



Overdose!

Drug overdose can cause brain injury, but it may not be only the drug that's to blame; it may be the patient or the administration of the substance

BY GEORGE PETERS AND BARBARA PETERS

Almost everyone has heard about overdoses. There are narcotics that are *controlled* substances, but have been involved in many adverse events that have befallen prominent personalities such as Michael Jackson, Anna Nicole Smith, and other noteworthy people. For many years, cocaine was used as a narcotic, a pain reliever and for anesthesia. Morphine and other opioids were also used to produce anesthesia despite their addictive properties and side effects. The synthesis of new anesthetics substantially reduced the propensity for systemic toxicity, offered some clinical benefits, and reduced the frequency of patient harm. Still, unnecessary procedural errors and unacceptable levels of injury still remain.

Tolerance

Even the most professionally trained among us seem to think and act as if people could be described with one simple metric or categorization. We hear groups of people described by an average, a limit or some descriptive representation. If rigidly applied, error is inevitable. The behavioral world is manifest as a descriptive variance, range or span between the lowest and highest, or other means of describing the expected variation in human response. Not all people are alike, and neither is their reaction or tolerance to certain drugs.

The graphic entitled "Susceptibility to Drugs" (See Figure 1) shows the traditional background bell or "normal" curve with three average people superimposed on the diagram. The first person has a drug tolerance of 3x which is a low tolerance or sensitivity to a drug. Less of a drug is needed for the desired effect. The third person is beyond 7x which is a high tolerance to a drug. More of a drug could be used. The person in the middle can take what may be recommended in the drug manufacturer's drug insert, a textbook or in customary clinical practice recommendations. This is what is meant, in part, by the need to "individualize" a dosage for a particular patient. Unfortunately, a physician may excessively narrow his/her choice of drugs, develop one standardized level of dose, unload or delegate injection and observational responsibilities to assistants, and actually neglect close personal supervision of the drugged patient. People do react differently to a given dose, so close monitoring is essential by those who can take immediate corrective action.

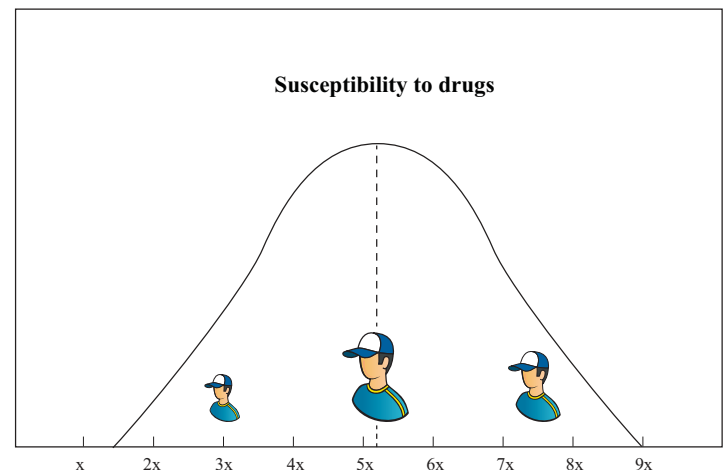


Figure 1: Biologic Variation in Dose

Compounded risk

The use of anesthetics is widespread, effective and relatively safe given the circumstances in which their use occurs. Perhaps, with highly restricted choice and application, this positive experience produces a comfort zone, a compliance demeanor and a practice silo. But, some physicians are venturesome, it is a professional area that keeps changing, there are unknowns because research experimentation with humans is generally forbidden, and the margins of safety disappear given certain practices.

For this discussion, we will restrict our commentary to the use of local anesthetics in highly vascular areas of the body such as the head (scalp). They may be injected subcutaneously or intradermally for a local effect, a seemingly benign approach.

The most commonly used drugs for this purpose are Lidocaine hydrochloride with epinephrine (adrenalin) and Marcaine (bupivacaine) with epinephrine. The epinephrine is a vasoconstrictor for a more bloodless surgery, it prolongs the duration of the anesthetic agent, and it has its own toxicity. These two agents may be supplemented with Vicodin, Darvocet, Valium, and Halcion. What all six drugs have in common is that they are all central nervous system depressants. Thus, the injuries of overdose may be to the cerebral cortex, upper brainstem (medulla), and



possibly the reticular activating system (RAS), the thalamus, and basal ganglia.

