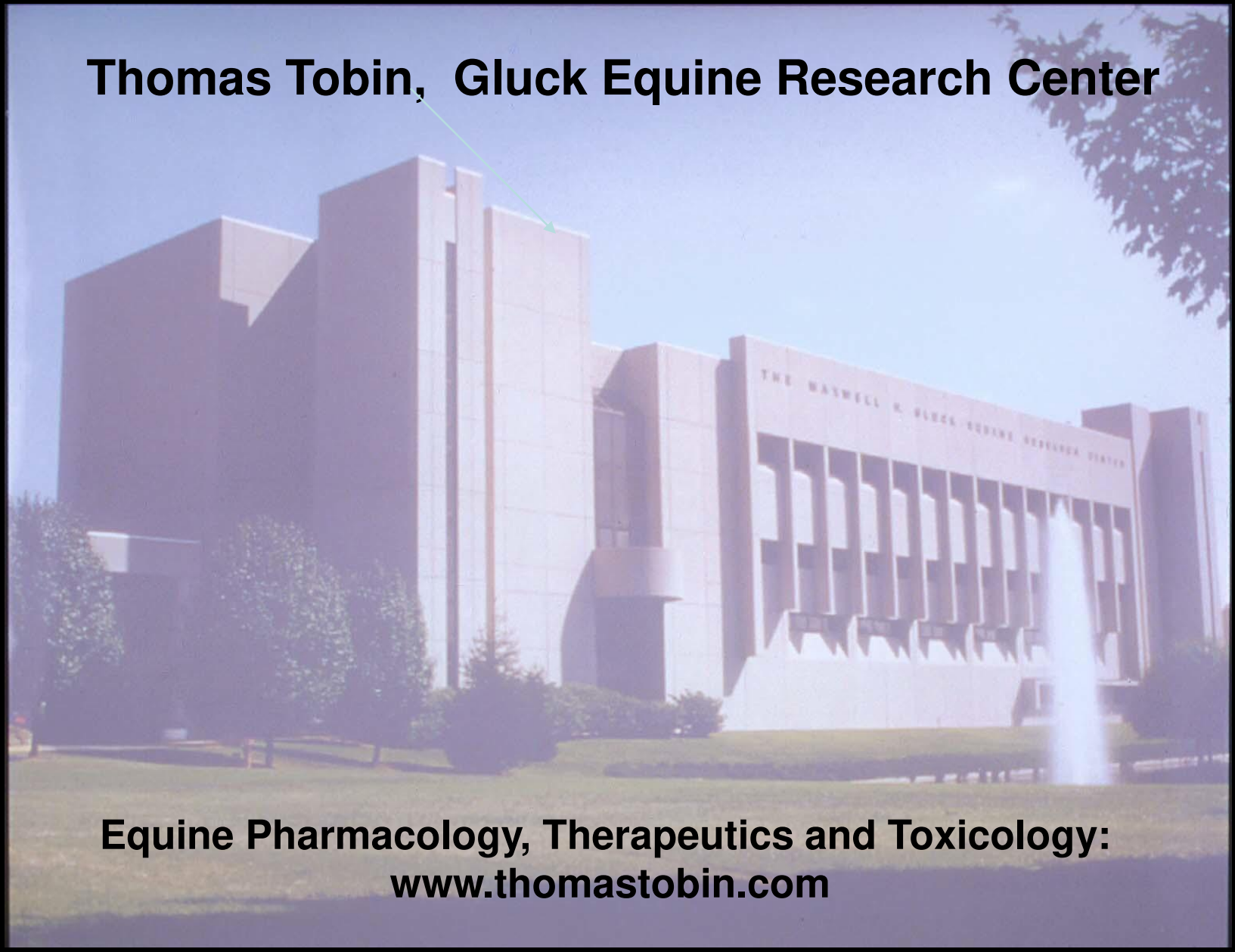
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Tramadol and Venlafaxine: Human Prescription Meds Occasionally Identified in Post-Race Urines

By

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for the

National HBPA, Carefree, Arizona,

Saturday, February 7th, 2015

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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.

