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Review of the Current Status of Thresholds/Withdrawal Time Guidelines for Therapeutic Medications in Performance Horses

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About 50 medications with potential to affect performance are regulated during competition. Optimal regulation is by concentration thresholds in plasma and urine. Equally important, veterinarians and horsemen need scientifically established "withdrawal times" linked to these thresholds. Thresholds and available withdrawal times in North America and elsewhere are reviewed; this thresholds based approach allows optimal use of therapeutic medications in performance horses and also allows immediate standardization of medication testing. Authors' addresses: 128C Maxwell Gluck Equine Research Center, University of Kentucky, Lexington, KY 40546 (Spencer, Karpiesiuk, Hughes, Tobin); Animal and Food Sciences Department, University of Kentucky, Lexington, KY 40456 (Camargo); Florida's Benevolent and Protective Association, Opa Locka, FL 33056 (Stirling); and Research Centre in Reproductive Medicine, University of Auckland, New Zealand (Casey); e-mail: ttobin@uky.edu. *Presenting author.

1. Introduction

Therapeutic medications are medications approved for use in horses in training with the goal of protecting the health and welfare of horses. Many medications have no direct effects on equine physiology and are of little regulatory interest.[1] On the other hand, many medications directly influence physiological systems in horses and thus have the potential to influence performance. These medications are generally considered inappropriate in horses during performance events, and use of these substances close to competition is generally regulated by post-event testing.[2]

Medication testing now readily detects substances at low part per trillion or lower concentrations,[3] thereby detecting ineffective residual traces of therapeutic medications. In lay terms, chemists can detect "tail-end" traces of therapeutic medications for days to weeks after cessation of treatment. What is urgently needed is a mechanism for limiting the sensitivity of testing for therapeutic medications.[4]

2. Limited Sensitivity Testing: Evaluating the Canadian Approach

The matter of limiting the sensitivity of testing for therapeutic medications was reviewed at an international workshop in Kentucky in 1994.[5] This

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workshop endorsed the Canadian approach, which was defined as "the deliberate non-selection of unnecessarily sensitive analytical methods for specific substances". Simply put, when the Canadians had developed a suitable analytical method, they "froze" the method and generated "withdrawal time guidelines" to assist horsemen in avoiding "positive" identifications for therapeutic medications.[5] Furthermore, the Canadians published a booklet setting forth "withdrawal time" guidelines for ~70 therapeutic medications, as a guide to veterinarians and horsemen.[6] Additionally, when the Canadians introduced a new test for a therapeutic medication, they alerted horsemen to the change in advance and allowed a grace period for horsemen to adapt to the new testing technology,[5] as recently has been done in California during the introduction of a new flunixin threshold.

3. U.S. Endorsement of the Canadian Approach

This Canadian approach was endorsed by the Association of Racing Commissioners International (ARCI) at their National Conference in Oklahoma City Oklahoma in April 1995, as follows[4]:
"The Association of Racing Commissioners International. . . recommends that its members specifically implement procedures to have an official veterinarian or veterinary consultant review findings for ARCI class 4 and 5 substances to address "trace" level detection so as not to lead to disciplinary action based on pharmacologically insignificant traces of these substances."

4. Identifying the Therapeutic Medications

The next problem was identifying the actual therapeutic medications.[5] In 2002, the Mid-Atlantic Regional Medication Meeting[7] addressed this problem by compiling a list of 32 medications, and at about the same time, the AAEP also addressed this matter. The Arthur Committee AAEP listing of ~50 therapeutic medications with recommended dosage schedules and frequencies of dosing has been largely adopted by the Racing Medication and Testing Consortium (RMTC)/ARCI, as set forth in Table 1.

5. The Matter of "Pharmacologically Insignificant Traces of These Substances"

Once a therapeutic medication has been identified, the next question is the matter of specifying the "pharmacologically insignificant traces of these substances." To understand this problem, a single 3-g dose of phenylbutazone contains ~6,000,000,000,000,000,000,000 (6 followed by 21 zeros) molecules, approximately the number of stars in the known universe. Large as this number is, the horse wastes no time with such an administration. The horse will eliminate about one half of the dose within about the first 7 h, and one half of the remaining half again in the next 7 h, and so forth until the phenylbutazone is completely eliminated. If the horse happens to eliminate phenylbutazone with a half-life of 7.22 h, 90% of the amount of phenylbutazone in its body is eliminated daily. In

