

Equine Pharmacology, Therapeutics and Toxicology [Forensic/Equine]



THIS PRESENTATION WAS CREATED BY THOMAS TOBIN, MVB, MRCVS, DABT, AND ALL CASE STUDIES ARE BASED ON DR. TOBIN'S OWN CLINICAL OR OTHER EXPERIENCE

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REVISITING RMTC XYLAZINE GUIDELINES WITH AUSTRALIAN ASSISTANCE

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for the

National HBPA Summer Convention, Denver,

[FRIDAY NOON draft] August 8th, 2015

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www.hbpa.org/resources/MedicationPolicy.pdf

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[XYLAZINE: LIKELY HELPS TO HAVE ACTUAL DATA BEFORE SETTING A THRESHOLD]

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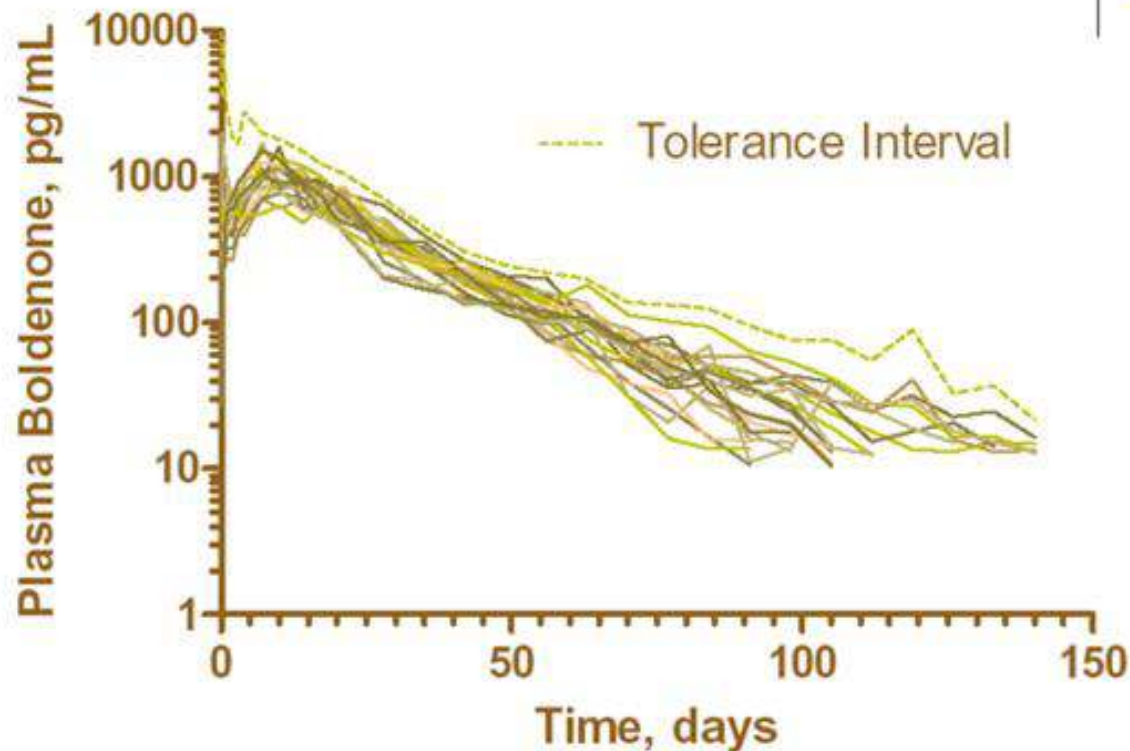
August 7-10th, 2015

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RMTC Equipoise™ Study UF Results



HOW LONG CAN A 500 MG DOSE REMAIN DETECTABLE???

ANSWER IS POSSIBLY 150 DAYS!! [SAMS, RMTC]

HALF-LIVES TO COMPLETELY ELIMINATE MEDICATION? → 66
[BOLDENONE, 66 X15 days= 1,056 days, or 2.9 years]

XYLAZINE TERMINAL PLASMA HALF-LIFE ??

1/ XYLAZINE: DOSE LARGE, 1 MG/KG, [500 MG/HORSE].

2/ GIVEN AS RAPID IV BOLUS: BOLUS ENTERS AND LEAVES BRAIN RAPIDLY; EFFECT OVER IN 1.5 HOURS.

3/ 1.5 HOURS ON→ $\frac{1}{2}$ GRAM OF LIPID SOLUBLE DRUG DISTRIBUTED THRU HORSE AND BEING ELIMINATED.