BenZoylEcgonine [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 ARCI 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.

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.

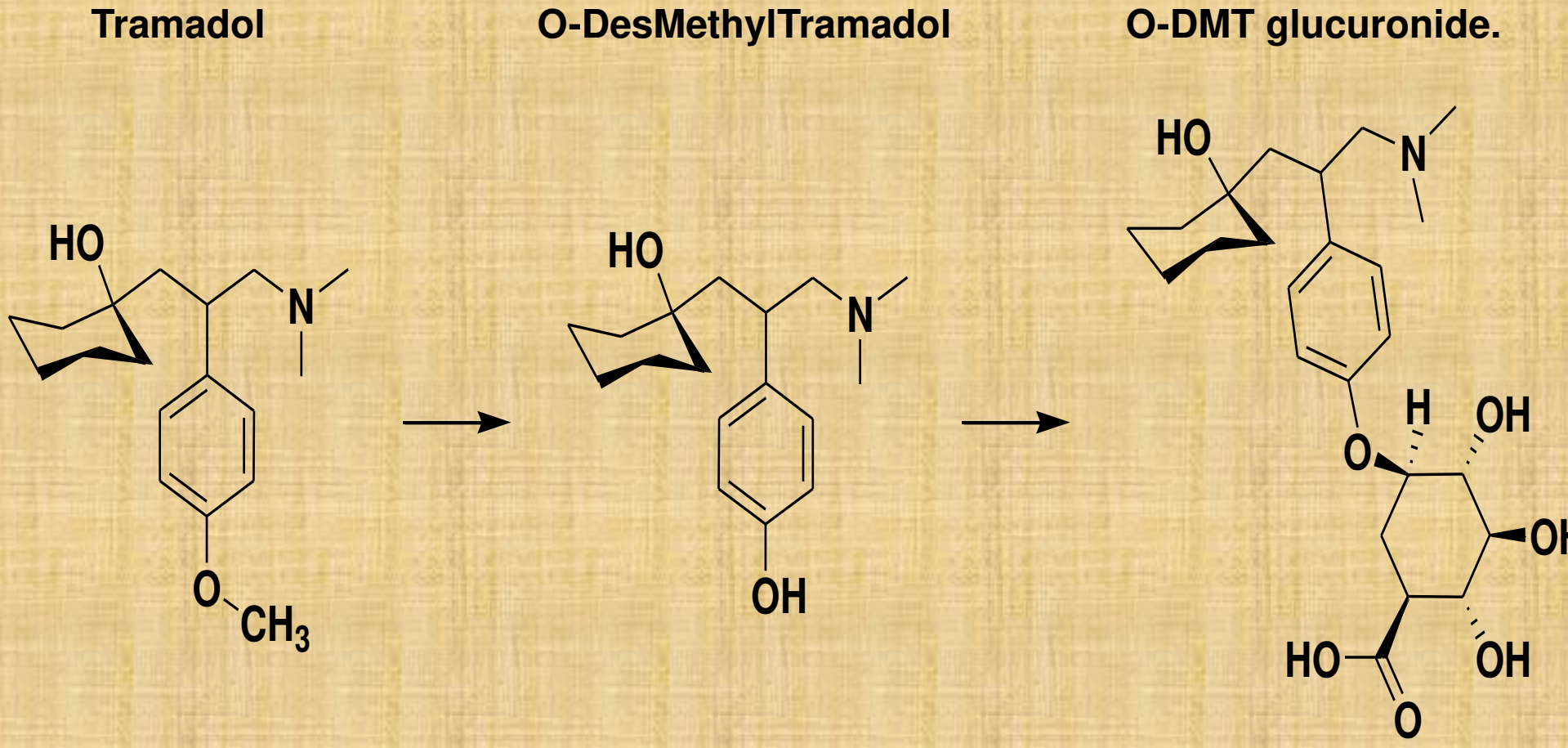

Figure 1. Tramadol and O-Desmethyltramadol glucuronide.
2-[(Dimethylamino)methyl]-1-(3-methoxyphenyl) Cyclohexanol, $C_{16}H_{25}NO_2$, 263.4 g/mol

