

Toxicology News

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Survival of the Fittest Drives Plants to Use Toxic Defenses

By Catherine Hammett-Stabler

The next time you step into someone's garden, pause and take a glance around. Then take a closer look. You may see that things are quite a bit different than they appear on the surface. Under the often-peaceful façade lies a jungle in which wars are being waged. In my garden, the results of vicious attacks by insects are all too apparent. One simply has to glance at some leaves to see where insects have enjoyed a meal. At times, I have to take the better living (or dying) through chemistry approach to help the plants out, but some plants need little assistance and fight dirty.

Plants can't run away when attacked. Many, however, have developed toxic chemicals that are constantly distributed or synthesized as a means of defense. Plants use these chemicals not only to fight off insects and other herbivores, but also to compete with other plants.

By no means an exhaustive list, Table 1 shows some of the types of compounds commonly encountered. The process of developing organic chemical defenses is complex and evolves as needed. Interesting examples of plants that rely on this type of defense include the milkweed, wild parsnip, and even a cultivated staple, corn.

Defense mechanisms

Members of the milkweed genus defend themselves by producing a sap that is toxic to most animals, with one notable exception: the monarch caterpillar. These insects have evolved so that they can feed on the leaves without harm, store the poison within their cells, and consequently become poisonous to their predators. After metamorphosing into adult butterflies, they retain this protective toxicity in their wings and skins (1).

Originally brought from Europe to North Amer-

Table 1. Examples of Toxic Compounds in Plants

Essential oils	Alkaloids
Glycosides	Saponins
Proteins and amino acids	Oxalates
Coumarins and furanocoumarins	Tannins
Glucosinolates	Plant acids
Alcohols	Phenols
Resins and resinoids	Terpenes
Minerals	

ica by early colonists as an herb, the parsnip (*Pastinaca sativa*) is now considered a noxious weed. Not only is the plant quite invasive, it also produces furanocoumarins, which cause phototoxicity on contact with skin. By testing seed specimens available through herbariums, Zangerl has shown that over the past 150 years the plant has increased the concentration of these compounds in conjunction with the introduction of the parsnip webworm (2).

Most varieties of corn release volatiles when attacked by certain caterpillars or larvae in an attempt to attract wasp predators of the insects. Recent studies suggest the release of these herbivore-induced plant volatiles follows a circadian pattern, with the plant producing and releasing higher concentrations during the daytime when the wasps are more likely to be active, compared with attacks that occur at night when the wasps are not active (3).

Epidemiology of plant exposures

Fortunately, most of these toxins are not directed at humans. By some estimates, 1–2% of the more than 250,000 plant species are thought to be poisonous to humans. It is estimated that there are about 4,700 poisonous plants worldwide, and 700 to

Continued on page 3

Inside...

Rozerem Case History	4
Zolpidem Remains Popular	5
Gel Barrier Tubes Still Controversial	6

Table 2. Examples of Poisonous Plants (not a complete list)