Table 1. RMTC Therapeutic Medications Routinely Used and Identified as Necessary by the Veterinary Advisory Committee

First priority group (currently in research)
1. Acepromazine
2. Butorphanol
3. Detomidine
4. Glycopyrrolate
5. Lidocaine
6. Mepivacaine
7. Methocarbarnol
8. Pyrilamine
Second priority group
9. Boldenone
10. Stanozolol
11. Testosterone
12. Dantrolene
13. Dexamethasone
14. Fluphenazine
15. Hydroxyzine
16. Nandrolone
Third priority group
17. Albuterol
18. Betamethasone
19. Diclofenac
20. Methylprednisolone
21. Reserpine
22. Triamcinolone
23. Trichlormethiazide
24. Xylazine
Fourth priority group
25. Atropine
26. Beclomethasone
27. Buscopan
28. Cromolyn
29. Isoxsuprine
30. Pentoxyfylline
31. Phenytoin
32. Prednisolone
Fifth priority group
33. Diazepam
34. Dipyrone
35. Flurprednisolone
36. Guaifenesin
37. Isoflupredone
38. Prednisone
Research already underway
39. Aminocaproic acid
40. Carbazochrome
41. Clenbuterol
42. Procaine penicillin
Already in body of model rules
43. Cimetidine
44. DMSO
45. Flunixin
46. Furosemide
47. Ketoprofen
48. Omeprazole
49. Phenylbutazone
50. Ranitidine

This table is reproduced courtesy of Dr. Scot Waterman and the Racing Medication and Testing Consortium. For each of these therapeutic medications, the RMTC is developing appropriate regulatory thresholds in plasma or urine and associated withdrawal time guidelines (January 2008).

Table 2: Current Thresholds/Regulatory Limits

	Medication	Concentration	Fluid	Jurisdiction
1)	Acepromazine	10 ng/ml	urine	OH
		25 ng/ml	urine	CA, WA, NM, LA
2)	Albuterol	1 ng/ml	plasma	LA, OK
		1 ng/ml	urine	CA, NM, WA
		5 ng/ml	urine	LA
3)	Arsenic	200 ng/ml	urine	TX
		300 ng/ml	urine	Intl
4)	Atropine	10 ng/ml	urine	CA, NM
		70 ng/ml	urine	OK
		75 ng/ml	urine	LA
5)	Benzocaine	50 ng/ml	urine	CA, WA, NM
6)	BZE*	50 ng/ml	urine	WA, unattributed
	(Benzoylecgonine)	100 ng/ml	urine	FL
		150 ng/ml	urine	IL, OH, LA, OK
		< 1 ng/ml	plasma	LA
7)	Betamethasone	60 ng/ml	urine	OH
8)	Boldenone	15 ng/ml (intact males only)	urine	ARCI, Intl, CA, DE
		< 200 pg/ml	plasma	PA (interim)
9)	Bupivacaine	5 ng/ml	urine	OH, WA
10)	Butorphanol	10 ng/ml	urine	OH
11)	Caffeine	250 ng/ml	serum	Canada
		1,000 ng/ml	urine	Canada
		10 ng/ml	plasma	Hong Kong, Jockey Club Brasileiro
		30 ng/ml	urine	Hong Kong
		100 ng/ml	urine	OK, OH, LA
		200 ng/ml	urine	FL
		25 ng/ml	plasma	LA
		100 ng/ml	plasma	WA, OR, MD, NE
12)	Carbon Dioxide	36 millimoles/L	plasma	Intl
13)	Clenbuterol	0.5 ng/ml	plasma	LA
		15 ng/ml	urine	LA
		1 ng/ml	plasma	OK
		1 ng/ml	urine	OH
		25 pg/ml	plasma	KY, WA, CA
		5 ng/ml	urine	CA, NM
14)	Dantrolene	100 ng/ml	plasma	OH, OK
15)	Dexamethasone	60 ng/ml	urine	OH
		100 ng/ml	urine	LA
		3 ng/ml	plasma	USEF
16)	Diclofenac	5 ng/ml	plasma	KY, OK, USEF
17)	Dimethylsulfoxide	500,000 ng/ml	urine	IL
		10,000 ng/ml	urine	OH
		10,000 ng/ml	plasma	KY, OR
		15,000 ng/ml	urine	Intl
		1,000 ng/ml	plasma	Intl, OK
18)	Dipyrone	1,000 ng/ml	plasma	OK, Jockey Club Brasileiro
19)	Eltenac	100 ng/ml	plasma	USEF
20)	Firocoxib	240 ng/ml	plasma	USEF
21)	Flumethasone	10 ng/ml	urine	OH
22)	Flunixin	20 ng/ml	plasma	RMTClAR, IL, KS, OH, WA, KY, MN, MD, IA, VA
		1,000 ng/ml	plasma	USEF, ID, NM
		500 ng/ml	plasma	CO
		250 ng/ml	plasma	OK
		40 ng/ml	plasma	Sweden
		50 ng/ml	plasma	CA, LA
		25 ng/ml	plasma	OR
	[Flunixin Subthreshold]	2 ng/ml	plasma	LA