What may be overlooked in terms of dosage are the cumulative effects (See Figure 2) that distort what appears in the blood plasma in terms of toxicity. The individual dose (1.) may produce a desired effect such as loss of consciousness or a “no pain” condition. The maintenance or reinforcing dose (2.) may be administered too early and the combined dosage may be too high. The drug may be eliminated or detoxified by the liver, but metabolites (M) are formed that enter the blood stream at an 80 percent toxicity level which may have an additive, synergistic, potentiation, or side effect. On top of this, another agent (A) may be injected. Still another anesthetic dose may be a component of a drug used for another purpose. Despite reliance on estimated drug duration times, the signs, symptoms, and adverse effects can appear four to six hours or more, after the last injection.

The shape of the curve, in the “Cumulative Effects” graphic, may vary as to the drug onset, peak value, duration, half-life and elimination factors. For example, the tail end often has a relatively flat and extended slope.

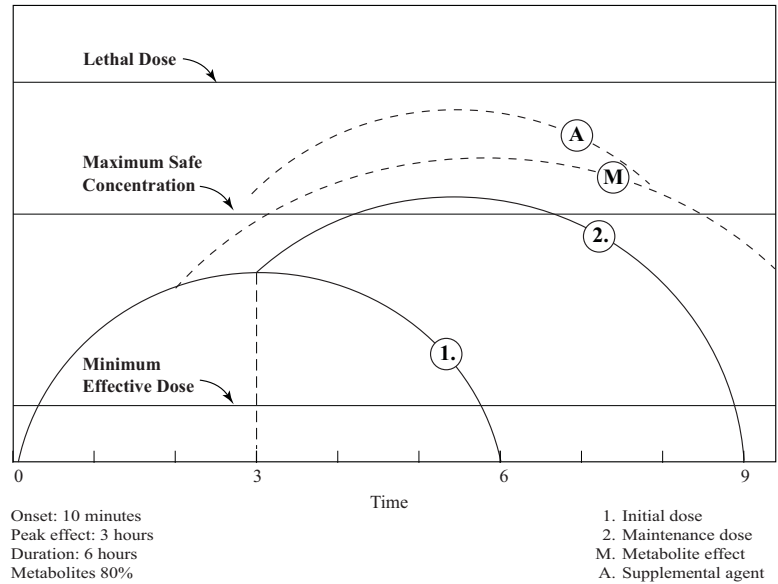


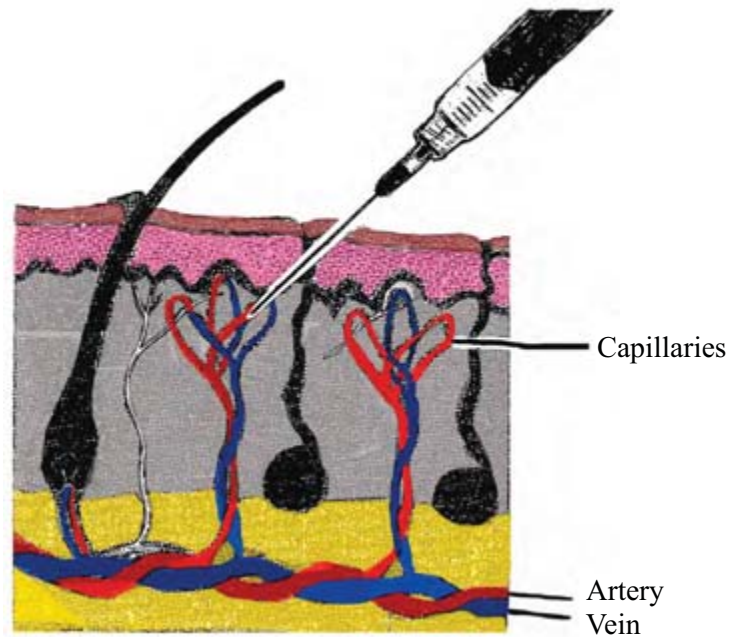
Figure 2: Cumulative Effects

Inadvertent error?

One of the most frequent causes of overdose has been called accidental intravascular injection. (See Figure 3) This occurs when the syringe needle is inserted into the skin at a 45-degree angle and intersects a blood vessel. The rupture may not be seen and the drug may be injected directly into the bloodstream. The graphic entitled “Intravascular Injection” shows the bevel-down needle piercing capillaries, but for thin skin (an age-dependent condition) the needle may cut into a larger blood vessel. A surgical scalpel may have already cut open a blood vessel. The presence of blood on the skin connotes some danger of the anesthetic drug being pulled into the venous bloodstream where it can have a strong direct effect on the heart and brain.

