cocaine not yet absorbed.

Distribution and Elimination:
The initial and subsequent distribution of cocaine is related to the route of administration and the near-term period allowing for redistribution during and immediately following the absorptive phase.

Example: Smoking *crack* cocaine initially results in high drug concentrations in brain tissue leading to the desired *rush* of physical and behavioral effects, followed by drug redistribution and elimination resulting in reoccurring cravings.

Example: Intravenous injection results in very high initial BDCs followed by an initial distribution phase associated with the movement of the drug into body tissues and fluids and then an on-going elimination phase. An illustration follows:

Injection → Distribution → Elimination

The initial concentration is blood is very high, followed by a rapid decline associated with distribution.

Intravenous Injection

Illustration: Cocaine Concentration Ratios

Time	Liver (L)	Blood (B)	B/L Ratio
6:00 p.m.	00 mg/Kg	00 mg/L	Injection
6:05	2	70	R = 35
6:10	8	20	R = 2.5
6:15	10	10	R = 1
6:20	12	6	R = 0.5
7:20	7	3	R = 0.44

Example: The oral consumption of cocaine results in intestinal absorption followed by hepatic-extraction leading to high concentrations in liver tissue. On-going absorption-extraction-redistribution-elimination leads to changes in drug concentrations. The following simulation compares the concentration of cocaine in liver and blood following the oral ingestion of part of an "8-ball" of cocaine.

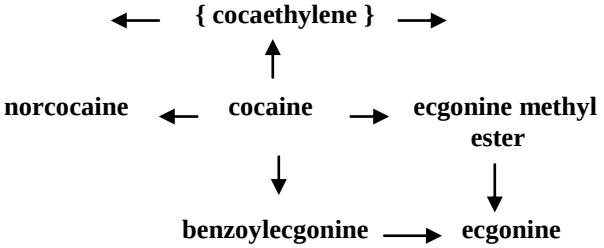
Oral Consumption

Illustration: Cocaine Concentration Ratios

Time	Liver (L)	Blood (B)	B/L Ratio
6:00 p.m.	00 mg/Kg	00 mg/L	Ingestion
6:30	22	01	R = .04
7:00	88	06	R = .07
7:30	99	09	R = .09
8:00	85	10	R = .12
9:00	50	07	R = .14

In some cases, the calculation of blood:tissue drug concentration ratios (Rs) can assist in determining the time between drug overdose and death or the route of drug administration.

Metabolism and chemical decomposition: The fate of cocaine is associated with a series of enzyme-catalyzed and chemical reactions. The relationship between four of the major cocaine metabolites follows.



All of these metabolites exhibit less biological activity than cocaine. Cocaethylene is discussed below.

Extrapolation of blood cocaine concentration:
Information regarding the time-course of drug use and tests results sometimes allow for the extrapolation or estimation of drug concentration at prior times. An example follows.

Example: You can sometimes extrapolate the approximate blood cocaine concentration at times prior to specimen collection. The following illustration assumes that the rate of elimination (i.e. $T_{1/2}$) is about one hour.

The Apparent Rate of Elimination of Cocaine

Hour	Cocaine Concentration
5 p.m.	Free-basing ends
6	0.8 mg/L
7	0.4
8	0.2
9	0.1

In this simulation, the blood cocaine concentration falls, every hour, to one-half of its prior concentration.

The interpretation of test results should consider specimen collection and preservation, test method and reliability, and drug and drug-metabolite test results.

The interpretation of premortem urine cocaine test results: Most hospital-based drug test results for cocaine are done in urine by a method that is optimized for the detection of cocaine metabolite, benzoylecgonine, and a positive test result is not quantitative. Therefore, absent other evidence, a positive result for cocaine metabolite(s) should only be considered as evidence of the last consumption of cocaine within the 72 hour period prior to the time of specimen collection.

The interpretation of postmortem cocaine test results: Because cocaine and metabolites of cocaine are subject to postmortem chemical decomposition, quantitative test results should be carefully interpreted**. In some cases, the review of postmortem test result should include the consideration of the following:**

- Prior or chronic use of cocaine including route of administration
- Time and conditions between death and autopsy
- Anatomic location of specimen collection
- Use of preservatives and storage conditions
- Time between autopsy and laboratory testing
- Testing process and procedure
- Cocaine and cocaine metabolite concentrations and concentration ratios
- Statements regarding the deceased's prior appearance-behavior-demeanor

Why should you engage a toxicologist?