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Knych -- 9 mg/kg

plasma concentrations of ODMT

Hrs	non-conj	conj
0.25	7.5	12
0.5	20	166
0.75	38	708
1	62	1150
2	41	2606
3	36	2350
4	20.8	1952
5	12.7	1421
6	8.92	1088
8	4.72	636
12	1.73	203
18	0.345	37
24	0.255	11.5
36	0.254	1.8
48	ND	1.53
72	ND	0.426

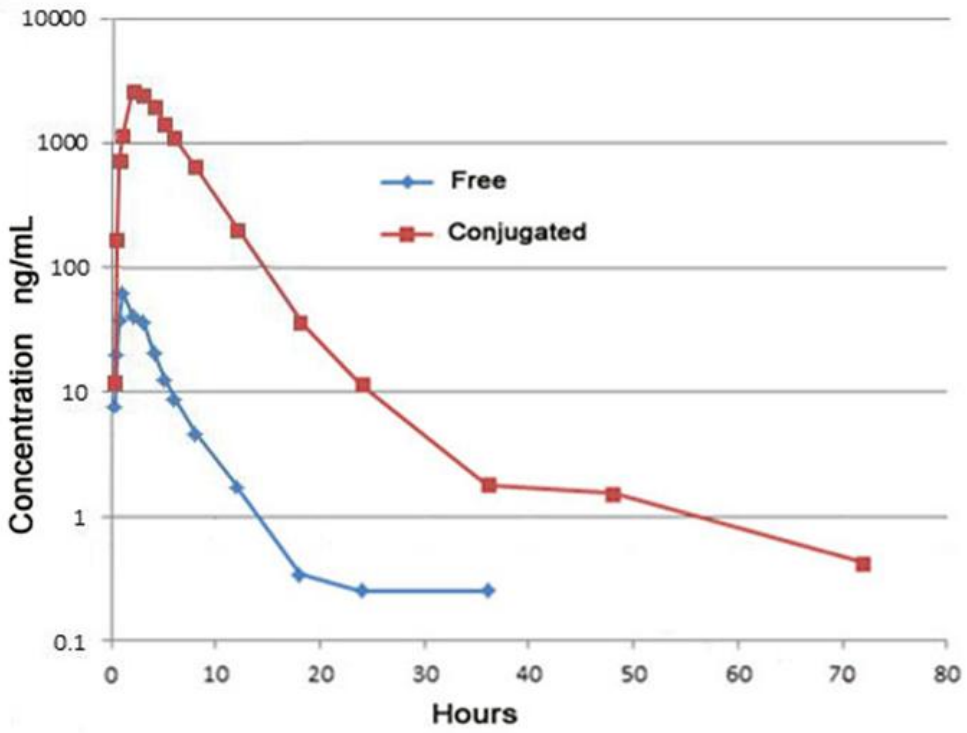

Figure 2: Plasma concentrations of free and conjugated O-desmethyltramadol

- **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. Knych[1,2,*], C. R. Corado[1], D. S. McKemie[1], E. Scholtz[3] and R. Sams[4] **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**

