RMTC: Regulating Medications Through Conjecture

WHERE DID THE SCIENCE GO?

Steven A. Barker, MS, PhD
Professor, Comparative Biomedical Sciences
Director, Analytical Systems Laboratory,
Laboratory for Drug Residue Studies and
the Equine Medication Surveillance Laboratory
State Chemist, Louisiana State Racing Commission

con·jec·ture

[k*uh*n-**jek**-cher]

☒

The formation or expression of an opinion or theory without sufficient evidence for proof; guess; speculation

sci·ence

[sī-ən(t)s]

Knowledge about or study of the natural world based on **facts learned through appropriate experiments and observations based on application of the scientific method.**

Regulation of medications should be based on good science, not just technology (LOD, LOQ of instruments).

It should permit adequate therapeutic treatment of horses, not limit the use of effective drugs based on "public opinion", emotion, hyperbole or uninformed or unproven speculation and mythology.

Studies to establish thresholds/withdrawal times should be based on scientific, pharmacological principles, using relevant dosing, routes, regimens and formulations to obtain needed data.

Good science requires that such studies address the effects of breed, weight, age and sex of horses and use statistically relevant numbers of animals for each to obtain an accurate assessment , including variability. Inherent variability must be taken into account.

2010 e-mail from Dr. Rick Sams, RMTC science advisor:

"1. I successfully argued for studies involving at least 20 Thoroughbred horses that are exercised regularly (although not immediately before sample collections).

2. The drugs were selected from the responses to the AAEP poll and were prioritized roughly based on frequency of positive findings (e.g., methocarbamol) although there are many exceptions (e.g., dantrium).

3. The first priority has been to get the data and then to determine best how to set the threshold (i.e., blood or urine, parent or metabolite, etc) although the goal from the beginning has been to use thresholds in plasma whenever they afford adequate withdrawal times.

4. It was assumed that none of the drugs on the list to be investigated would be permitted on race day so a 24-hour withdrawal time was mandatory in every case. If the drug was not detectable in plasma for 24 hours, then we would need to improve the detection of the drug, detect it in urine, or test for its metabolites in blood or urine. SO far we have been able to detect the parent drug for at least 24 hours.

5. When we examined the first group of drugs (i.e., acepromazine, butorphanol, detomidine, glycopyrrolate, lidocaine, mepivacaine, methocarbamol, and pyrilaimine), it seemed fairly obvious that pharmacodynamic studies would not tell us any more than we already knew...these drugs are unlikely to exert substantial or race altering effects for more than about 24 hours."

But that’s not what we got.

DRUG	# of Horses	Breed	Sex	Weight	Age	Dose/Route	Threshold/Analyte	Sample	Withdrawal	Duration of Effect	Basis for Threshold
Acepromazine	6	TB	4G-2M	470-550kg	3-5 yrs	0.15 mg/kg-oral	10 ng/ml HEPS	Urine	48 hrs	1-4 hrs, 24 hrs	All horses had detectable
						RMTC list shows 0.05 mg/kg					drug in blood at 48 hrs. Why urine?
Betamethazone						9 mg-IA	0.010 ng/ml	Plasma	7 days	<72 hrs	Study not made available
Butorphanol	10	TB	5G-5M	500 +/- 25kg	3.8+/-0.8 yrs	0.1 mg/kg-IV	300ng/ml	Urine			Time?
							2ng/ml	Plasma	48 hrs	<2 hrs	Time?
Clenbuterol	28	Mix	17G-11M	470+/-25kg	2-6 yrs	0.8ug/kg bid					
						30days-oral	0.14 ng/ml	Urine			LOQ of the method
							LOD	Plasma	14 days	<12 hrs	LOD of the method
Dantrolene	8	7TB-1SB	4G-4M	582+/-52kg	10+/-4 yrs	500 mg paste					
						or capsules	0.1 ng/ml	Plasma	48 hrs	<24 hrs	LOQ of the method
Detomidine	10	DWB	10M	580+/-69kg	7+/-4 yrs	40ug/kg oral gel	1 ng/ml COOH-detomidine	Urine			LOQ of the method
							LOD	Plasma	72 hrs	<24 hrs	LOD of the method
Dexamethasone	6	TB	3G-3M	523+/-44kg	6-10 yrs	0.05 mg/kg;IV,IM,IA	0.005 ng/ml	Plasma	72 hrs	<72 hrs	LOQ of the method
Diclofenac*	6	TB	6G	520-587kg	5-11 yrs	7.2g 1% to 1-4 fetlocks					
						bid for 10 days	5 ng/ml	Plasma	48 hrs	<12 hrs	Threshold permits use <24 hrs
DMSO*	6	TB	6M	452-511kg	2-18 yrs	1 g/kg, 0.1 g/kg-IV	10 ug/ml	Plasma	48 hrs	<12 hrs	Study did not measure 48 hr
Firocoxib						0.1 mg/kg, 4 days	20 ng/ml	Plasma	14 days	<24 hrs	Study not published
Flunixin*	5	NA	5M	498+/-59kg	8-12 yrs	1.1 mg/kg-oral, IV	20 ng/ml	Plasma	24 hrs	<24 hrs	Pharmacology
Furosemide	47	TB, mix	M,G,C,F	NA	NA	0.5 mg/kg-IV	100 ng/ml, SG<1.010	Plasma	4 hrs	<4 hrs	Pharmacology