4/ HOW FAST ELIMINATED? TERMINAL PLASMA HALF-LIFE OF XYLAZINE? 30 MINUTES?? 1 HOUR?? LONGER??

5/ RECENT WORK SHOWS THAT THE TERMINAL PLASMA HALF-LIFE OF XYLAZINE IS “LONGER” AND THE PUBLISHED RMTC THRESHOLD IS MOST LIKELY INCORRECT.

XYLAZINE:

1/ RELATED TO DETOMIDINE. [Mol Mass 220.33]

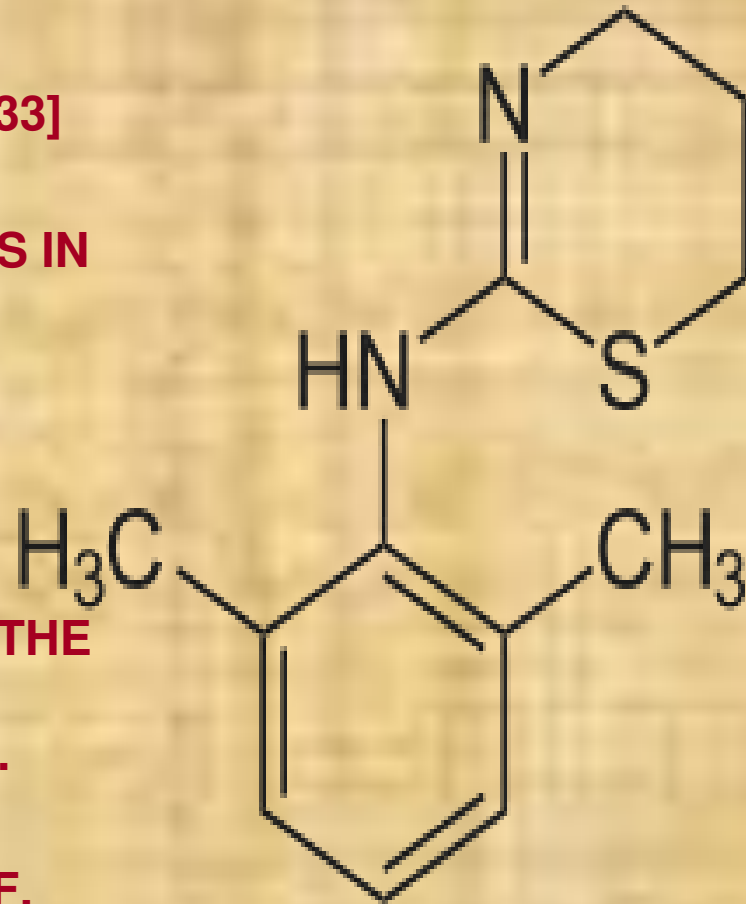
2/ BLOCKS ALPHA-2-ADRENERGIC RECEPTORS IN BRAIN.

3/ HORSE IMMEDIATELY RELAXES; HEAD DROOPS AND APPROACHES THE FLOOR

4/ FOLLOW EFFECT OF DRUG BY MEASURING THE CHIN-FLOOR DISTANCE WITH A VERY SOPHISTICATED WALMART MEASURING TAPE.

5/ OVERT PHARMACOLOGICAL EFFECTS BRIEF, OVER WITHIN 1.5 HOURS.