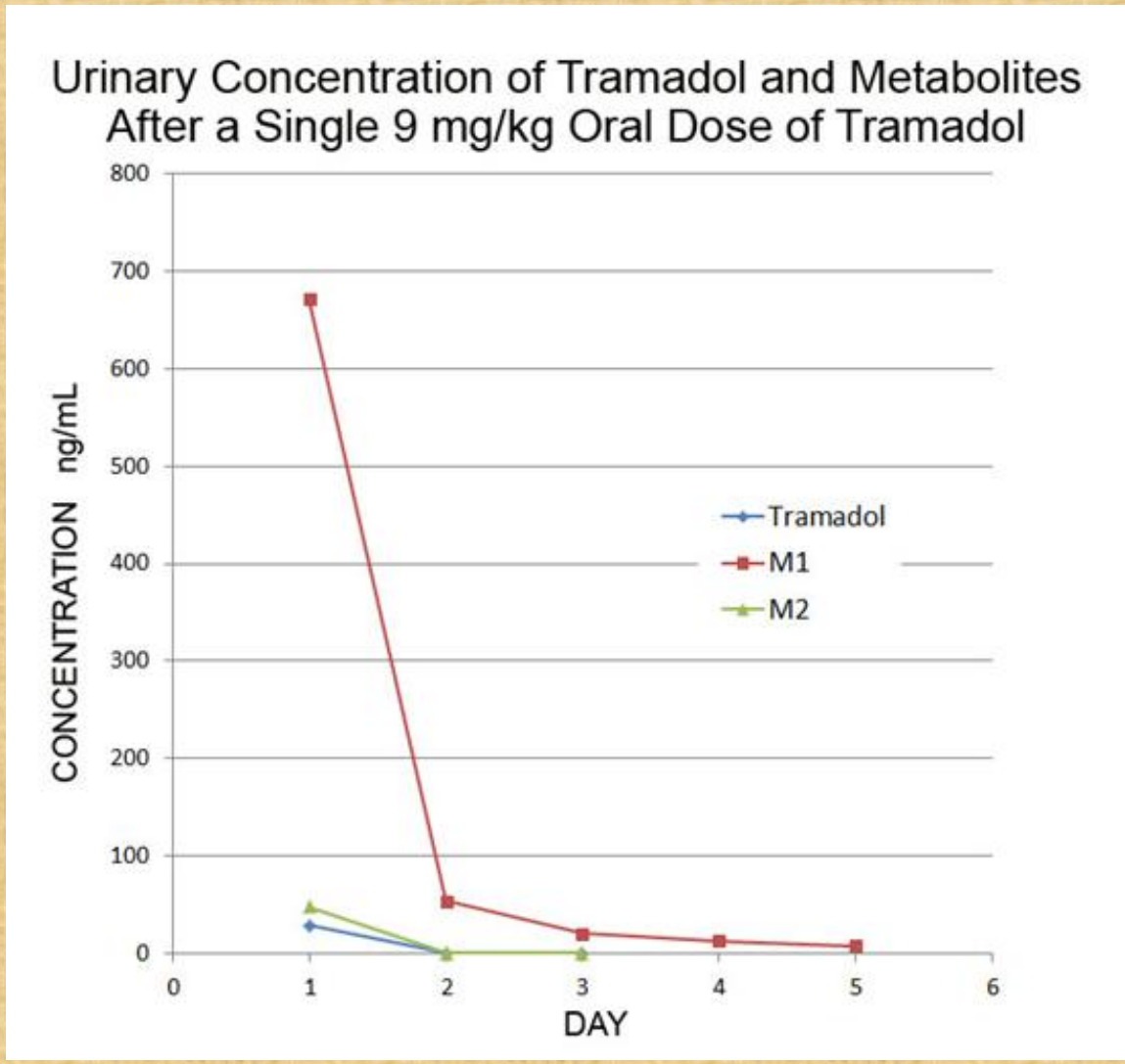

Figure 3. Tramadol and M1 [O-Desmethyltramadol] and M2 Metabolite (free + conjugated). We do not know the actual peak urinary concentrations of conjugated urinary O-Desmethyltramadol, but they seem likely to be significantly above 1 ug/ml. From Knych et al, J Vet Pharm Ther, 2013

Table 2. Tramadol Violations, courtesy of the Association of Racing Commissioners International [ARCI]