Table 2: Continued

	Medication	Concentration	Fluid	Jurisdiction
23)	Furosemide	100 ng/ml	plasma	RMTC , Others, Jockey Club Brasileiro, TX, OR, CA, KY, MN, DE, MD, IL
		80 ng/ml	plasma	ID
		50 ng/ml	plasma	OK
24)	Glycopyrrolate	60 ng/ml	urine	OH
25)	Hydrocortisone	1,000 ng/ml	urine	OH, Intl
26)	Ibuprofen	100 ng/ml	serum	KY
27)	Imipramine	20 ng/ml	plasma	Jockey Club Brasileiro
28)	Indomethacin	50 ng/ml	plasma	Jockey Club Brasileiro
29)	Isoflupredone	60 ng/ml	urine	OH
30)	Isoxsuprine	1,000 ng/ml	urine	IL, OH
31)	Ketoprofen	10 ng/ml	plasma	RMTC, AR, IL, KS, LA, CA, WA, OR, KY, MN, CO, IA, OH
		250 ng/ml	plasma	USEF
		100 ng/ml	plasma	OK
		50 ng/ml	plasma	NM
	[Ketoprofen Subthreshold]	0.5 ng/ml	plasma	LA
32)	Lidocaine	25 ng/ml	plasma	Jockey Club Brasileiro
		< 1 ng/ml	plasma	LA
		50 ng/ml	urine	OH, WA
		25 ng/ml	urine	LA, OK
33)	Meclofenamic Acid	1,000 ng/ml	plasma	OH, KY, NM, ID
		2,500 ng/ml	plasma	USEF
34)	Mephenesin	200 ng/ml	plasma	Jockey Club Brasileiro
35)	Mepivacaine	5 ng/ml	urine	OH
		10 ng/ml	urine	CA, WA, NM
		25 ng/ml	urine	LA
36)	Methocarbamol	1,000 ng/ml	plasma	OH, OK
		4,000 ng/ml	plamsa	USEF
37)	Methoxytramine	4,000 ng/ml	urine	Intl
38)	Methylprednisolone	1,000 ng/ml	urine	OH
39)	Morphine	120 ng/ml	urine	LA
		100 ng/ml	urine	OK
		50 ng/ml	urine	England, OH, WA
		< 1 ng/ml	plasma	LA
40)	Naproxen	40,000 ng/ml	plasma	USEF
		10,000 ng/ml	plasma	OH
		5,000 ng/ml	plasma	ID
		750 ng/ml	plasma	OK
41)	Nandrolone	1 ng/ml (geldings, fillies, mares)	urine	ARCI, CA, DE
		45 ng/ml (intact males only)	urine	WA, CA
		< 200 pg/ml	plasma	PA (interim)
42)	Oxyphenbutazone	5,000 ng/ml	plasma	N. Am., RMTC/ARCI, AZ, AR, FL, KS, IL, OH, LA, MT, ID, NM, CO, IA, WV, DE
		165,000 ng/ml	urine	LA, MT, WV
43)	Pentazocine	50 ng/ml	urine	OH
44)	Phenylbutazone	5,000 ng/ml	plasma	N. Am., ARCI, AZ, AR, IL, KS, FL, LA, TX, CA, NM, ID, WA, OR, MI, IA, CO, KY, MN, MT, OK, VA, WV, WY
		700 ng/ml	plasma	Jockey Club Brasileiro
		2,000 ng/ml	plasma	PA, MD
		2,500 ng/ml	plasma	DE
		15,000 ng/ml	plasma	USEF
		165,000 ng/ml	urine	LA, ID, MA, MT, WV
	[Phenylbutazone Subthreshold]	1 ng/ml	plasma	RMTC/ARCI, LA