Plant	Toxic portion	Toxic chemicals	Symptoms
Black locust	Leaves, sprouts, bark, seeds	Lectins	Gastrointestinal (GI) distress, weakness
Bleeding heart	Foliage, roots	Alkaloids, isoquinolines	Large amounts: GI distress, arrhythmias
Buttercups	All parts	Ranunculin	Diarrhea, vomiting
Caladium	All parts	Oxalates	Intense irritation of lips, mouth, and throat
Cassava	All parts	Linamarin	Neuropathies, respiratory arrest
Castor bean	Seeds	Ricin	Respiratory distress, hypotension, liver and renal dysfunction, death
	Leaves, stems	Ricinine	GI distress
Chrysanthemum	Leaves, stalks	Arteglasin	Dermatitis
Dieffenbachia (dumbcane) Elephant ear	Leaves, stems, sap	Calcium oxalate, oxalic acid, possibly others	Intense burning and irritation of mouth and tongue, mucosal inflammation, eye damage
Elderberry	Bark, roots, leaves, uncooked berries	Sambunigrin (cyanoglycoside)	GI distress
Foxglove	Leaves	Digitoxin	Inhibition of Na, K ATPase; cardiotoxic, GI distress, confusion
Hemlock	All parts	Coniine, conicein	Paralysis, death
Holly	Leaves, twigs, >5 berries	Alkaloids, saponins	GI distress
Hyacinth, narcissus, daffodil	Bulbs	Alkaloids, oxalates	Nausea, vomiting, diarrhea, dermatitis, can be fatal
Lantana	Green berries	Lantadenes	Respiratory depression, renal dysfunction, GI distress
Mistletoe	All parts, berries	Tyramine, phoratoxin, viscotoxin	Nausea, vomiting, GI distress, seizures, possible cardiotoxicity
Oaks	Foliage, acorns	Tannins	Large amounts: renal dysfunction
Oleander	Leaves, branches	Nerioside, oleandroside	Cardiotoxic, GI distress
Peace lily	Leaves	Oxalates	Irritation of lips, mouth, and throat
Philodendron	Leaves, stems	Oxalates	Contact dermatitis; burning of lips, mouth, throat; renal failure
Pokeweed	All parts	Phylolaccagenin, aglycones, other saponins, oxalates	Nausea, vomiting
Pothos, devil's ivy	All parts	Calcium oxalate	Diarrhea, GI distress, dermatitis
Rhododendron, azaleas, laurels	Leaves, twigs, flowers, nectar	Acetyl-andromedol, camphor, laurel oil, safrole	GI distress, bradycardia, atrioventricular block, sweating, blurred vision, respiratory depression
Tomato, potato	Leaves, stems, unripe fruit, green skin	Tomatine, solanine	GI distress, headache, flushing
Water hemlock	All parts	Cicutoxin, cicutol, faltarindiol	Burning pain in mouth, severe vomiting, seizures, death
Wild and cultivated cherries	Twigs, foliage	Prunasin, amygdalin	Nausea, vomiting, diarrhea, respiratory depression
Wisteria	Seed	Wistarine, alectin, glycosides	Headache, GI distress
Yew	Berries, foliage	Taxine	GI distress, possible sudden death

Toxic Plants

Continued from page 1

1,000 in the United States. These are rough estimates because the exact number of plant species has yet to be determined.

Unfortunately, poisonous plants have no distinguishing characteristics. Many poisonous plants in the wild have features that are similar to those of non-poisonous plants at various times of their development. This has resulted in numerous reports in the medical literature of harmful plants being ingested in error instead of desired wild herbals. In addition, chemical composition and toxicity vary across species within a given genus. Differences between varieties and cultivars have been documented.

Furthermore, toxicity varies across the plant's physical structures. All parts of one plant may be poisonous, while poisons concentrate in the seeds, flowers, or roots of another. The picture is further complicated because the chemical composition of a plant changes during the growing season and dormancy, and in response to soil and growing conditions. Fortunately, plants account for less than 5% of toxin exposures reported through the annual Toxic Exposure Surveillance System of the American Association of Poison Control Centers (4).

A review of the past 10 years of reports shows several interesting trends. Not surprisingly, most ingestions occur in children less than 6 years old, when they are more likely to explore by putting things in their mouths. Brightly colored berries, pods, leaves, and pretty flowers are interesting, attractive, and difficult for children to resist. The common impression that the poisonous parts of these plants are bitter or unpleasant tasting is not necessarily true, and should be remembered when dealing with pediatric cases (5).

Adult ingestions are often accidental, with many cases resulting from misidentification for herbal use. The good news is that the number of exposures appears to be declining. Whether this is related to herbals now being classified separately, a reduction in reporting, or some other phenomenon isn't clear.

Most frequently reported plant poisonings

The plants most frequently reported to local poison control centers are those common to many households and gardens (Figure 1). These include philodendron, peace lily, dieffenbachia (dumbcane), jade plant, pothos, and rubber tree, along with several that have seasonal popularity: Christmas cactus, poinsettia, and holly. Many of the plants mentioned in incidents reported to poison control centers are considered non-poisonous, including jade plant, rub-

