Lidocaine Positives in Arkansas

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An examination of likely environmental exposure and the unusual ARCI medication rule on lidocaine

In late May, news broke that two of Bob Baffert's trainees, Charlatan and Gamine, who won races at Oaklawn on May 2, had unconfirmed post-race identifications (positive tests) for lidocaine on that day. Social media and the backstretches of many racetracks have been abuzz with speculation about the dual violations, ranging from "innocent until proven guilty" to "the horses were drugged." The results of the split sample testing, released just before press time for this issue, confirmed the presence of lidocaine, so it is worth a review of this therapeutic medication and where positives may come from.

Lidocaine identifications in post-race samples occur at a consistent rate of six to eight a year across the country, according to the Association of Racing Commissioners International (ARCI) database. When the lidocaine metabolite in the blood is identified, the levels are typically very low. Are these levels consistent with intentional administration close to race day or consistent with innocent environmental transfer of inconsequential amounts of lidocaine? The answer is in the science.

Lidocaine: What Is It?

Lidocaine is primarily used as a local anesthetic and is most commonly injected into the skin or close to nerves for the purpose of numbing the structure. Lidocaine is similarly used in people, often in dental procedures to block tooth pain. In veterinary medicine, lidocaine is used to numb the skin in the event of a cut or laceration to suture the wound.

Lidocaine also may be used as a regional anesthesia for lameness detection. Because horses are unable to explain why they have an uneven gait or lameness, veterinarians must deduce the source. For example, if a horse is lame as the result of a hoof abscess, the hoof is anesthetized with lidocaine or a similar local anesthetic injected over the nerve supply to the hoof. If the lameness is eliminated after such a "hoof block," the lameness has successfully been localized to the hoof region.

The final and less common application of lidocaine is for systemic pain control. Horses do not tolerate narcotic pain medications well, so in some cases, such as protracted abdominal pain (colic), lidocaine may be administered as a continuous infusion. This is usually done in a hospital setting because of the requirements for continuous infusion, such as through the use of an intravenous bag.

Lidocaine as a Banned Substance

Lidocaine is not a banned substance in racehorses, per se. It is recognized as a *therapeutic* substance, evidenced by its place on the Controlled Therapeutic Medication

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Schedule (CTMS), promulgated by the ARCI, as a part of the Uniform Medication Model Rules. In fact, it is expected that a veterinarian would use lidocaine in the normal course of a racetrack practice.

Because of this expectation, the CTMS includes a threshold for the primary metabolite of lidocaine, with a Class 2B penalty, absent mitigating circumstances (see sidebar, ARCI Uniform Classification Guidelines for Foreign Substances and Recommended Penalties Model Rule). Class 2 violations are for the substances second-most likely to affect the outcome of a race. This is a curious classification for lidocaine, because it cannot actually enhance the racing performance of a normal horse.

Why Regulate a Non-Performance-Enhancing Medication at All?

Lidocaine's use in veterinary medicine is unquestioned, and its ability to enhance performance in a sound horse is universally accepted as nil. However, performance enhancement is not the only reason that medications are regulated in sports that feature animals. Equally important is the regulation of substances that may adversely affect their health and welfare. There is no question that using a local anesthetic intentionally to block the pain of an injury in a horse, and thereby allowing it to race, is inappropriate. Therefore, the existing ARCI regulation that places a 2B penalty on the *intentional* use of such a substance, absent mitigating circumstances, is appropriate. However, if the science fails to support the published threshold, and the regulator is unable to substantiate how the threshold was developed, how can such severe penalties be imposed on trainers and owners? Further, could there be lidocaine detected in the blood or urine of a horse when no intentional administration has taken place? Of course, there can.

How Lidocaine Is Regulated

The logical regulation of therapeutic medications should allow for their therapeutic use, preclude performance-enhancing or pain-blocking effects at the time of the race and simultaneously prevent inappropriate positive tests as a result of innocent environmental transfer of small amounts of the substance. Unfortunately, as with other therapeutic medications, this logical and commonsense regulation of lidocaine did not occur when the thresholds were set by the Racing Medication and Testing Consortium (RMTC). When the lidocaine threshold was set, the focus was on how to prevent the use of it within 72 hours, and neither the lack of pharmacological effect at 72 hours nor the possibility of inadvertent environmental transfer was considered.

The medication rule for lidocaine presented by the ARCI is shown in figure 1. It states that the threshold is *"20 picograms per milliliter of total 3-0H-lidocaine in plasma or serum,"* with a withdrawal guideline of 72 hours. The supporting information is from *European Horseracing Scientific Liaison Committee data; Iowa State University study.* The National HBPA and North American Association of Racetrack Veterinarians, as well as scientists and regulated horsemen, have long been critical of therapeutic medication thresholds based on science that cannot be reviewed.