Table 2: Continued

	Medication	Concentration	Fluid	Jurisdiction
45)	Prednisolone	1,000 ng/ml	urine	OH
46)	Prednisone	100 ng/ml	urine	OH
47)	Procaine	750 ng/ml	urine	Hong Kong
		5 ng/ml	plasma	LA
		25 ng/ml	plasma	Canada, OK
		100 ng/ml	plasma	Jockey Club Brasileiro
		50 ng/ml	urine	OH, LA
		10 ng/ml	urine	CA, NM
		25 ng/ml	urine	WA
48)	Promazine	20 ng/ml	plasma	Jockey Club Brasileiro
		50 ng/ml	urine	OH
		25 ng/ml	urine	CA, WA, NM
49)	Pyrilamine	5 ng/ml	plasma	Jockey Club Brasileiro
		50 ng/ml	plasma	OK
		50 ng/ml	urine	WA, OH
50)	Salicylates	750,000 ng/ml	urine	CA, WA, OH, NM
51)	Salicylic Acid	750,000 ng/ml	urine	OH, Intl, TX
		6,500 ng/ml	plasma	Intl
		65,000 ng/ml	plasma	OK
52)	Scopolamine	75 ng/ml	urine	LA
53)	Stanozolol(16βa-hydroxystanozolol)	1 ng/ml	urine	ARCI, CA
		<200 pg/ml	plasma	PA (interim)
54)	Strychnine	100 ng/ml	urine	OK, LA
55)	Sulfa Drugs	1,000 ng/ml	urine	OR
56)	Terbutaline	10 ng/ml	urine	OH
57)	Testosterone (epitestosterone)	20 ng/ml (geldings)	urine	Intl, ARCI, CA
		55 ng/ml (fillies & mares)	urine	Intl, ARCI, CA
		< 200 pg/ml (females & geldings)	plasma	PA (interim)
		< 1000 pg/ml (intact males)	plasma	PA (interim)
58)	Tetramisole	80 ng/ml	plasma	Jockey Club Brasileiro
59)	Theobromine	2,000 ng/ml	urine	OH, USEF, TX, WA
		400 ng/ml	urine	FL
60)	Theophylline	400 ng/ml	urine	FL

*BZE is the major urinary metabolite of cocaine.

simple terms, every day a zero "drops off" the original number of molecules, and by about day 21, the number of phenylbutazone molecules left in the horse will be about zero.[4,8] The take-home message is that the therapeutic effect of phenylbutazone is lost after ~24 h, but detectable "traces" of the medication remain in the body for 20 days. A threshold is therefore an instruction to the chemist not to report identifications below the threshold concentration, because these concentrations are "pharmacologically insignificant traces (concentrations) of these substances."[4]

6. Defined Regulatory Thresholds

In the United States, the approach has been to specify the threshold as a concentration of a specific analyte in a specific matrix, for example, 5 μg/ml of phenylbutazone in plasma. As well as being the best approach scientifically, this approach is virtually mandated in the United States, because the large number of testing laboratories and techniques in the United States makes the approach of "standardization" of the tests themselves extremely challenging.

7. The First Regulatory Thresholds: Urinary and Then Plasma Thresholds for Phenylbutazone

The earliest (pre-1980) regulatory threshold in place in the United States was for urinary "phenylbutazone and its metabolites" at 165 μg/ml.[9] However, in the early 1980s, following the introduction of "The Corrupt Horseracing Practices Act," a plasma threshold for phenylbutazone of 2 μg/ml was introduced.[10] This threshold was later adjusted upward to 5 μg/ml in plasma, assisted by contributions on the "masking" problem from our group.[11,12] This 5-μg/ml threshold in plasma gained broad acceptance in the United States and was adopted by the RMTC/ARCI.