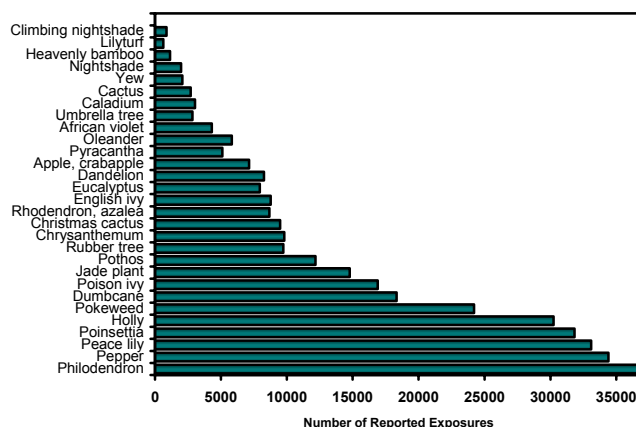


Figure 1. Cumulative Plant Exposures Reported to Poison Control Centers, 1996–2006

ber tree, Christmas cactus, dandelion, pyracantha, and African violet. Although most of us have heard about the toxicity of poinsettias, the domesticated cultivars found today are relatively low in toxicity. However, many individuals experience a dermatological reaction when exposed to the sap.

In contrast, peace lily, dieffenbachia, and oleander are quite toxic. Additional examples of poisonous plants, along with the possible symptoms, are seen in Table 2. This list is by no means complete, or even extensive, but demonstrates that some plants we may consider harmless are potentially toxic.

Table 3 presents some excellent information resources. Veterinary and agricultural resources are often valuable because plant poisonings are actually a greater problem with pets and livestock than humans.

References

1. Attenborough D. *The private life of plants*. Princeton, New Jersey: Princeton University Press, 1995.
2. Zangerl AR, Berenbaum MR. Increase in toxicity

Table 3. Useful Resources

Federal Government

Food and Drug Administration: www.fda.gov

Agricultural Research Service: www.ars.usda.gov

U.S. Army Center for Health Promotion and Preventive Medicine: chppm-www.apgea.army.mil

Regional Poison Control Centers

Carolinas Poison Control:

www.ncpoisoncenter.org/Consumers/Plants.cfm

Regional University-Based Programs

Cornell University: www.ansci.cornell.edu/plants/index.html

North Carolina State University:

www.ces.ncsu.edu/depts/hort/consumer/poison/poison.htm

Regional Agricultural or Extension Agents

Connecticut Agricultural Experiment Station:

www.caes.state.ct.us

of an invasive weed after reassociation with its coevolved herbivore. *Proc Natl Acad Sci U S A* 2005;102:15529–32.

- Shiojiri K, Ozawa R, Takabayashi J. Plant volatiles, rather than light, determine the nocturnal behavior of a caterpillar. *PLoS Biol* 2006;4:e164.
- Toxic Exposure Surveillance System Report Archives. www.AAPCC.org
- Frohne D, Pfander HJ. *Poisonous plants*, 2nd ed. Portland, Oregon: Timber Press, 2005.

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Case History: Overdose of Rozerem in Suicide Attempt

By Frank McGeorge and John M. Wilson

A 16-year-old female with cerebral palsy presented to the emergency department with a history of ingesting 40 Prozac (fluoxetine; 10 mg) and 15 Rozerem (ramelteon; 8 mg) tablets three-and-a-half hours prior to presentation. She had made a prior suicide attempt by lacerating her wrists.

On physical exam, the patient had a flat affect, speaking with a soft voice. Her vital signs were: blood pressure, 123/82; pulse, 94/min; respiratory rate, 18/min. She was placed on oxygen, provided intravenous fluids, and given 25 g of charcoal orally. Her chemistry laboratory results were all normal: Na, 139; K, 4.0; Cl, 105; CO₂, 27; Glu, 91; BUN, 11; Cr, 0.5; Ca, 9.4. So were her hematology results: WBC, 6.6; RBC, 4.71; Hct, 41.1; Hb, 14.0; Plt, 254. Ethanol was not detected and a comprehensive urine toxicology screen reported fluoxetine and metabolite and ramelteon.

The patient was stabilized on site and transferred to a mental health facility. The patient survived without significant events, but presented in another suicide attempt about two months later.

