Tramadol and Venlafaxine: Human Prescription Meds Occasionally Identified in Post-Race Urines

By

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www.thomastobin.com
HIGHLY SENSITIVE TESTING

The reason for this presentation and much of the medication related turmoil in racing today is the between one million and one billion fold increase in the sensitivity of equine drug testing and the driven application of this continually improving technology.
Environmental Substances Identified in Post-Race Urines

Human related substances are common in our environments, and traces of these substances are frequently detected in post-race urines.

BenZoylEcggonine [BZE], the major urinary metabolite of cocaine, was early identified, now regulated by a 150 ng/ml urinary threshold.

In the nineties “trace” levels of caffeine were being “called” in Florida, Kent Stirling led elimination of these “calls” and now regulated by an ARCl 100 ng/ml plasma threshold.

I will now review a sequence of trace levels identifications of Tramadol in post-race urines and propose a regulatory threshold for Tramadol in equine urine.

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TRAMADOL

1/ An OPOID medication used in human and vet. medicine for moderate-severe pain, a Schedule IV Controlled Substance.

2/ Human dose is up to 400 mg/day, about 1/10 the potency of morphine; In humans, Tramadol is pharmacologically active as its metabolite, O-Desmethyltramadol.

3/ In the horses, O-Desmethyltramadol is VERY rapidly glucuronidated and excreted in the urine as O-Desmethyltramadol glucuronide.

4/ Tramadol is therefore essentially ineffective in the horse.

5/ Pharmacologically ineffective because it is very rapidly metabolized and excreted in the horse.
Figure 1. Tramadol and O-Desmethyltramadol glucuronide.

2-[(Dimethylamino)methyl]-1-(3-methoxyphenyl) Cyclohexanol, $\text{C}_{16}\text{H}_{25}\text{NO}_2$, 263.4 g/mol
Figure 2: Plasma concentrations of free and conjugated O-desmethyltramadol

- Note that the plasma concentrations of glucuronidated tramadol [Red symbols] run about 100 fold higher than plasma concentrations of free Tramadol [Blue symbols]. Table from K. Knych¹,²,*, C. R. Corado¹, D. S. McKemie¹, E. Scholtz³ and R. Sams⁴ Pharmacokinetics and pharmacodynamics of tramadol in horses following oral administration Journal of Veterinary Pharmacology and Therapeutics Volume 36, Issue 4, pages 389–398, August 2013
Figure 3. Tramadol and M1 [O-Desmethyltramadol] and M2 Metabolite (free + conjugated). We do not know the actual peak urinary concentrations of conjugated urinary O-Desmethyltramadol, but they seem likely to be significantly above 1 ug/ml. From Knych et al, J Vet Pharm Ther, 2013
Table 2. Tramadol Violations, courtesy of the Association of Racing Commissioners International [ARCI]