Case	Year	Jurisdiction	Penalty	Concentration	Breed	Substance Reported	Sample Type
Welch[1]	2014	Indiana	15 days, DQ		SB		
McClain	2013	Illinois	180 days, $1000		SB	O-Desmethyl tramadol	Urine
Leu[2]	2013	Illinois	1 year, DQ		SB	O-Desmethyl tramadol	Urine
Cobb[3]	2013	Kentucky	In litigation	"trace"	TB	O-Desmethyl tramadol	
Chilcott[4]	2013	New Zealand	DQ, $3300	100 pg/ml	SB	O-Desmethyl tramadol	
Langford[5]	2012	Louisiana	6 months, DQ	declined split sample	TB		Blood
Pate[6]	2012	Kentucky	6 months, DQ	A sample: 19 ng/ml B sample: 11 ng/ml	TB	Desmethyl tramadol	
Godinez[7]	2012	California	$10,000 original fine. Reduced to $1,000 30 days		QH	O-Desmethyl tramadol	
Reed	2011	Pennsylvania	30 days, $5000, DQ		TB		
Loney[8]	2010	Kentucky	6 months, DQ		SB	O-Desmethyl Tramadol	
Watkins[9]	2010	Kentucky	180 days,		TB	O-Desmethyl tramadol	
Ward[10]	2010	Kentucky	180 days, DQ			O-Desmethyl tramadol	
Bell	2010	Ohio	180 days, $500			O-Desmethyl tramadol	
Edmunds[11]	2009	Queensland	6 months			Tramadol, Desmethyl tramadol	urine
Baumeister	2008	New York	60 days, $250, DQ		SB		
Morgan[12]	2008	New York	90 days, $500, DQ		SB		
Bellamy	2006	Illinois				O-Desmethyl tramadol	
Siedelman/ Woods	2003	Illinois				O-Desmethyl tramadol	
Keir	2002	New York	45 days, $250			Desmethyl tramadol	
Maymo[13]	2000	Puerto Rico	5 years, $2,750				Urine
Anderson	1999	West Virginia	60 days			Hydroxyl tramadol	
Siedelman	1999	California	45 days				
Stokes	1999	California	30 days				
Ciatto	1997	New York	60 days, $250			Tramadol metabolites	

[1] http://harnessracingupdate.com/restricted/pdf/hru/hru020714.pdf?CFID=92249922&CFTOKEN=21362692

[2] https://www2.illinois.gov/irb/Documents/StandardbredRulings/2013%20mayjune%20HARNESS%20rulings.PDF

[3] http://www.drf.com/news/kentucky-commission-upholds-suspension-trainer-carol-cobb

[4] http://www.jca.org.nz/non-race-day-hearings/non-raceday-inquiry-riu-v-n-a-chilcott-27-april-2012-decision-dated-4-december-2013-1

[5] http://www.bloodhorse.com/horse-racing/articles/70718/fontenot-langford-given-lengthy-suspensions

[6] personal communication with Peggy Pate, April 2014 http://sports.espn.go.com/sports/horse/news/story?id=581078

[7] http://www.chrb.ca.gov/Stewards/Minutes/Minutes_Los_Al/Minutes_LA_12_01_22.pdf

[8] http://www.rmtcnet.com/content_recentrulings.asp?sort=violation

[9] http://www.bloodhorse.com/horse-racing/articles/55283/ky-trainers-suspended-for-class-i-positives

[10] http://www.bloodhorse.com/horse-racing/articles/55283/ky-trainers-suspended-for-class-i-positives

[11] http://www.harnesslink.com/News/John-Edmunds-disqualified-for-6-months-71845

[12] http://rulings.racing.ny.gov/searchrulings.detail.php?ID=27719

[13] http://asci.uvm.edu/equine/law/cases/racing/maymo.htm

TRAMADOL

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.

TRAMADOL

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.

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TRAMADOL

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.

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.

VENLAFAXINE

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.