8. Plasma Threshold for Furosemide

The Corrupt Horseracing Practices Act also focused attention on furosemide. In this area, the AAEP identified 250 mg IV of furosemide at 4 h before post as an appropriate treatment for exercise-induced pulmonary hemorrhage (EIPH), and it was soon established that this regimen did not interfere with urinary drug detection.[10,13] This "4-h rule" was

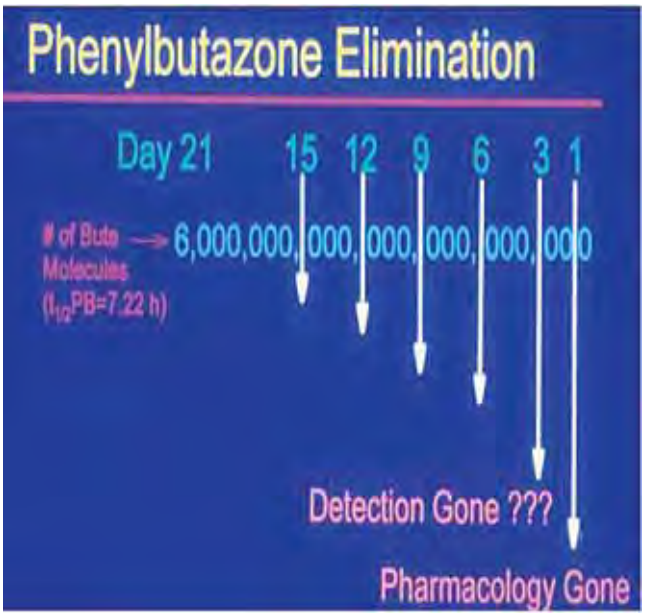

Fig. 1. Phenylbutazone Elimination: When a dose of phenylbutazone is administered to a horse, more phenylbutazone molecules are administered than there are stars in the known universe, that is about 6 followed by 21 zeros molecules, a very large number of molecules. Pharmacology is lost when the first 90%, or the first zero, is eliminated. The threshold is an instruction to the chemist to ignore the remiaming approximately 6×10^{20} molecules or thereabouts.

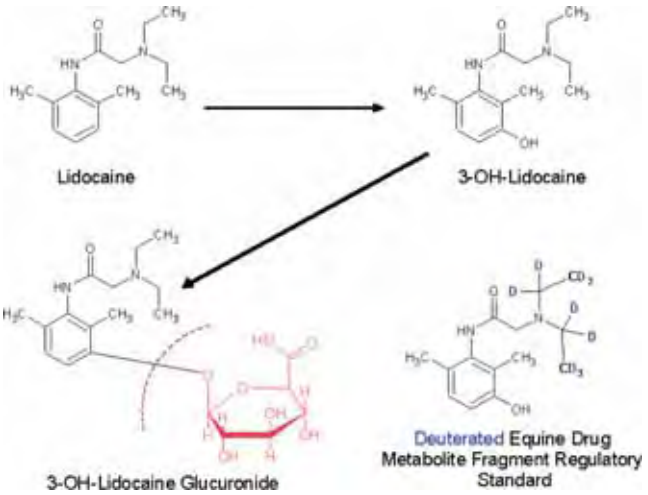

Fig. 2. Lidocaine Metabolism: Lidocaine is first metabolized to 3-hydroxylidocaine, which is then linked to glucuronic acid, yielding 3-hydroxylidocaine glucuronide, a highly water-soluble molecule. Drug testing programs are generally not structured to handle highly water-soluble molecules, so the chemist "hydrolyzes the urine sample" using the enzyme beta-glucuronidase, yielding free 3-hydroxylidocaine, which is then recovered from the urine sample and analyzed following the same general principles as for lidocaine.

first enforced by detention barns, but in the early 1980s, the Kentucky Horsemen's Benevolent and Protective Association commissioned a study to establish an equivalent plasma threshold for furosemide. Experimental work on 49 horses suggested 30 ng/ml as an appropriate plasma threshold for furosemide[14]; for regulatory application, this threshold was increased to between 50 and 100 ng/ml. Additionally, current regulatory protocols are based on preliminary screening of urine samples to identify those with a specific gravity of $<$1.010, at which point interference with drug detection becomes a concern. In such cases, the blood sample is analyzed for furosemide, and if the plasma concentration of furosemide is $>$100 ng/ml, an offense may be deemed to have occurred.[15] This regulatory protocol was well established in North America by 2000 and was also adopted by the RMTC/ARCI.