Consider cocaine as the example drug-of-interest:

Consider the absorption, distribution, elimination, and decomposition of cocaine … the quantitation of cocaine and metabolites … and the extrapolation of test results: *The rise and fall of a subject's blood cocaine concentration depends on the nature and time-course of consumption (e.g. what chemical form, by what route, in what amount, over what period of time was cocaine used) and the related features including the rate of absorption, the distribution and redistribution of cocaine between body tissues and fluids, and the rate of elimination … while extrapolation using these factors depends on reasonable assumptions regarding the decomposition of cocaine between specimen collection and testing as well as the accuracy of the test result(s).*

Now consider the on-going analysis of case-related evidence or questions-of-interest including the estimation of the period of time when cocaine was last consumed, the route-and-amount of last consumption, the time-course of expected physical and behavioral effects, and the risk of accident-incident-injury-or-death. These are some of the considerations in a forensic case analysis.

When should you engage a toxicologist?

Only after an initial phone consultation

Special topics relating to cocaine include the following:

Cocaethylene *is the product of a transesterification reaction between cocaine and ethanol … its presence indicates the prior use of alcohol and cocaine at about the same time period. Cocaethylene is biologically active.*

Unique crack cocaine markers *resulting from the smoking of cocaine free-base include a pyrolytic product (methylecgonidine, MED) that is absorbed and rapidly converted to ecgonidine (ED). The selective extraction and detection MED and ED is currently considered an analytical marker for smoking cocaine. The quantitation of urine ED might prove to be a reliable marker for the active use of cocaine.*

Examples of other drug-related cases that often include the estimation of the amount of drug consumed or the extrapolation of drug concentration at some prior time include the following:

Oxycodone	**Morphine**	**Methadone**
Alprazolam	**Diazepam**	**Cocaine**
Marijuana	**Antidepressants**	

For related discussions, see Therapeutic Drug Monitoring, Postmortem Toxicology, and Review of Death Cases.

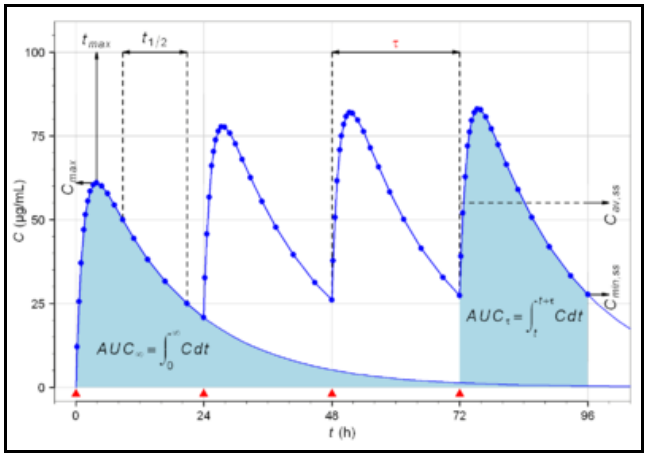
Therapeutic Drug Monitoring (TDM)

Therapeutic drug monitoring is a clinical tool that takes advantage of generally accepted relationships between drug dosage, drug concentrations in body fluids such as blood serum, and the expected clinical response.

The ability to monitor the concentration of therapeutic drugs has dramatically influenced the field of clinical pharmacology and toxicology. The underlying rationale is that, for most drugs, the pharmacological effect tends to be proportional to drug concentration in extracellular fluids such as blood serum.

Clinical experience and pharmacological studies of dose-effect relationships have clearly demonstrated that measurement of drug concentration in blood serum yields a much better correlation with the desired clinical effect than does the total daily drug dosage.

One of the clinical objectives of TDM and dosage adjustment is to achieve a therapeutic effect with reduced risk of adverse effects: Avoid a Cmax drug concentration that is above the therapeutic range and expected to result in an increased risk of adverse effects, while avoiding a *Cmin* drug concentration that is below the therapeutic range.