Venlafaxine **O-DesMethylVenlasfaxine** **O-DMV glucu** ronide

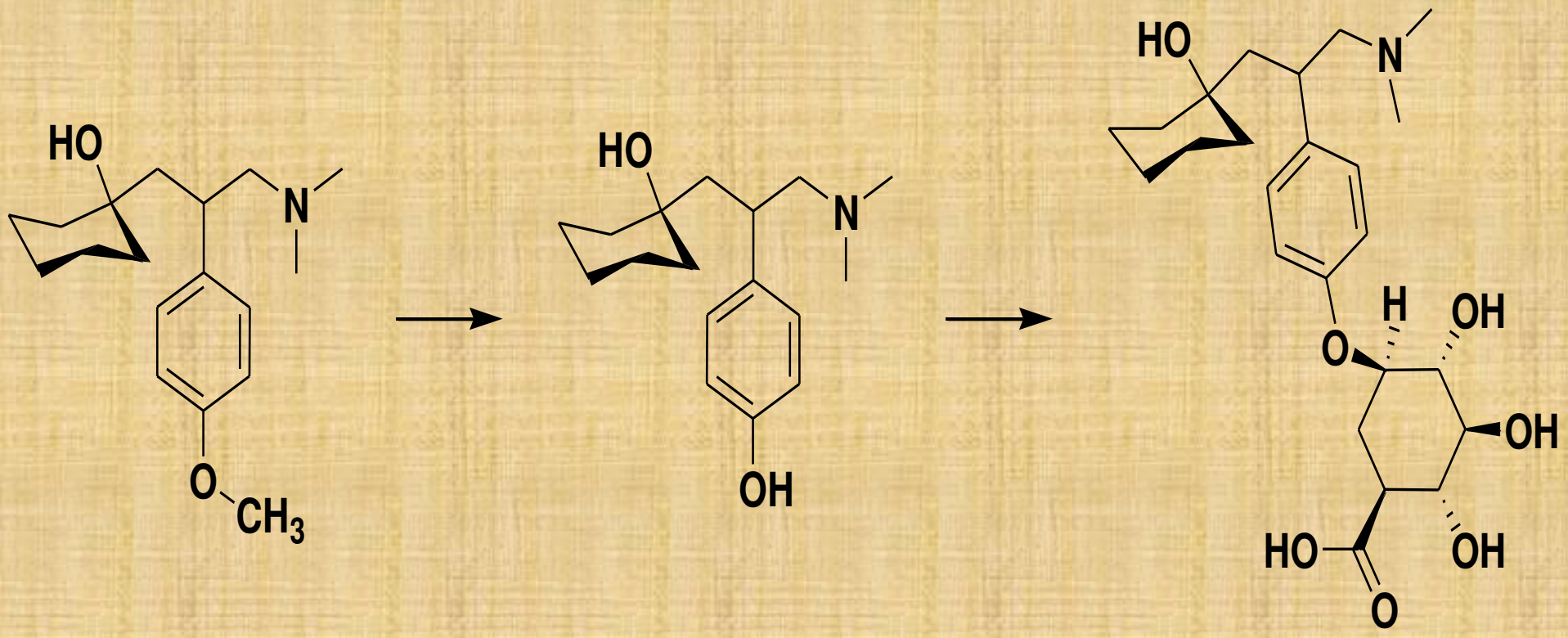

Figure 3 Figure 1. Venlafaxine $C_{17}H_{27}NO_2$ Molecular mass 277.402
(*RS*)-1-[2-dimethylamino-1-(4-methoxyphenyl)-ethyl]cyclohexanol

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

The research presented here has been supported by grants from the Kentucky Horse Racing Commission and the Kentucky Equine Drug Research Council, The Grayson-Jockey Club Research Foundation, the National Institutes of Environmental Health Sciences, a gift from Mrs. John Hay Whitney and the following divisions of the Horsemen's Benevolent and Protective Association: National, Canada, Florida, Nebraska, Kentucky, Ontario, Indiana, Charles Town, Ohio, Arkansas, Michigan, Pennsylvania, Alabama, Arizona, Iowa, Louisiana, Oklahoma, Tampa Bay Downs, Washington, Minnesota, Oregon, Texas and Mountaineer Park. The continuing support of the University of Kentucky, the Director and Faculty of the Gluck Equine Research Center and the University of Kentucky Equine Research Foundation are also gratefully acknowledged.

ACKNOWLEDGEMENTS

Figures 2 and 3 adapted from K. Knych[1,2,*], C. R. Corado[1], D. S. McKemie[1], E. Scholtz[3] and R. Sams[4] **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**

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