9. Other Regulatory Thresholds in Plasma

As well as phenylbutazone, two other non-steroidal anti-inflammatory medications, flunixin and ketoprofen, are AAEP/RMTC/ARCI approved for use in horses. More recently, the RMTC/ARCI has proposed a 20-ng/ml plasma threshold for flunixin, apparently based on use of this threshold in the mid-Atlantic area,[7] and this threshold has been adopted by a number of states. In California, however, research on ~20 horses in training has suggested a 50-ng/ml plasma threshold for flunixin, and this threshold is now in place in California, along with a 10-ng/ml threshold for ketoprofen, both with suggested 24-h withdrawal times.[16] Similarly, California has in place a clenbuterol regulatory threshold of 25 pg/ml in plasma, with a suggested 96-h withdrawal time, based on in-house research in California on ~20 horses in training.[16]

These are the principal scientifically defined plasma thresholds in place today in the United States. The majority, although not all, of the other in place thresholds are in urine, which thresholds are both scientifically more difficult to justify and technically more difficult to implement than plasma thresholds.[17]

10. Urinary Thresholds for Therapeutic Medications

With regard to the implementation of thresholds in urine, there are two major technical challenges: in the first place, it is often technically difficult to accurately quantify the actual threshold substance in urine, and second, it may also be difficult to establish that the regulatory threshold truly represents a "pharmacologically insignificant traces (concentrations) of these substances," as we will now detail for lidocaine.

11. Urinary Thresholds: Quantifying Urinary Drug Metabolites

When you administer lidocaine to a horse, what the chemist finds in the urine sample is generally not lidocaine, but lidocaine metabolites. Among these,

the one that racing chemists chose to focus on was 3-hydroxylidocaine glucuronide, so this was the urinary metabolite selected for our urinary threshold evaluation work.[18,19] Based on the work done in our laboratory, in which we carefully defined the relationships between dose of lidocaine, its local anesthetic effect, and urinary drug metabolite concentrations, we suggested that concentrations of 3-hydroxylidocaine of <310 ng/ml recovered from urine were likely to be "pharmacologically insignificant traces (concentrations) of these substances."[19,20]

We extended this research to cover a number of other local anesthetics, and our work in this area became an invited review in the *Journal of Veterinary Pharmacology and Therapeutics*[4]; this research essentially established a scientific basis for the regulation of therapeutic medications by the use of urinary thresholds, although it should be clearly understood that regulatory thresholds based on plasma concentrations of parent medication are scientifically and forensically much more satisfactory and should always be used when appropriate technology is available.[4]

12. Currently in Place Thresholds in North America

In a project supported by the National Horsemen's Benevolent and Protective Association, we have recently reviewed the in place thresholds in North America for the RMTC/ARCI therapeutic medications, as set forth in Table 2; the full document can be reviewed at www.hbpa.org. This table sets forth, to the best of our ability, the currently in place concentration thresholds in North American racing and worldwide for therapeutic medications, endogenous, dietary, and environmental substances, and much of these data were obtained from racing authority websites. As such, the information presented in Table 2 is subject to change by the relevant racing authorities, and Table 2 represents our best analysis of the information available as of May 2008.

13. The Pressing Need: Withdrawal Time Guidelines

Regulatory thresholds, as defined verifiable concentrations, are independently quantifiable and form the scientific basis of medication regulation, especially so if medication regulations are standardized between different laboratories, jurisdictions, or nations. On the other hand, a regulatory threshold, expressed as a concentration in plasma or urine, is not a particularly useful piece of information to horsemen and veterinarians, who need explicit guidelines as to when to withdraw a medication to avoid exceeding the regulatory threshold.[9]

This information is called a "withdrawal time guideline" and is expressed as the time before post at which the last medication administration is unlikely to exceed the threshold. As such, the withdrawal time guideline is generally expressed in terms of the number of days that the medication must be withdrawn, but it is also important to define the specific dose and or number of daily doses and number of days and is best expressed in terms of a specific medication formulation. This is because the withdrawal time is clearly affected by dose, to a lesser extent, by the number of doses administered, and possibly by the formulation of the medication.[9]

At this time, the most detailed withdrawal time guideline data published for an equine therapeutic medication is that for furosemide,[14] as referenced above. More recently, as set forth above, studies have been performed in California on flunixin, ketoprofen, and clenbuterol, apparently involving ~20 horses in training, and on which the California thresholds are reportedly based, but these studies are currently unpublished in the scientific literature.