Having selected a drug, the features of dosage adjustment include the following:

- Weight of drug in each dose
- Route of administration
- Drug formulation (e.g. sustained release)
- Frequency of daily use (i.e. doses per day)
- Time of daily use
- Special instructions (e.g. *with food*)

Therapeutic drug monitoring takes into account the following variables:

The patient's age, weight, height, sex, and general physical condition as well as significant injury or pathology affecting the patient's absorption-distribution-elimination-response to a drug

The route of drug administration, dosage form, and dose expressed as total drug weight or weight per unit body mass of the patient (i.e. milligrams of drug per kilogram of body mass)

The biological activities (i.e. effects) of drug and drug-metabolites

The relationships between the time-line relating to the introduction of drug therapy, subsequent changes in drug dosage, expected or measured BDC, and expected or observed or reported effects including any adverse effects

For example: If a drug such as phenobarbital is discontinued, the time required to realize the nearly complete elimination of the drug from blood serum is equivalent to about five or six times the drug's elimination half life (e.g. more than five days). If the daily dosage for phenobarbital is increased, it also takes the equivalent of about five or six half-lives (e.g. more that five days) for the drug concentration to reach its higher steady-state concentration.

The practical clinical use of therapeutic drug monitoring test results should consider the patient's disorder, patient factors, clinical response, and the generally accepted therapeutic range for the medication(s) prescribed, and drug-drug interactions.

The generally accepted therapeutic range is the concentration range generally associated with an optimal relationship between risk and benefit to the patient.

For some drugs such as the antidepressant amitriptyline, the consideration of the therapeutic range must consider the biologically active drug (amitriptyline) and the biologically active metabolite (nortriptyline).

Premortem quantitative drug test results can assist the forensic toxicologist in case review. For example, TDM or other quantitative drug test results can be used when considering the following:

Are the test results consistent with commonly prescribed dosage regimens or the subject-specific dosage regimen or available pharmacy records?

Do the results suggest the recent or acute over-use of the drug rather than a longer-term or chronic overuse of the drug?

Given the evidence regarding the nature of the drug over-use (i.e. acute or chronic), what can be concluded regarding the extent of that drug over-use?

How does the reported drug concentration compare with the reported and/or expected drug-related effects?

A Case Vignette Follows

Case Vignette:

Following a two car high speed MVA, one of the operators was transported to Kimble Community Hospital and then University Hospital, where his medical care and treatment included comprehensive blood serum toxicology testing. The results follow:

His Two-hour Post-MVA Test Results

Phenobarbital	***5 mcg/ml***
Phenytoin	***ND (<5 mcg/ml)***
Amitriptyline	***1.92 mcg/ml***
Nortriptyline	***0.22 mcg/ml***

An alcohol test was ordered but not reported.

His prior medical records indicated on-going treatment for a seizure disorder following an alcohol-related fall and chronic depression. No prior drug levels were documented.

Phenobarbital and phenytoin

The post-MVA phenobarbital level of 5 mcg/ml is less than the usual therapeutic range of 20-40 mcg/ml and indicates a subtherapeutic concentration at the time of the MVA. The results for phenobarbital and phenytoin are consistent with poor patient compliance following the last documented prescription refills 112 days prior to the MVA.

Amitriptyline and nortriptyline

The test results are consistent with a recent self-administered over-medication with amitriptyline and a total drug-and-metabolite concentration that is in the toxic range. The concentration ratio for the drug (amitriptyline) and the metabolite (nortriptyline) of 1.92 to 0.22 suggests a recent increase in the use of amitriptyline. The total concentration for these two biologically active chemicals would be consistent with an increased risk of adverse drug-related effects.

Alcohol

As a result of on-going discovery, his blood serum alcohol concentration (BSAC) test result at Kimble Community Hospital was disclosed. His one hour post-MVA BSAC was 297 mg/dl.

The Kimble Hospital ER record indicated two i.v. sites (RAC and LAC i.v.s, wide open) prior to admission; but his admission hematology test results included a normal hemoglobin and hematocrit. His recorded weight was 170 pounds.