Before administering an injection, the syringe plunger should be pulled back (aspirated) to determine if a blood vessel has been penetrated. There have been recommendations to rotate the needle 180 degrees, aspirate twice and wait 15 seconds. Adriani, nearly a half century ago, listed accidental intravascular injection as a major cause of overdose. That warning still appears in the latest publications where there are warnings to avoid intravascular injection by the use of aspiration, such as in the drug’s package insert.

For one of these drugs, the current package insert for Lidocaine states that repeated doses may cause significant increases in blood levels with each repeated dose and that tolerance to elevated blood levels varies with the status of the patient. The package insert also warned that clinicians



Adapted from *The Merck Manual* (Ref. 1)

Figure 3: Intravascular Injection



who use Lidocaine should be well-versed in dose-related toxicity and should ensure the immediate availability of oxygen, cardiopulmonary equipment and resuscitative drugs. Added caution is needed because small doses of local anesthetics injected into the head area may produce adverse reactions similar to the systemic toxicity seen with unintentional intravascular injections of larger doses.

Therapeutic window

The amount of a dose, between the start of a desired therapeutic effect (efficacy) and an adverse effect (danger), is known as the therapeutic window. This is a concept that greatly simplifies communication to a lay (jury) audience. For Lidocaine, a narrow window exists, but the window can be closed 50 percent or more from the increased risk of age (elderly patients), hypertension (high blood pressure), and diabetes-2 (kidney insufficiency). That is, the dosage should be cut in half for safety or the standard adult dose is twice what should be given.

Differential diagnosis

When a patient suffers a loss of consciousness and brain function, the first reaction (presumption) is that it might be from a stroke (CVA or cerebrovascular accident). It is a stroke if there is a lack of blood flow (ischemia) to the brain that causes a lack of oxygen (anoxia) that is necessary for the function and life of the brain. The blood flow may be blocked by a cerebral thrombosis or arterial embolism (clot). Alternatively, there may be a leakage of blood from a blood vessel rupture resulting in a hemorrhage (hematoma). The formal World Health Organization definition is a neurological deficit of cerebrovascular cause that persists beyond 24 hours. Under 24 hours, it is known as a transient ischemic attack (TIA) that resolves quickly.

There is usually a rush to image the brain (by CT and MRI scans for existence of obstructions) and Doppler ultrasound (for blood flow and carotid stenosis). A series of images and readers may be informative. But frequently nothing may be found in terms of specific causation as to stroke (a cryptogenic origin). Something else may be the cause. In fact, there may be some reluctance to consider a drug overdose or direct poisoning of the central nervous system because it may involve someone in the same peer group or institutional healthcare endeavor. Thus, the overall factual circumstances, in some detail, become very important and there may be strong conflict of medical opinions.

Causation

After an anesthetic enters the bloodstream, it is carried in the blood plasma (proteins) to the central nervous system (the brain). The anesthetic passes through the porous membrane of the blood vessels and enters the extracellular space (See Figure 4). It moves by diffusion into the neurotropic cells where it affects cellular structure and function. It also moves through the glial

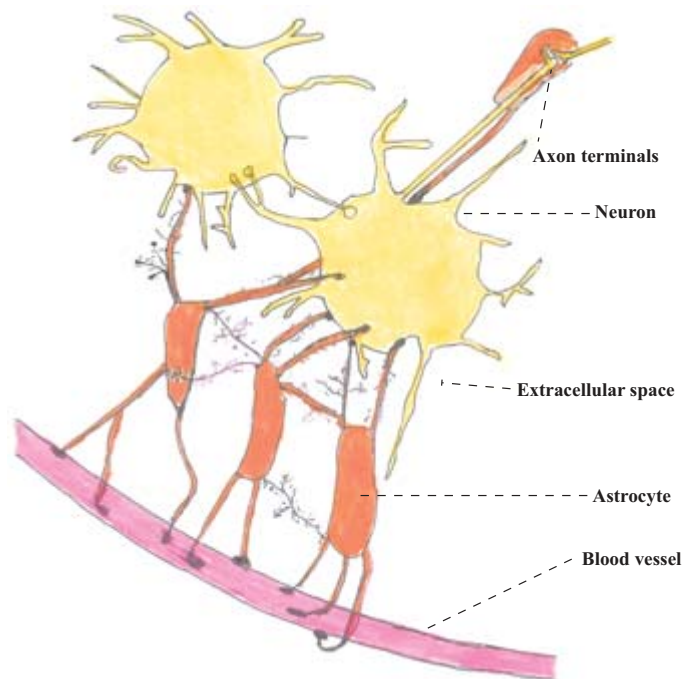


Figure 4: Blood Plasma Pathway

cells, particularly the astrocytes, that are attached to the blood vessels and neurons. Freeman indicates that glial cells are multifunctional, anchoring the neurons to their blood supply, and transporting nutrients, oxygen, and anesthesia to the neurons (Science, 5 Nov. 2010, 774-778).