<table>
<thead>
<tr>
<th>Case</th>
<th>Year</th>
<th>Jurisdiction</th>
<th>Penalty</th>
<th>Concentration</th>
<th>Breed</th>
<th>Substance Reported</th>
<th>Sample Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Welch</td>
<td>2014</td>
<td>Indiana</td>
<td>15 days, DQ</td>
<td></td>
<td>SB</td>
<td>O-Desmethyl tramadol</td>
<td>Urine</td>
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<tr>
<td>McClain</td>
<td>2013</td>
<td>Illinois</td>
<td>180 days, $1000</td>
<td></td>
<td>SB</td>
<td>O-Desmethyl tramadol</td>
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</tr>
<tr>
<td>Leu</td>
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<td>Illinois</td>
<td>1 year, DQ</td>
<td></td>
<td>SB</td>
<td>O-Desmethyl tramadol</td>
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<td>Cobb</td>
<td>2013</td>
<td>Kentucky</td>
<td>In litigation</td>
<td>&quot;trace&quot;</td>
<td>TB</td>
<td>O-Desmethyl tramadol</td>
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<td>Chilcott ²</td>
<td>2013</td>
<td>New Zealand</td>
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<td>100 pg/ml</td>
<td>SB</td>
<td>O-Desmethyl tramadol</td>
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<td>Langford</td>
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<td>Louisiana</td>
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<td>declined split sample</td>
<td>TB</td>
<td>Desmethyl tramadol</td>
<td>Blood</td>
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<tr>
<td>Pate</td>
<td>2012</td>
<td>Kentucky</td>
<td>6 months, DQ</td>
<td>A sample: 19 ng/ml</td>
<td>TB</td>
<td>Desmethyl tramadol</td>
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<td>Godinez</td>
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<td>Reduced to $1,000</td>
<td>QH</td>
<td>O-Desmethyl tramadol</td>
<td>Blood</td>
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<tr>
<td>Reed</td>
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<td>Pennsylvania</td>
<td>30 days, $5000, DQ</td>
<td></td>
<td>TB</td>
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<td>6 months, DQ</td>
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<td>SB</td>
<td>O-Desmethyl tramadol</td>
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<td>New York</td>
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<td>Maymo</td>
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1http://harriersracingupdate.com/restricted/pdf/hru/hruehu020714.pdf?CFID=92249922%CFTOKEN=21362692
2https://www2.illinois.gov/irb/Documents/StandardbredRulings/2013%20mayjune%20HARESS%20rulings.PDF
5http://www.bloodhorse.com/horse-racing/articles/70718/fontenot-langford-given-lengthy-suspenisons
6personal communication with Peggy Pate, April 2014 http://sports.espn.go.com/sports/horse/news/story?id=581078
7http://www.chrb.ca.gov/Stewards/Minutes/Minutes_LA_12_01_22.pdf
8http://www.rmtcnet.com/content_recentrulings.asp?sort=violation
9http://www.bloodhorse.com/horse-racing/articles/55283/ky-trainers-suspended-for-class-i-positives
10http://www.bloodhorse.com/horse-racing/articles/55283/ky-trainers-suspended-for-class-i-positives
11http://www.harnesslink.com/News/John-Edmunds-disqualified-for-6-months-71845
13http://asci.uvm.edu/equine/law/cases/racing/maymo.htm
1/ Tramadol less potent than morphine in humans, close to pharmacologically inactive in the horse

2/ Morphine “cut-offs” of 50-100ng/ml are in place in many states.

3/ We have lower concentration Tramadol identifications in urine, one apparently very low.

4/ At least some of these Tramadol identifications are associated with prescriptions to humans working close to or with these positive horses.
5/ Tramadol is stable in the environment and is found at significant concentrations in European urban waste water.

6/ Indiana reported a Tramadol identification in a Harness trainer with a 30 year history of no medications positives. Indiana considered the ARCI penalty inappropriate and the penalty imposed was greatly reduced from the ARCI recommended minimum penalty.
7/ We suggest that a urinary concentration “cut-off” for Tramadol similar to the in place 50 ng/ml Morphine “cut-offs” currently in place in many states.
VENLAFAXINE

1/ A human antidepressant of the serotonin-norepinephrine reuptake inhibitor class. Prescribed in humans for Major Depressive Disorder [MDD], Generalized Anxiety Disorder [GAD] and related conditions.

2/ The human dose is 250mg/day, and may be higher in some patients.

3/ Venlafaxine is stable in the environment, a search concerning environmental venlafaxine brought up a large number of citations.

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VENLAFAXINE

4/ Worldwide, there have been a number of sporadic venlafaxine identifications in racing horses and one in a greyhound, apparently the only positive for the trainer in 30 years of racing.

5/ In one Canadian case the possibility of environmental contamination was suggested. Venlafaxine positive horse urine was therefore put on hay being fed to a horse.

6/ The horse went positive for venlafaxine, but the Canadian authorities were apparently less than impressed by this finding.
7/ Recently there has been a cluster of 5 low concentration O-Desmethylvenlafaxine identifications in racing horses from two trainers in Mumbai.

8/ These identifications are apparently associated with one section of the racetrack and are in the order of 1 ng/ml or less.

9/ The substance identified in the urine is O-Desmethylvenlafaxine, not unlike the situation for O-Desmethyltramadol.
Figure 3 Figure 1. Venlafaxine $C_{17}H_{27}NO_2$ Molecular mass 277.402 (RS)-1-[2-dimethylamino-1-(4-methoxyphenyl)-ethyl]cyclohexanol
VENLAFAXINE

9/ It appears that as for O-Desmethyltramadol, the glucuronide metabolite of O-Desmethylvenlafaxine is excreted at relatively high concentrations in urine.

10/ The sequence of events for these environmental Venlafaxine and Tramadol identifications are similar:

10.1: The substance is chemically **STABLE** in the environment.

10.2: The substance is **ORALLY ABSORBED** from the environment by the horse.

10.3: The urinary metabolite is excreted at **HIGH CONCENTRATIONS** relative to the dose.

10.4: Resulting in forensically insignificant **LOW CONCENTRATION** urinary identifications.
Acknowledgements

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