Ramelteon

Ramelteon (Figure 1) was approved by the Food and Drug Administration in 2005 for the treatment of insomnia. It is a melatonin-receptor agonist, primarily at MT1 and MT2 (1, 2). It displays little activity at serotonin and dopamine receptors, or gamma-aminobutyric acid-A (GABA), benzodiazepine, adrenergic, cholinergic or opiate sites. Ramelteon exhibits rapid absorption and a short elimination half-life of one to three hours, suggesting immediate onset and little after-effect. Metabolism is extensive on

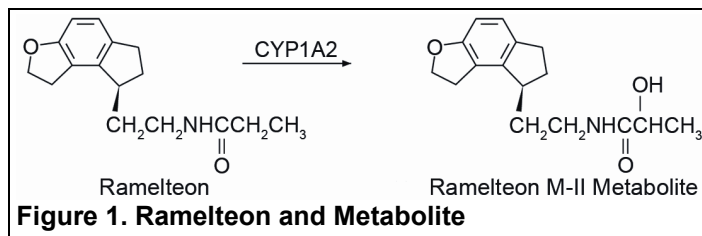


Figure 1. Ramelteon and Metabolite

first pass, and pharmacological activity is likely due to a combination of ramelteon and the monohydroxy metabolite, which achieves serum concentrations as high as 40 times those of the parent drug, but has fivefold to tenfold lower receptor affinity (3).

Toxicity data are limited. Clinical trials found a number of neurological effects, as might be expected. The estimated dose in this history, 120 mg, is consistent with clinical evaluations using up to 160-mg doses to assess abuse potential. No safety or tolerability concerns were seen (4).

A significant issue with ramelteon may prove to be metabolic drug-drug interactions. Inhibitors such as fluvoxamine, ketoconazole, and fluconazole, and inducing agents such as Rifampin, have demonstrated substantial influences on ramelteon clearance. Fluvoxamine, for example, resulted in a 190-fold increase in the ramelteon area under the curve (AUC) (1).

Fluoxetine, the co-ingested agent in this history, has been shown to produce a 50% increase in the ramelteon AUC and increased concentrations of the active metabolite (2, 5). No serum levels were measured to corroborate this observation in this case evaluation.

References

- McGechan A, Wellington K. Ramelteon. *CNS Drugs* 2005;19:1057–65.
- Levien TL. Ramelteon: a melatonin receptor agonist in the treatment of insomnia. *US Neurol Dis* 2006;1–7.
- Karim A, Tolbert D, Cao C. Disposition kinetics and tolerance of escalating single doses of ramelteon, a high-affinity MT1 and MT2 melatonin receptor agonist indicated for treatment of insomnia. *J Clin Pharmacol* 2007;46:140–8.
- Physicians' desk reference, 60th ed. Montvale, New Jersey: Thomson Healthcare, 2006.
- Sainati SM, Karim A, Tolbert D, Cao C. Effects of multiple doses of fluoxetine on the systemic exposure of a single dose of ramelteon (Tak-375) in healthy adults. *Sleep* 2004;27(Suppl):A48.

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Zolpidem Remains Popular For Treatment of Insomnia

By Felix Boakye-Agyeman

A widely reported and commonly treated medical problem, insomnia affects about 10% of the adult population. Hypnotic drugs remain the treatment of choice for most cases (1). One of the most popular of these drugs is zolpidem, commercially known as Ambien (Sanofi-Aventis).

Zolpidem causes relaxation and induces sleep. It is used to treat symptoms of sleep disorders such as difficulty falling asleep, frequent waking during the night, or waking up too early in the morning.

Zolpidem has also been used for other purposes. In one case, a 48-year-old woman had been comatose for two years as a result of oxygen deprivation after a suicide attempt by hanging. Within 20 minutes of receiving zolpidem, she was able to communicate, eat, and move about (2). Zolpidem has also been shown to improve symptoms of some neurological disorders such as Parkinson's disease (3) and to have weak anticonvulsant effects in animals (4).

Method of action

Zolpidem is a selective benzodiazepine receptor agonist, but is not chemically related to benzodiazepines, barbiturates, or other drugs with known hypnotic properties. It is an imidazopyridine and is chemically known as N,N,6-trimethyl-2-p-tolylimidazo[1,2-a]pyridine-3-acetamide L-(+) tartrate (2:1) (4, 5). It acts at the gamma-aminobutyric acid-A (GABA_A) receptor by interacting with the GABA-benzodiazepine receptor complex (5). Zolpidem acts at inhibitory receptors in the central nervous system, binding to the ω_1 receptor of the GABA_A α subunit. This binding site distinguishes zolpidem from benzodiazepines, barbiturates, and other sedatives in that their affinity is not limited to the ω_1 receptor (5). Zolpidem does not cross-react with benzodiazepines, opiates, barbiturates, cocaine, cannabinoids, or amphetamines in two standard urine drug screens, and it has not been shown to have any effect on other drugs.