His BSAC of 297 mg/dl is the same as 0.297%; and a BSAC of 0.297% is equivalent to a whole blood alcohol concentration (BAC) of about 0.25%. The result indicated a total prior alcohol consumption equivalent to more than 15 ounces of 80-proof liquor and a BAC of at least about 0.20% at the time of the MVA. At the time of the MVA, he was legally intoxicated, physically and behaviorally impaired, and at substantially increased risk of both MVA and an alcohol-induced seizure.

Premortem Drug Testing

Blood, blood serum, and urine drug screening

Over 85 percent of the hospitals in the United States routinely offer only limited urine drug screening based on four to eight different immunochemical tests for specific drugs or their metabolites or drug classes representing only a small fraction of the potential drugs of abuse.

Hospital-based Patient Drug Testing:

Qualitative drug testing by immunoassay and the interpretation of a positive test result

Immunoassay Tests: Immunoassays are the most frequently employed hospital-based test methods used to detect the presence of drugs or drug-metabolites in urine:

Chemical test reagents including a semi-synthetic antibody to a specific drug or drug-metabolite or drug-class are mixed with the test specimen (usually urine or blood serum); an antibody binds to a prototypical drug or drug-metabolite characteristic of a class of drugs; the binding of the antibody to drug or metabolite affects the binding of antibody to other chemical reagents; the effect of this competitive process is monitored using a selective physical-chemical reaction and an automated instrument such as a spectrophotometer; and standards or positive and negative control samples are used to establish a test "cut-off" for the presumptive identification of positive and negative specimens. *While hospital laboratories seldom confirm positive drug test results, a positive result is generally consider to be a reliable indication of the prior use of the specific drug or a member of the drug class. However, recent studies suggest that some tests for amphetamines are subject to an interference-effect.*

Test specimens-test reliability-results interpretation

Urine: The biological specimen most frequently used to test for prior drug use. The time-window within which the prior use of a drug would usually be detected depends on the frequency-route-extent-and-last use of the drug, the absorption-distribution-elimination of the drug or drug-metabolites, the date of specimen collection, the volume of specimen tested, and the sensitivity of the test method**.**

The most frequently performed urine drug test batteries include the following tests for a drug or class of drugs:

Amphetamines	Opiates	Cocaine
Benzodiazepines	Cannabinoids	

Test Reliability: Performance characteristics are used to describe test reliability. Definitions of two of these performance characteristics follow:

False positives: Specimens that should test negative actually test positive.

False negatives: Specimens that should test positive actually test negative.

Interpretation of a positive urine drug test: A true positive urine drug test result means that the person consumed sufficient drug to account for the detection of a specific drug or drug-metabolite or a member of a class of drugs in the urine specimen. However, without case-specific assumptions or reliable evidence, a positive test does not establish details related to prior drug use:

- When the drug was last taken?
- The route by which the drug was last taken?
- How much drug was last taken?
- The drug concentration in urine?
- The drug concentration in blood?
- The expected effect(s) on a person?
- The relationship between drug use and some other event such as an accident?

Blood serum: Very few hospitals follow a recommended practice of reserving blood or blood serum for possible quantitative analysis following interpretation of the urine drug test results. With quantitative test results, a toxicologist would be in a better position to estimate the time of last use and/or the amount of drug consumed and/or the expected clinical course or to recommend therapeutic options.

Because the concentrations of drugs and drug metabolites in blood are usually lower than they are in urine and a much smaller volume of blood is usually collected for drug testing, qualitative blood or blood serum drug screening is less effective compared to urine drug testing. As mentioned earlier, the better approach would be to reserve blood for quantitative drug testing.

Postmortem Drug Testing

Postmortem specimens:

A good set of blood specimens

Generally, the best single blood specimen is blood from the femoral vein.

Tissues

Liver, brain, and muscle are sometimes submitted along with blood and urine in order to provide for a more comprehensive evaluation of potential perimortem and postmortem drug distribution.

Urine

Urine is relatively "clean" and plentiful; and urine usually contains relatively high concentrations of drugs and drug-metabolites. Urine is a good specimen to use for initial screening tests. While drug concentration and drug:drug-metabolite ratio sometimes suggest when the drug was taken, the concentration of a drug in urine is not a good measure of drug-related effects.