	# of Horses	Breed	Sex	Weight	Age	Dose/Route	Threshold/Analyte	Sample	Withdrawal	Duration of Effect	Basis for Threshold
Glycopyrrolate	8	TB	8G	518-580kg	5-10 yrs	1 mg, IV	0.003 ng/ml	Plasma	48 hrs	<12 hrs	Time? Great variability @ 48 hrs
Ketoprofen*	6	5SB,1TB	6G	465-660kg	3-11 yrs	2.2 mg/kg-IV	10 ng/ml	Plasma	48 hrs	<24 hrs	Study quant. to 10 hrs, not 48 hrs
Lidocaine*	12	SB	12G	497+/-12kg	NA	0.8 mg/kg-SC (400 mg for 500kg) RMTC list shows 200 mg	0.020 ng/ml 3-OH-lidocaine	Plasma	72 hrs	<4 hrs	3-OH-lidocaine was not reported in plasma; study was for 12 hrs
Mepivacaine*	12	SB	12G	498+/-17kg	NA	400 mg-SC RMTC list shows 0.07 mg/kg (35 mg for 500kg)	10 ng/ml 3-OH-mepivacaine Mepivacaine-LOD	Urine Plasma	72 hrs	<4 hrs	No LODs given; Urine 3-OH mepivacaine at 7-13 ng/ml at 72 hrs
Methocarbamol	20	TB	11G-9M	468-605kg	5-10 yrs	15 mg/kg-IV; oral (6)	1 ng/ml	Plasma	48 hrs	<12 hrs	LOQ of the method
Methylprednisolone*	6	TB	3G-3M	541+/-56kg	7.5+/-1.8yrs	200 mg-IA	0.1 ng/ml	Plasma	7 days	<72 hrs	LOQ of the method
Omeprazole*						RMTC shows 100 mg total 3.9 mg/kg	1 ng/ml Sulfide metab.	Urine	21 days 24 hrs	<12 hrs	ARCI Rule? No study reference
Phenylbutazone	62,15,16	TB,SB,mix	NA	386-500kg	NA	Various regimens-oral,IV	2.0 ug/ml	Plasma	24 hrs	<24 hrs	Pharmacology
Prednisolone*	5	mix; heaves	4G-1M	NA	13-30 yrs	1 mg/kg-oral	1 ng/ml	Plasma	48 hrs	<48 hrs	LOQ was 10 ng/ml; no 48 hr time
Procaine penicillin*						NA	25 ng/ml	Plasma	Time of entry		Ref. for SC procaine for nerve block
Triamcinolone acetonide*	12	TB	6G-6M	NA	3-6 yrs	0.1 mg/kg-IM;9 mg-IA	0.1 ng/ml	Plasma	7 days	<72 hrs	LOQ of the method
Xylazine						IV	0.01 ng/ml	Plasma	48 hrs	<4 hrs	Study not made available

Many of the studies (8-10) use too few horses (8 or less) to be statistically relevant and to provide scientifically necessary accuracy. Where are all of the RMTC 20-horse studies promised and apparently performed? Where is all of the "secret data" and studies held by other parties?

For the majority of studies;

There is no consideration of differences in breed.
There is no consideration of differences due to sex of the animal.
There is no consideration for the effects of age.
There is no consideration of the effects of weight.
There is no consideration of the effects of exercise.

The effect of food intake on bioavailabilty of oral drugs is not adequately addressed.

Some of the drug administrations are based on the use of outdated or inappropriate formulations.

There are significant errors and/or inconsistencies between the RMTC stated doses and the doses used in the studies cited.

Several of the studies cited did not measure drug or metabolite concentrations used for regulation at the withdrawal time established.

There appears to be either no or an inconsistent application of any safety factor, taking into account horse-to-horse variability and the resulting statistics.

Several of the thresholds are LOD, a factor that will be different from lab-to-lab and that will change with each new generation of instruments used for testing. This does not help to establish State-to-State consistency.

Thresholds are, with few exceptions, based on technology (LOD, LOQ), not the science of pharmacology.

Of the 24 drugs, the data/references for the basis of the withdrawal times and thresholds for 5 of these drugs have yet to be produced.

This approach greatly compromises the veterinarian-client relationship and limits, to no known purpose, the ability of veterinarians to practice veterinary medicine.

While over 70 drugs were recommended for listing, only these 24 have been considered to date.

What are the thresholds for drugs not on the list? Zero tolerance?

Is this really what the National Thresholds are based on?

SERIOUSLY?