Zolpidem is absorbed rapidly from the gastrointestinal tract and exhibits a short half-life of about 2.5 hours (4). Its absorption is inhibited when it is ingested with a meal, which delays and lowers the maximal serum concentration. If rapid sleep onset is required, it should not be administered with food.

The recommended dose for most adults is 10 mg or less at bedtime (4, 5). Dosage should be individu-

alized; it should be lowered to about 5 mg in the elderly and in individuals with hepatic insufficiency because of their greater sensitivity and the risk of it not clearing rapidly. Individuals with compromised renal function should be closely monitored, although dosage adjustments may not be necessary (4).

Overdose can cause impairment of consciousness ranging from somnolence to coma, cardiovascular effects, respiratory compromise, and even death. In the case of overdose, a physician should be seen immediately; the physician may want to contact a poison control center for up-to-date treatment information (4).

Analysis

Zolpidem has been screened and identified using thin-layer chromatography and gas chromatography/mass spectrometry. It has been quantified by high-pressure liquid chromatography, liquid chromatography tandem mass spectrometry, and capillary electrophoresis. It has not been found to cross-react with drugs used in standard urine immunoassays (6). Recently enzyme-linked immunosorbent assay kits have become available.

Side effects and consequences

The most frequent side effects are daytime drowsiness, dizziness, headache, nausea, and vomiting; these occur in less than 1% of patients per episode. In rare cases, it may cause allergic reactions such as swelling of the tongue or throat, shortness of breath, or more severe complications (4, 5). Some patients have suffered from impaired concentration, continuing or aggravated depression, and manic reaction. Memory problems have not been found in clinical trials. Hazards like sleepwalking, eating or driving while not fully awake, and amnesia of particular events have been reported. Therapeutic concentrations may progressively impair an individual's ability to operate an automobile (7). The amnesia caused by zolpidem has led to its use in drug-facilitated sexual crimes (8).

References

1. Morgan K, Clarke D. Longitudinal trends in late-life insomnia: implications for prescribing. *Age Ageing* 1997;26:179-84.
2. Brefel-Courbon B, Payoux P, Ory F, et al. Clinical and imaging evidence of zolpidem effect in hypoxic encephalopathy. *Ann Neurol* 2007;62:102-5.
3. Daniele A, Albanese A, Gainotti G, Gregori B, Bartolomeo P. Zolpidem in Parkinson's disease. *Lancet* 1997;349:1222-3.

4. Physicians' Desk Reference, 60th ed. Montvale, New Jersey: Thomson Healthcare, 2006.
5. Brunton LL, ed. Goodman and Gilman's the pharmacological basis of therapeutics, 11th ed. New York: McGraw-Hill, 2006.
6. Piergies AA, Sainati S, Roth-Schechter A. Lack of cross-reactivity of Ambien (zolpidem) with drugs in standard urine drug screens. *Arch Pathol Lab Med* 1997;121:392-4.
7. Logan BK, Couper FJ. Zolpidem and driving impairment. *J Forensic Sci* 2001;45:105-10.
8. Negrusz A, Juhascik M, Gaensslen RE. Estimate of the incidence of drug-facilitated sexual assault in the U.S.: final report. www.ncjrs.gov/pdffiles1/nij/grants/212000.pdf (Accessed Oct. 12, 2007).

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Serum Separator Tubes Are Still Controversial for TDM

By Amitava Dasgupta & Catherine Hammett-Stabler

Most therapeutic drug monitoring (TDM) measurements are performed using serum. The list of drugs for which TDM was recommended changed little for almost 15 years, but recently many clinicians have recognized its benefits for many new drugs as well as old ones that were once touted as being so safe that monitoring was not necessary. These include many chemotherapeutic and antiepileptic drugs.

The appropriate device to use for sample collection has long been controversial, with some laboratories permitting the use of serum separator tubes containing gel barriers and others prohibiting their use.

The gel barrier tubes are preferred for most routine chemistry analyses. As TDM assays have made their way onto the automated platforms, the consolidation of as many tests as possible into a single sample tube facilitates pre-analytical processing and testing. Non-laboratory personnel involved in sample collection have fewer decisions to make regarding sample type. Less sample handling and fewer transfers mean fewer identification errors. And the gel-barrier provides longer sample and analyte stability in many cases. These tubes have distinct advantages, but their use in TDM has been questioned.