Why 3-Hydroxylidocaine?

When medications are administered to horses, or any other animals, they are modified and ultimately eliminated by the animal's body. Typically, the liver facilitates the elimination of substances in the urine, although the animal's body may use other means of disposal, depending on the substance.

To exert its anesthetic effect, which lasts just under two hours, lidocaine is injected around nerves. Its blood concentration peaks rapidly at about 20 minutes and then drops off. The rate at which lidocaine is eliminated from the blood depends on how it is metabolized. It is rapidly converted into related molecules, called metabolites, the most abundant of which is 3-hydroxylidocaine glucuronide.

The regulation of lidocaine is somewhat unique in horse racing, in that the inactive glucuronide form of the molecule is the regulated analyte in blood. The reasons for this are unclear because the research data from which this threshold was derived have never been published or presented. However, because the 3-hydroxylidocaine glucuronide remains in the blood for a prolonged period after lidocaine administration, it appears to be the only means to identify lidocaine 72 hours after its use.

The animal's liver works very hard to render medications inactive and ready for elimination from the body. One of the mechanisms the liver employs to accomplish this is to add a glucuronide to the molecule. This addition, such as in the case of lidocaine, renders the molecule inactive and considerably more soluble in water, making it readily eliminated at relatively high concentrations in the urine. As a consequence of this metabolic pathway, many substances that are glucuronidated are regulated by their level in urine and not in blood. The regulation of lidocaine by 3-hydroxylidocaine in blood requires a step in the testing process that is typically reserved for urine testing, and that is the process of hydrolysis, or removal of the glucuronide from the molecule before testing.

Where Does the Current Science Stand on 3-Hydroxylidocaine?

Recent research from Dr. Lawrence Soma at the University of Pennsylvania provides insight into the pharmacokinetics of lidocaine administered to horses. It confirms that 3-hydroxylidocaine, as its inactive glucuronide form, is found in the blood of treated horses. However, this research also shows that lidocaine itself is found at higher concentrations in blood at all times, points during which there is a pharmacological effect and beyond. Since the relevant effect on the animal results from lidocaine and not its inactive 3-hydroxy metabolite, there is no good relationship between the threshold and the effect of lidocaine on the horse. It is a snapshot of a medication administration or exposure in the past with no relevance to its effect on the horse at the time of the race.

The ARCI withdrawal time guideline appears to be taken solely from the European Horseracing Scientific Liaison Committee's 72-hour detection time (figure 2), with no actual relationship to the dose recommendation suggested in the CMTS. Detection times as employed by the EHSLC differ greatly from recommended withdrawal times, because they are based simply on the longest time of detection among usually six or so horses, as shown in figure 2. A substantially longer time period must be used for a withdrawal time to account for individual variation between horses. In clinical practice, almost no racetrack

Lidocaine	20 picograms per milliliter of total 3-0H-lidocaine in plasma or serum	72 hours	200 milligrams of lidocaine as its hydrochloride salt administered subcutaneously	European Horseracing Scientific Liaison Committee data; Iowa State University study	Applies to total major hydroxylated metabolite (i.e., includes conjugates)

Figure 1. The ARCI threshold, withdrawal guideline, dose and route of administration for lidocaine

Detection Times				
Substance	Preparation	Dose	Route of Administration (No. of horses)	Detection Time (hours)
Lidocaine	Norocaine® Norbrook Laboratories	300mg/15ml, single dose 60mg/3ml, single dose	s/c(6) s/c(6)	72 ↑

Figure 2. European Horseracing Scientific Liaison Committee's detection time for lidocaine

practitioner actually uses lidocaine at any dose within 72 hours of racing because of the high degree of uncertainty with the RMTC/ARCI recommended withdrawal times.

The source of ARCI's regulatory threshold of 20 pg/ml in blood for 3-hydroxylidocaine remains elusive. No scientific data were available when the threshold was originally set, and the subsequent University of Pennsylvania study does not lend support to the threshold. It would seem likely that 20 pg/ml was the lower limit of quantitation of the analytical procedure when the regulatory threshold was set. What remains completely unclear, however, is 1) why the ARCI chose to adopt a lidocaine threshold unrelated to any published science and unsupported by the subsequent science that has been published, and 2) why they chose to go with the more cumbersome analytical procedure of the 3-hydroxylidocaine glucuronide metabolite when the more direct analysis would be for the parent substance, lidocaine.