6/ QUESTION: WHAT ARE THE BLOOD LEVELS OF XYLAZINE AT 48 HOURS POST-ADMINISTRATION



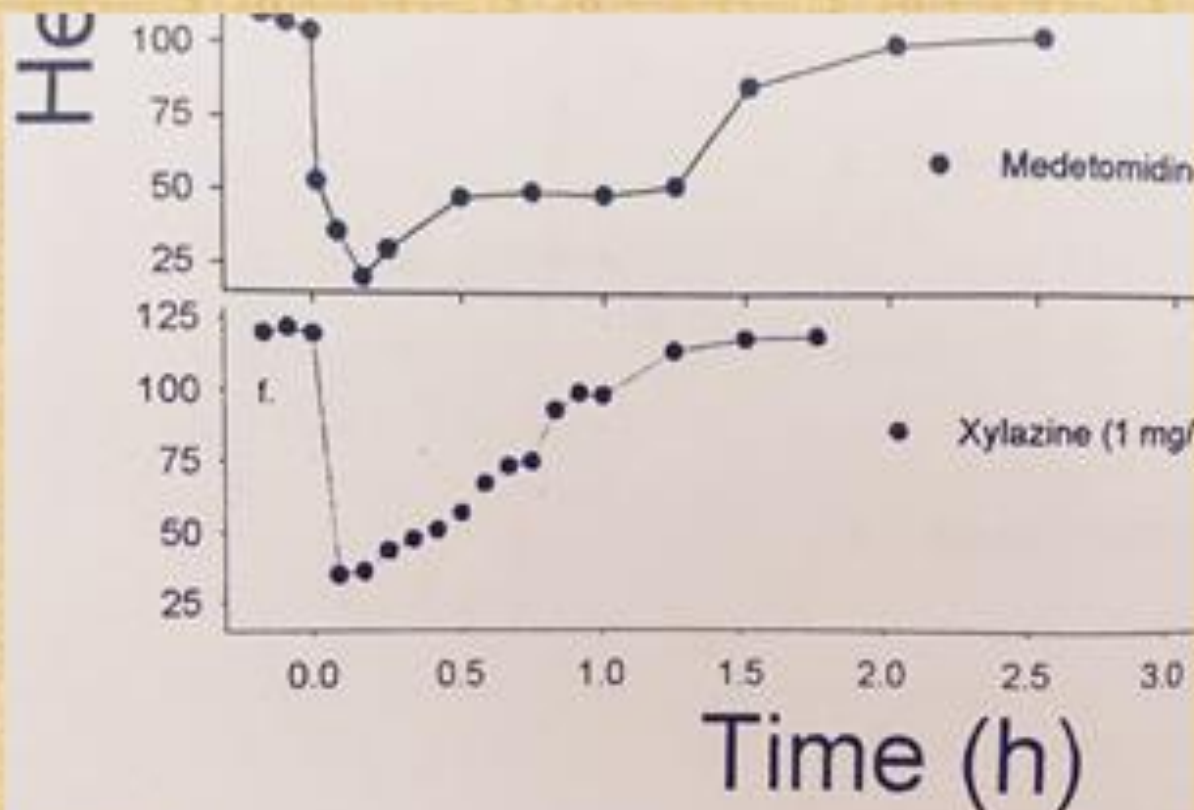
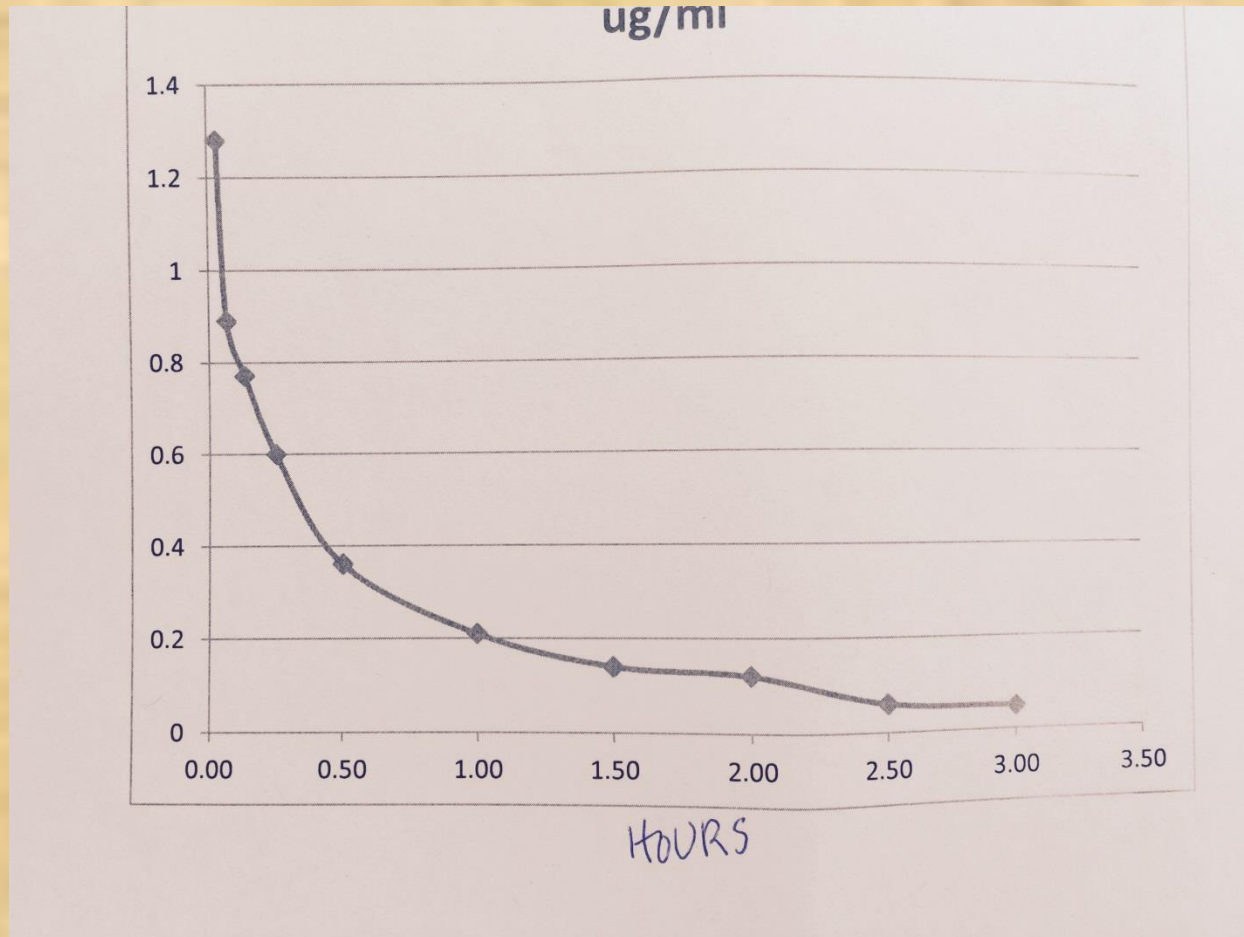