These glial cells (neuroglia) wrap around the synapses, in particular the axon terminals. As they swell from the anesthetic agent, together with the swelling of the neurons, in the limited space of the skull, it forces a general compression and vasoconstriction of the brain. This cytotoxic edema (swelling) causes cerebral ischemia (disruption of blood flow) that results in hypoxia (an oxygen shortage). In particular, astrocyte edema compresses the capillary lumens causing a lack of perfusion and the resulting cerebrovascular insufficiency that leads to cellular apoptosis, infarct and necrosis (cellular death).

Liability

Those who administer anesthetic drugs have been keenly aware of the threat of legal liability if something goes wrong. For many years, there have been professional lectures and articles, reports of cases settled or tried, and the formulation of recommended practice guides and checklists.

In 1965, one popular anesthesiology textbook discussed medicolegal safeguards. It stated that legal actions have risen constantly, that malpractice could be considered an occupational



hazard, that anesthetic mishaps are one of the most vulnerable medicolegal hazards, and that malpractice actions could be accompanied by other actions such as assault and battery. Moore listed ways to avoid medicolegal actions including good patient rapport, consent forms, accurate charts and records, consulting with other specialists, laboratory workups or a complete patient history, and to keep the insurance company informed of complications. Also, it warned that physicians should have the maximum amount of insurance since this is the “only and ultimate safeguard in a lawsuit.”

Since that time, there have been considerable public relations emphasizing the noble objectives of the healthcare profession and the presumed need for legal constraints such as MICRA and tort reform. It has grown increasingly defensive such as what to do after a mishap to minimize damages or evade fault by “dodge and cover.” Lawyers should be aware of this context from which defenses can arise. In essence, it has become more loss control than injury prevention, more self-policing than independent appraisal, and containment rather than compensation. Thus, tests may be criticized, rogue performers protected, and an aura of perfection maintained. Despite this, we admire the high professional level of performance and deep concern for patients that we observe from most medical practitioners. But, there are some “bad apples” that continue to cause unnecessary injury.

Human factors and safety

The selection of expert witnesses includes specialists in pharmacology and neurology familiar with recent brain research, but other disciplines should be considered depending on the circumstances.

Just as a variation in drug tolerance by patients exists, the same bell-shaped curve can be used to describe expected behavioral variation in performance by anesthesiologists and others who utilize pain-killing drugs. Thus, prevention of clinical errors entails a reduction in behavioral variation to an acceptable margin of error. Despite the self-help or peer remedies in this domain that have not worked sufficiently, the help of independent behavioral research scientists (such as human factors experts) should have been sought as a preventive measure. This should have had application to the non-anesthesiologist physician who occasionally uses pain-killing drugs and to the activities of nurse specialists. This expert area includes proven warnings, instructions, procedures, test doses, patient evaluation and monitoring,

and error avoidance techniques. It can be argued that even the best could benefit by less subjectivity in medical decisions, less conflict among authorities and guidelines, less confusion in directions and cautions, and less reluctance to test and assess by some. The “infiltration-as-you-go” mentality does not suggest proper professionalism when dealing with toxic substances. Token or un-tailored informed consent does not meet human rights principles. The objective of discovery should be answers to the questions of what anesthesia errors occur; why, when, by whom; any misdirections; and how error-prone behavior can be prevented. The question is how this type of evidence could be presented and by which expert and witness.

The impressive advances in bioscience, biochemistry, medical devices, and design (system) safety suggest that devices can now be designed to help prevent drug overdoses. For example, a blood plasma monitor for specific drugs that automatically adjusts for proper doses and signals (voice warnings) about transgressions of a maximum allowable dose or cumulative dosage. Smart intravenous infusion pumps, intended to double-check a programmed dose, detect errors, and sound alarms, are in use today. Similarly, a metering device for continuous drug flow rather than periodic hypodermic syringe injections or incremental dose intervals, that produce surges in drug effects. The metering reliability technology has benefited from recent medical device pumps (external and implanted). Reduction of human error, by use of such devices, also has been considered a liability prevention measure, but is more properly a matter of saving lives and avoiding injury. The threat of litigation should be enhanced in this area rather than diminished or compromised since it seems essential in achieving appropriate social expectations for safety and health from anesthesia.



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