The High No-Effect Dose of Lidocaine

Threshold research on lidocaine as a therapeutic medication has previously been presented in the veterinary scientific literature in peer-reviewed papers. In the 1990s, the Tobin group proposed regulation of local anesthetics based on the concept of the high no-effect dose (HNED, the amount slightly below what could cause an effect), and they published a series of scientific articles on the subject. In the case of lidocaine, this dose was 4 mg. Next, they identified the lidocaine metabolite levels associated with this dose. The peak blood concentration of the HNED of lidocaine at 20 minutes after injection was about 2,000 pg/ml, and at 120 minutes, the timeframe when all possible effect had worn off, the level was about 400 pg/ml. This indicates that no possible effect of the lidocaine could be present at a threshold of 400 pg/ml.

The High Sensitivity of Current Testing Technology

As we have repeatedly laid out in these pages, the sensitivity of drug testing of horses has increased to a level unparalleled in history. Liquid chromatography-tandem mass spectroscopy (LC-MS/MS) is a technology that has revolutionized every branch of science that looks at molecules, including drug testing. In 1999, there were 95 articles utilizing LC-MS/MS in PubMed, the database that chronicles scientific publications. In 2019, that number had exploded to 3,410. The LC-MS/MS concept was so groundbreaking that the scientists (Fenn, Tanaka and Wuthrich) who developed the technology behind it received the Nobel Prize in 2002. This technology opened the door to being able to almost simultaneously separate and identify thousands of compounds that may be present in a drug sample. While clearly a benefit to the drug-testing industry because very minute quantities of many substances can be detected in blood and urine samples, the logic of regulating therapeutic substances at these levels must be questioned. At the very least, the scientific evidence behind the promulgated thresholds must be available for inspection.

Environmental Sources of Lidocaine

The end result of the highly sensitive nature of drug testing in horse racing is that many positive tests result from inadvertent environmental transfer of drugs from either the people around and handling the horses or the stalls in which the horses are kept prior to the race. Lidocaine is a long "off-patent" medication, widely available as a generic prescription medication and listed as the 216th most commonly prescribed medication in 2016. It is also readily available in non-prescription strength as both patches and creams

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(Salonpas, Icy Hot Patch, Aspercreme), which have been shown to be as effective as the prescription preparations. Lidocaine is stable in the environment and readily absorbed by animals through the skin. As such, lidocaine is a classic environmental transfer substance. It has been identified in 90 percent of landfill runoffs at a level of up to 147 pg/ml, and as high as 500 pg/ml in streams in the southeastern United States. Additionally, when receiving stalls at Charles Town Races were investigated for the presence of medications, lidocaine was among those identified (*The Horsemen's Journal*, Winter 2017).

Confidentiality laws governing human medical records preclude employers from questioning employees about their existing medical conditions or prescribed medications. This opens a panoply of potential sources of contamination of racehorses by casual contact with humans. Employees of trainers, racetracks and racing commissions come into contact with horses and could serve as the source of inadvertent transfer of lidocaine. Assuming that horses absorb lidocaine in a similar manner to humans, it would require 1/40th of a milliliter (1/100th of a teaspoon) of lidocaine cream to cause a positive test at a level of 100 pg/ml of the 3-hydroxylidocaine metabolite in blood.

Legal Issues Surrounding a Randomly Assigned Threshold

The ARCI model rule on lidocaine is concerning because the threshold, withdrawal guidelines and dosing specifications are not supported by published science. This concern becomes critically important relative to a state-issued occupational license. A horseman's license is "a property interest sufficient to invoke the protection of the due process clause." *Barry v. Barchi*, 433 US 55, 64 (1979). Therefore, a license may not be taken or suspended without both procedural and substantive due process.

Procedural due process requires the right to reasonable notice of the alleged violation and the opportunity to be heard "at a meaningful time and in a meaningful manner." *Armstrong v. Manzo*, 380 US 545, 552 (1965). Substantive due process requires a rational relationship between a legitimate governmental purpose of a rule and the means selected for the desired end. This means there must be a nexus or rational relationship between the ARCI rule and the means chosen for that desired end—such as maintaining and preserving the integrity of racing.

RMTC-accredited laboratories are capable of detecting substances, including lidocaine and metabolites such as 3-hydroxylidocaine glucuronide, at thresholds far below what has been seen before. As in the case of lidocaine, the unit of measure is a picogram. A picogram is one-one billionth of a gram; in lay terms, one second is one-one billionth of your life when you are 32,000 years old. This is significant relative to the licensee's substantive due process rights.

The principles of substantive due process require that a racing commission, in the case of therapeutic mediations such as lidocaine, establish race-day thresholds. In the case of lidocaine, 20 pg/ml of total 3-hydroxylidocaine glucuronide in plasma or serum should reflect a scientifically accepted correlation. In short, there must be a rational relationship between the level or concentration of the controlled therapeutic medication and the potential for such concentration to affect and aid the performance of the equine athlete.