Gastrointestinal contents

The inspection-recovery-testing of g.i. contents often allows for the determination of the type(s) of the drug(s) taken (e.g. pill v. capsule v. pulverized products), the minimum amount of drug taken (based on g.i. volume and drug concentration), and the time the material was taken (e.g. before or with or after the last meal).

Vitreous humor

Vitreous humor is relatively immune to the effects of postmortem decomposition and disequilibria that could affect the interpretation of the drug test result. When a drug is suspect, a good set of specimens would include blood, urine, and one other biological specimen.

Injection sites

The dissection and analysis of injection sites can sometimes detect concentrations of parent drug(s) consistent with recent i.v. drug use. The quantitative analysis of a control specimen taken from an "equivalent" anatomic location should be compared with the results for the injection site.

Hair and nasal swabs

Head hair can be cut near the root, sectioned to reflect the time-line of hair growth, and tested to determine the use of some drugs and the apparent time-course of that drug use. A nasal swab can be used to test for the recent use of cocaine or other drugs taken by nasal insufflation.

Pills, powders, syringes, and residues

Identify pills and capsules by manufacturer code; determine if the remaining number of pills or capsules is consistent with the deceased prescription drug records and prescribed dosage; check with a toxicologist to ensure that each of the suspect materials would be detected by the drug test procedures employed by the laboratory; and, in some cases, determine the percent purity of drug powders such as cocaine, heroin, PCP, and amphetamines.

Drug test results:

Qualitative test results

A qualitative drug test result only relates to the apparent presence (i.e. detection) or the apparent absence of a specific drug or drug metabolite or class of drugs. It is important to know the analytical or drug universe for the test procedure and the sensitivity or detection limit for each drug or class of drugs or drug metabolite(s).

Remember that a negative qualitative drug test result does not mean that the drug was not consumed. It only means that the drug was not detected and that, if the test is reliable, any drug consumption near to the time of specimen collection did not result in a detectable concentration of the drug or drug metabolite. It is important to know if-how-and-why the drug test universe and test sensitivity are relevant to drug-related case-specific questions.

The most frequently employed qualitative urine drug test batteries include six to eight drugs or drug classes; while the most frequently employed blood serum drug test batteries usually include fewer than five drugs or drug classes. These types of limited drug test batteries reflect only a small portion of what might reasonably be viewed as a potential drug universe.

If a qualitative test battery reports an unspecified numerical test result that only reflects an instrumental response compared to some defined cut-off response or detection limit, it does not mean that the numerical result is a reliable quantitative test result.

Semi-quantitative test results

Semi-quantitative test results are approximations of the concentrations of chemicals in the test specimen. Semi-quantitative tests are less accurate than quantitative tests.

Quantitative test results

A case-specific assessment of quantitative accuracy is usually based on the review of laboratory documentation. When considering an evaluation of the accuracy of a quantitative test, you should ask an experienced toxicologist to discuss case-relevance, reported results, processes relating to results review, potential discovery requests, and options relating to retesting.

When considering the accuracy of quantitative test results, you should first discuss the case and result-related information with an experienced forensic toxicologist. Do not retest without consultation.

Interpretation of quantitative postmortem drug test results:

After one considers the case-related evidence and the reliability of the test result, a quantitative postmortem drug test result is sometimes a very important part of the analysis of a death case … especially in cases when the drug detected was prescribed for the deceased:

When the drug quantitated was prescribed for the deceased, examples of interrelated questions and considerations include the following:

- What was the prescribed dosage regimen?
- What do the pharmacy records indicate?
- When was the drug supposed to be taken?
- How was the drug supposed to be taken?
- What was the prescribed dosage?
- What were the previously reported effects?

The approach to case analysis should include a step-by-step cross-referencing process involving the comparison of evidence and expectation and explanation.

When the drug quantitated was not prescribed for the deceased, examples of interrelated questions and considerations include the following:

- What is known about the source of the drug?
- What is known about how - when - where - in what amount - by what route - with what reported effect the drug was used?
- Were other drugs involved? *See above*
- What is known about the deceased's history during the 24 hours prior to the time of death?

All of these considerations should include the deceased's relevant medical and personal history, information and records relating to prior use of prescription or non-prescription drugs, and relevant physical evidence.