Finally, no withdrawal time guideline is foolproof. A withdrawal time guideline is simply a guideline, and given the numerous variables involved in medication formulation, administration, bioavailability, metabolism, and interaction with other medications and unique aspects of the animal's physiology, there is always a statistical probability of exceeding the regulatory threshold.[9] The probability may be small; for example, the calculated probability of exceeding the first proposed 30-ng/ml regulatory threshold for furosemide was <1 in 1000, a small probability in terms of an individual horse.[14] On the other hand, however, if a jurisdiction tests 10,000 samples per year, this 1 in 1000 probability means 10 innocent or statistical "overages" in a year, supporting the widespread regulatory practice of increasing the furosemide regulatory threshold to 100 ng/ml, as has been adopted by the RMTC/ARCI.

When establishing a withdrawal time guideline, it is therefore important that the guideline be based on research in a significant number of horses, at least 20, and more if possible, and that the statistical probability of an innocent "overage" at the threshold be defined, so that regulators are aware that, although the threshold is presented as an absolute value, a defined probability of any individual animal exceeding the threshold because of chance exists.[9]

14. Closing Comments

In closing, it is now clear that the regulation of therapeutic medications in the United States will be by defined regulatory thresholds. Many, perhaps most of these thresholds will be for the parent medication in plasma, but it seems that some regulatory thresholds will be set in urine. This is because, for a number of potent tranquilizers and local anesthetics, regulatory thresholds in plasma are not considered practical, and the regulatory threshold will be based on specific metabolites or metabolite fragments in urine.[5]

The concept of regulatory thresholds is well established in the United States and a secondary threshold, called a subthreshold, is now making its appearance. For example, the RMTC/ARCI rule on non-steroidal anti-inflammatories permits one of three non-steroidal

anti-inflammatories to be present up to a specified threshold, let us say 20 ng/ml for flunixin in plasma. So what happens if a plasma sample shows 19 ng of flunixin, below the flunixin threshold, but with a small but detectable trace of phenylbutazone? The ARCI/RMTC answer to this is simple, there is a defined subthreshold for phenylbutazone, and in this circumstance, concentrations of phenylbutazone of up to 1 μg/ml are permitted (RMTC Model Rule at rmtcnet.com).

With regard to withdrawal times, it seems likely that the withdrawal time guideline will be expressed in days and linked to a specific medication formulation, dose, in some cases number of doses, and route of administration, as set forth in the AAEP list of therapeutic medications. It is to be hoped that the data on which the threshold/withdrawal time guidelines are based will be published in the refereed scientific literature, so the scientific basis for the threshold is available for review, and the statistical uncertainty associated with the withdrawal time guideline will be available for review by industry professionals.

In summary, many medications used in horses have the potential to influence performance and may not be present at effective concentrations during competition. Fifty such therapeutic medications are recognized by the AAEP and the RMTC, and for these substances, the RMTC is establishing regulatory thresholds and linked withdrawal time guidelines. A regulatory threshold is a specified concentration of the medication or a derivative thereof in plasma or urine, whereas a withdrawal time guideline is a suggested time before an event to cease medication administration to avoid exceeding the regulatory threshold.

Long-established plasma thresholds include phenylbutazone, 5 μg/ml, listed as a 24-h withdrawal time, and furosemide, 100 ng/ml, generally a 4-h withdrawal time and activating only when the urinary specific gravity is $<$1.010; these thresholds have been adopted by the RMTC. Other thresholds include numerous jurisdictions with the current RMTC plasma thresholds for flunixin (20 ng/ml) and ketoprofen (10 ng/ml). However, California has in place thresholds for flunixin, 50 ng/ml, and ketoprofen, 10 ng/ml, both with suggested 24-h withdrawal times, and clenbuterol, at 25 pg/ml, with a suggested 96-h withdrawal time.

Numerous other regulatory thresholds, principally in urine, are in place throughout the United States. This review has set forth the scientific basis for regulatory thresholds for therapeutic medications in plasma and urine, reviewed the various "in-place" published and unpublished regulatory thresholds for the AAEP/RMTC and a small number of other therapeutic medications in various U.S. jurisdictions. We also explicitly note the current widespread lack of research-based information on withdrawal time guidelines linked to most of the currently in place regulatory thresholds, which problem is being approached at a national level under the auspices of the RMTC.

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