The current threshold for lidocaine is apparently established not by regulatory science but rather by the technical limit of detection of testing technology. Thus the threshold is subject to change based on the next new and improved model of laboratory testing equipment and not on scientific testing, data or proof. When a published threshold for an otherwise permissible substance is exceeded, but there is an absence of scientific proof that the amount detected is sufficient to affect performance, that results in the rule/threshold being subject to scientific attack on the basis of a violation of the licensee's due process rights, as well as being subject to an argument that the threshold is arbitrary and capricious by definition. For example, in the case of Princess of Sylmar, the runner-up in the 2014 Delaware Handicap, after a betamethasone overage

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in her post-race sample, the Delaware Park stewards opted not to move forward on the case when it became apparent that the RMTC guidelines for betamethasone, which had been adopted in the state, were not subject to peer review and were not grounded in science. The ARCI's current rule regarding lidocaine would likely be subject to the same ruling in a court of law based on its lack of peer-reviewed and published scientific data, testing and bases.

Good Faith Investigation of Positive Tests

The sensitivity of LC-MS/MS testing of horse racing has outpaced commonsense regulation. The extent of investigation in most jurisdictions is limited to the testing of a split sample to confirm the primary laboratory's identification. A significant proportion of positive tests are for substances susceptible to environmental transfer. It is the goal of all participants in horse racing to compete on a level playing field, with clean, healthy competitors, and for the best horse on the day to win the race. Regulations should not have a Russian roulette effect in which random horses are taken down and trainers penalized for irrelevant concentrations of medications that have no effect on racing. Each positive test for therapeutic medications for humans or horses should have a thorough forensic investigation, both of the circumstances surrounding the horses and also of the complete chemistry of the blood and urine or other sample.

Such an investigation for a lidocaine positive would include testing of both the blood and urine for the parent molecule lidocaine and the 3-hydroxy metabolite. For example, if a horse was inadvertently exposed to an environmental trace of lidocaine close to post time, it is not inconceivable that the urinary concentrations of the 3-hydroxy metabolite would be below the EHSLC regulatory threshold, fully consistent with a small level of exposure and potentially mitigating/exculpatory evidence. This would be the case if the trace transfer occurred in the paddock from a groom, the trainer or the identifier or even the assistant starter on the track.

The take-home message of this article is simple: Low-level identifications for many substances, including lidocaine, commonly result from inadvertent transfer to the horse from its environment. Substances widely available over the counter, such as lidocaine, will continue to pose problems for racing commissions and horsemen alike until the industry takes the approach of conducting thorough, legitimate and appropriate forensic investigations. Levels of substances at high risk for environmental transfer to the horse should be carefully evaluated. When such substances exhibit levels consistent with environmental transfer, these facts can and should be used as mitigating circumstances in determining the penalties. **HJ**

The ARCI Uniform Classification Guidelines for Foreign Substances and Recommended Penalties Model Rule, as amended in January 2020, classify lidocaine as a Class 2 drug. Class 2 substances are defined as:

Drugs that have a high potential to affect performance, but less of a potential than drugs in Class 1. These drugs are 1) not generally accepted as therapeutic agents in racing horses, or 2) they are therapeutic agents that have a high potential for abuse. Drugs in this class include psychotropic drugs, certain nervous system and cardiovascular system stimulants, depressants, and neuromuscular blocking agents. Injectable local anesthetics are included in this class because of their high potential for abuse as nerve blocking agents.

The corresponding recommended penalty for a lidocaine positive is a Class B penalty. A licensed trainer with a first-time positive test for lidocaine, absent mitigating factors, faces the following Class B penalty: A minimum 15-day suspension. The presence of aggravating factors may result in a maximum 60-day suspension. Additionally, the licensed trainer faces a minimum fine of $500, absent mitigating circumstances. The presence of aggravating factors may result in a fine of $1,000.

If the violation is a second offense, the minimum period of suspension is 30 days, absent mitigating factors, and a maximum of 180 days if aggravating factors are determined. A second offense carries a minimum fine of $1,000, absent mitigating circumstances, and a maximum fine of up to $2,500 if aggravating factors are present. Finally, if the positive result for lidocaine is a third offense within a 365-day period, in any jurisdiction, the penalty is a minimum of a 60-day suspension, absent mitigating circumstances, with a maximum suspension of one year if aggravating circumstances are present. Also, if the positive constitutes a third offense, the licensed trainer faces a minimum fine of $2,500, absent mitigating circumstances, and a maximum fine of $5,000 or 5 percent of the purse, whichever is greater, should aggravating factors be involved. In addition, the state commission may take any additional action deemed necessary.

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