The Effects of Drugs

Drugs-and-Accident

Case-specific Questions:

- **What are the toxicology test results?**
- **How reliable are these results?**
- **What do the results mean?**
- **What contributed to the accident?**

Important concepts:
Keep in mind that physical and behavioral effects and the associated risk of accident are affected by a number of factors:

- The concentration of the drug(s) and biologically active metabolite(s)
- Tolerance to or sensitivity to the drug(s)
- Drug-drug interaction(s)
- Physical and medical conditions
- Situational/circumstantial factors
- Environmental factors
- Social and/or emotional factors

Drugs and MVA and Falls:

The use of antidepressants and opiod analgesics by older drivers was associated with increased risk of injurious motor vehicle collisions. *Epidemiology 5(6):591-98 (1994)*

Persons who use minor tranquilizers were 4.9 times as likely to be involved in serious road accidents as those who did not use tranquilizers. *Ref. to Skegg et al. in Am J Psych 142(5):543*

Methadone and Death or Accident:

Relevant factors include the methadone dosage regimen and recent changes in that regimen, other drug use, history of complaints or adverse effects, the 24 hour premortem period, physical evidence, and postmortem or post-accident toxicology.

Marijuana-and-MVA:

Case Vignette: An 18 y.o. involved in a MVA was transported to University Hospital. Over the next two hours, he received approximately 4.5 liters of i.v. fluids and the equivalent of 0.75 liters of packed red blood cells and 0.5 liters of whole blood. He died two hours post-admission. Postmortem toxicology results follow:

Blood THC	**4 ng/ml**
Blood THC-COOH	**19 ng/ml ***
Urine drug screen	**THC +**

**THC-COOH is a major metabolite of marijuana (THC). THC-COOH has no effect on a person (i.e. it is not biologically active).*

Case review included the following:

The passage of time

The deceased's clinical course did not suggest that the rate of elimination of THC would have been substantially reduced between the time of the accident and the time of death. The estimation of THC concentration at the time of the MVA included the consideration of the elimination of THC.

The infusion of fluids and blood products

The dilution-effects associated with i.v. therapies were not established; but the effects probably reduced the THC concentrations by less than five percent.

Premortem elimination

Based on evidence that the deceased finished smoking marijuana at least 30 minutes prior to the MVA, example simulations of his blood THC level at the time of the MVA were prepared.

The postmortem blood specimen

Because most studies relating to THC levels and the effects of THC are based on plasma specimens and the reported blood:plasma ratio for THC is about 0.6, the reported postmortem blood THC level was corrected to obtain the expected equivalent plasma THC level of 7 ng/ml.

Concentration-related effects

Compared to alcohol, the effects of THC are less predictable; but some studies have reported concentration-related effects at THC levels as low as 2.5 ng/ml. However, a set of effects … even a set of adverse effects … does not always establish a "substantially increased risk of MVA".

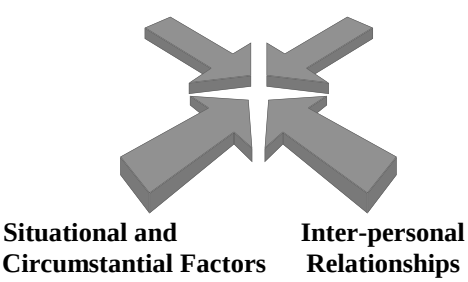
Behavior: Drugs-Alcohol-Assault

Drug Use and Aggressive Behavior:

A Common Theory: Alcohol and Drugs

Alcohol-related theories of aggressive behavior are probably applicable to a consideration of the relationship between the use of some drugs and aggressive behavior.

Alcohol/drugs and Behavior: Case Factors



Behavioral theories include the following:

Physiological disinhibition theory: Alcohol/drugs increases aggression directly by depressing the brain center that normally inhibits aggressive behavior.

Expectancy theory: Alcohol/drugs increase aggressive behavior because people expect it to.

Indirect cause theory: Alcohol/drugs increase aggression by causing changes within the person that increase the probability of aggression (e.g. by reducing intellectual function).