The controversy

The controversy began almost as soon as the tubes were introduced in the late 1970s. One early

study calling attention to the problem was simple but elegant (1). Quattrocchi et al. collected blood from patients receiving digoxin, lidocaine, pentobarbital, phenobarbital, quinidine, chloramphenicol, theophylline, gentamicin, phenytoin, and tobramycin, and divided it between tubes containing a gel barrier (SST, Becton, Dickinson and Company) and plain tubes. Drug concentrations were measured across several days at specified time intervals. The authors found a small, statistically significant change in the measured serum concentrations for the more lipophilic drugs, such as lidocaine, pentobarbital, and phenytoin. The effect appeared to be related to the amount of time the specimen was in contact with the gel and the volume of blood, but not the initial drug concentration. Although they concluded that the effect suggested a slow but passive absorption by the gel for certain lipophilic drugs, they recommended that the SST tubes could be used if at least 2 mL of blood were collected and the samples processed immediately.

Similar results for these tubes and those from other manufacturers were reported by Cai et al. (2), Koch and Platoff (3), Landt et al. (4), and Parish and Alexander (5). Each of these studies concluded that the problem was encountered most often with lipophilic drugs and that adsorption of the problematic drugs could be minimized if the tubes were completely filled, maintained at room temperature or lower, and rapidly processed. If testing was not performed within one hour of collection, the general consensus was that an aliquot should be removed and placed in another container for storage.

Study limitations

Unfortunately, these studies had limitations that made it difficult to agree with these conclusions. Usually the investigators tested only one of the available gel tube brands. Some studies did not use the tubes for sample collection from patients actually receiving the drug measured. Instead, samples were collected from drug-free healthy volunteers, the serum separated and placed in the gel tube, and the drug added.

The studies were logistically cumbersome and often expensive, with multiple determinations performed on each sample across the study interval. As a result, it was common to find the sample size for each drug tested limited to 1-5 replicates. This small sample size not only limits the range of drug concentrations covered, but it limits consideration of other variables that may contribute to adsorption.

Further complicating the picture were reports of differences encountered between lots of tubes. For these reasons, in 1996 the National Academy of

Clinical Biochemistry committee that developed a series of guidelines for TDM services recommended the tubes not be used until sufficient data were obtained (6).

Karppi et al. reported one of the most thorough studies of the subject in 2000 (7). This study used both spiked and authentic patient serum specimens in three types of gel barrier tubes: SST tubes, Venoject II (Autosep), and Vacuette (Greiner Labortechnik). Three brands of non-gel, plain tubes were used for comparison. The researchers used immunoassay and chromatography to assess the stability over 24 hours of 41 drugs, including tricyclic antidepressants, benzodiazepines, antiepileptic drugs, asthma drugs, aminoglycosides and other antibiotics, and cardioactive drugs.

Recovery results were similar among the various brands of tubes studied. With the exception of carbamazepine, the changes observed in the concentrations of the antiepileptic drugs, antibiotics, digoxin, theophylline, and diazepam and its metabolites were considered to be minimal (0–5%). In contrast, significant adsorption was observed over time for drugs in the antidepressant and benzodiazepine classes, with apparent loss of sample increasing in proportion to contact with the gel. As extensive as this study was, however, it was still limited because authentic patient samples were not used for each drug and each tube type.

Changes in tubes

It should be kept in mind that the tubes used in the aforementioned studies are not the same as those on the market today. The tubes are typically plastic and there have been changes in the formulations of the gels. One of the few studies of the new generation of tubes, conducted by Bush et al., was encouraging in that it found less than a 10% loss of carbamazepine and phenytoin with prolonged storage of the two drugs in SST II gel tubes (8). A limitation of the study was that samples were not collected using the SST II tubes, but instead, aliquots of serum were placed in the tubes. After storage on the gel for seven days, the investigators found that phenytoin concentrations declined by 4% and carbamazepine concentrations declined by 7%.

Additional studies, in which the authors collected samples from patients receiving the two drugs, demonstrated that the effect was time- and volume-related. As with the previous generation, the effect was minimized when the tubes were filled to capacity.

Although this article has focused on the issue of drug adsorption by the gel, we should mention that

another problem has been reported with all types of collection devices. From time to time, constituents from the gels or reagents added to enhance clotting, from the stoppers, and so on, have been documented to elute into the samples and interfere with many methods. These occurrences have been very difficult to troubleshoot because only a few methods may be impacted and the bias may be subtle (9–12).

The greatest value in reviewing the older studies lies in the development of robust protocols to evaluate current and future generations of collection devices. Validation of collection and storage tubes should be a part of any method evaluation or development and should be considered when troubleshooting. Whether or not gel barrier tubes should be used for collecting samples for TDM remains controversial and, at least for some time to come, we will find two

NACB President Comments on Serum Separator Tube Use

The National Academy of Clinical Biochemistry issued a statement on the use of serum separator tubes in 1996. That document has been retired, but many laboratories still use it, and many of the issues it addresses remain.

Clinical & Forensic Toxicology News asked Catherine Hammett-Stabler, NACB president and co-chair of its TDM Guideline Committee, for an updated statement about the use of serum separator tubes:

“The pre-analytical aspects of therapeutic drug monitoring (TDM) were among the many areas deemed in need of further investigation by the National Academy of Clinical Biochemistry TDM Guideline Committee in 1996. This need for investigation continues today because even the most basic evaluations of collection or storage tubes are difficult (and costly) to conduct. In addition to the logistical issues of such a study, one has to remember that the product tested today may be different in the next lot due to differences in chemical sources, manufacturing changes, etc.

“My lab continues the practice we adopted many years ago of using non-gel tubes for serum-based TDM. These tubes are especially appropriate now that we’re using more chromatography-based analytical methods. While this practice continues to be right for us, it may not be for every lab. It is perhaps more important to keep in mind that *anything* the sample comes in contact with has the *potential* to cause interference *regardless* of the analytical method.”

camps: those who use gel barrier tubes and those who do not.

References

1. Quattrocchi F, Karnes HT, Robinson D, Hendles L. Effect of serum separator blood collection tubes on drug concentrations. *Ther Drug Monit* 1983;5:359–62.
2. Cai W, Leader G, Porter W, Chandler M. Influence of serum separator tubes on total and free phenytoin concentrations and dosage. *Ther Drug Monit* 1993;15:427–30.
3. Koch T, Platoff G. Suitability of collection tubes with separator gels for therapeutic drug monitoring. *Ther Drug Monit* 1990;12:277–80.
4. Landt M, Smith CH, Hortin GL. Evaluation of evacuated blood-collection tubes: effects of three types of polymeric separators on therapeutic drug-monitoring specimens. *Clin Chem* 1993;39:1712–7.
5. Parish R, Alexander T. Stability of phenytoin in blood collected in vacuum blood collection tubes. *Ther Drug Monit* 1990;12:85–90.
6. Warner A, Annesley T, eds. *Guidelines for therapeutic drug monitoring services*. Washington, D.C.: National Academy of Clinical Biochemistry, 1999.
7. Karppi J, Akerman K, Parviainen M. Suitability of collection tubes with separator gels for collecting and storing blood samples for therapeutic drug monitoring. *Clin Chem Lab Med* 2000;38:313–20.
8. Bush V, Blennerchasset J, Wells A, Dasgupta A. Stability of therapeutic drugs in serum collected in Vacutainer serum separator tubes containing a new gel (SST II). *Ther Drug Monit* 2001;23:259–62. Erratum in *Ther Drug Monit* 2001;23:738.
9. Drake SK, Bowen RAR, Bemaley AT, Hortin GL. Potential interferences from blood collection tubes in mass spectrometric analyses of serum polypeptides. *Clin Chem* 2004;50:2398–401.
10. Sampson M, Ruddel M, Albright S, Elin RJ. Positive interference in lithium determinations from clot activator in collection containers. *Clin Chem* 1997;43:675–9.
11. Yen HC, Hsu YT. Impurities from polypropylene microcentrifuge tubes as a potential source of interference in simultaneous analysis of electrochemical detection. *Clin Chem Lab Med* 2004;42:390–5.
12. Bowen RAR, Chan Y, Ruddel ME, et al. Immunoassay interference by a commonly used blood collection tube additive, the organosilicone surfactant silwet L-720. *Clin Chem* 2005;51:1874–82.

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Readers are invited to submit questions they would like answered by an expert. And an e-mailable PDF copy of this newsletter is available: cftnews@aacc.org.

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