Worker's Compensation: Death Case

Information and case analysis

Case Vignette:

As the result of a work-related accident, the subject was permanently disabled and prescribed medication for chronic pain (narcotics), muscle spasm (cyclobenzaprine), and depression (amitriptyline). He was last seen by his wife about 12 hours prior to discovering his body on the family room couch. He was pronounced dead at the scene and his body was transported to the Office of the Medical Examiner. An autopsy was done 24 hours later.

Prior medical history

Prior medical history included concerns expressed by treating physicians regarding the deceased's dependence on narcotics and poor compliance with the prescribed use of antidepressants. Three physicians were identified; and review of the patient's medical records disclosed some duplication of prescriptions for narcotics.

Prior pharmacy records

24-month records from three local pharmacies were reviewed and compared with the available medical records and prescriptions. The pharmacy records indicated that three physicians prescribed narcotics (oxycontin or hydrocodone) in the 12-months prior to death. The records of one of these physicians were not included in the deceased's prior medical history. Discovery was expanded to include this physician.

Prior medical-pharmacy claims

This review disclosed claims related to one out-of-state pharmacy that provided oxycontin 11 months prior to death. A related medical record was never identified and further discovery was not pursued.

Police report of death

The police report of the death investigation referred to a suicide note, concern regarding depression, and reference to a recent suicidal ideation. One empty prescription container for the most recent month's prescription of cyclobenzaprine was found in a waste basket located in the kitchen. Assuming that month's medication was used as directed beginning with the day it was refilled, 22 pills were missing.

Physical evidence

Physical evidence recovered by the police included six containers from pharmacies-of-record. The evidence was consistent with an impression that the deceased had accumulated narcotics by *doctor shopping*.

Statements relative to the 24 hours prior to death

The deceased was last seen alive in the late evening hours … about 8 hours prior to the time he was discovered. He was described as being quiet but in generally good spirits.

Statements of close friends or others

No other statements were obtained.

Ambulance report

The EMS record indicated initial rigor consistent with death at least six hours prior to arrival.

Death-related medical records

There was no emergency medical treatment.

Autopsy report and related notes

The autopsy report included findings of pulmonary edema and pre-existing heart disease. Stomach contents, heart blood, and urine were submitted for toxicology.

Toxicology test results

Stomach contents were positive for amitriptyline. Urine was not tested. Blood drug test results follow:

Amitriptyline	3450 ng/ml
Nortriptyline	1005 ng/ml
Oxycodone	120 ng/ml
Cyclobenzaprine	22 ng/ml

Results interpretation

While the test results for the antidepressant (amitriptyline) and its metabolite (nortriptyline) are well in excess of the therapeutic range and potentially lethal, these postmortem drug levels could have been increased as a result of a perimortem disequilibrium or postmortem diffusion and/or redistribution. Nevertheless, assuming a doubling of the actual premortem drug levels, the adjusted tricyclic concentrations would still be considered potentially lethal. *Both amitriptyline and nortriptyline are potentially cardiotoxic and the subject of case reports of fatal cardiac arrhythmia.*

Cyclobenzaprine is also potentially subject to a postmortem redistribution process, and the results should be interpreted with caution. However, the test result did not indicate an overdose.

Oxycodone is not thought to be subject to a postmortem redistribution process. The level is in the toxic range.

Deposition of a *knowledgeable person*

The deceased's wife testified that her husband had not consumed oxycodone for at least two months prior to his death. She also testified regarding her discussions with her husband and his treating physicians regarding his apparent reliance on "pain medication".

A written report addressed all relevant topics:

Doctor Shopping and/or drug accumulation

Expected drug dose:concentration relationships

Amounts of drugs consumed
Self over-medication or overdose

Interpretation of drug test results

Cause of death

Inconsistency of other case testimony

Foreseeability of Drug-related Risk

Illustration: Ecstasy (MDMA)

Case consultation regarding the foreseeability of risks associated with the sale and use of MDMA included the estimated absolute and relative risks of ER treatment, hospital admission, and death due to MDMA compared to the same risks for other drugs including prescription medications, OTC preparations, and illicit drugs. Analyses considered NIDA, DAWN, and FDA data bases as well as published literature, death reports, and DEA reports of distribution-and-sales and number of users.

Updated 02/25/2013