Figure 1

TIME COURSE OF XYLAZINE HEAD DROOP RESPONSE

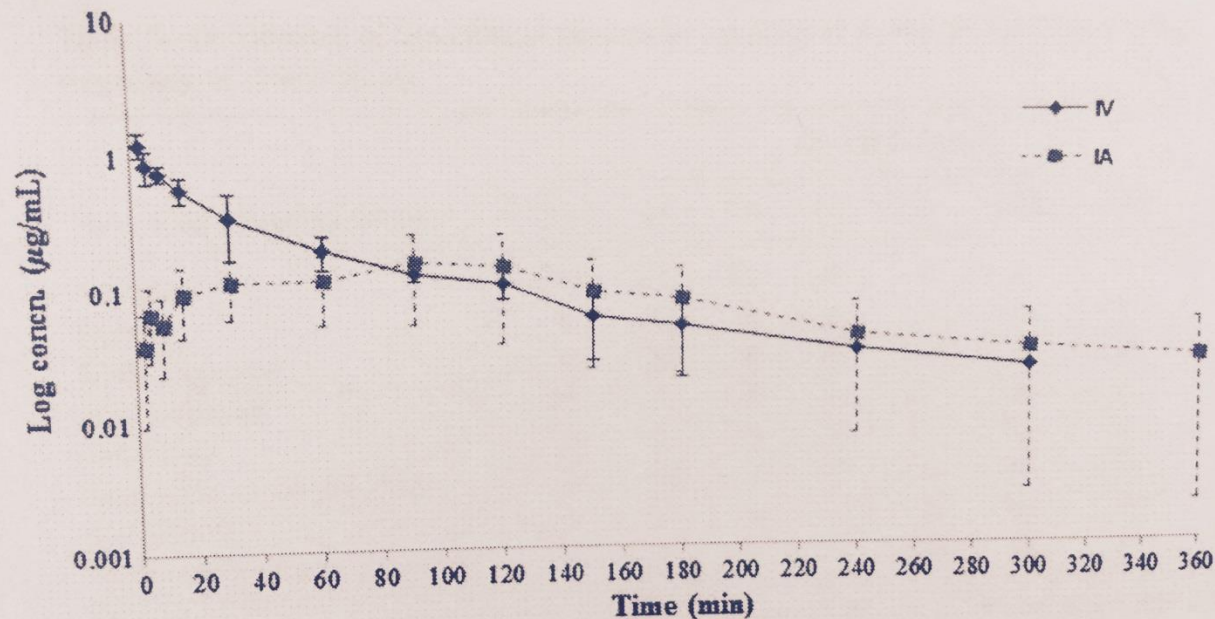
THE SOLID CIRCLES SHOWS THE CHIN-FLOOR DISTANCE FOLLOWING RAPID INTRAVENOUS INJECTION OF 500 MG OF XYLAXZINE. THE RESPONSE IS COMPLETE WITHIN MINUTES AND IS APPARENTLY COMPLETELY OVER WITHIN 1.5 HOURS.



TIME COURSE OF PLASMA XYLAZINE CONCENTRATIONS

THE SOLID CIRCLES SHOWS THE PLASMA CONCENTRATIONS OF XYLAZINE FOLLOWING RAPID INTRAVENOUS INJECTION OF 500 MG OF XYLAXZINE. THE RAPID DROP IN BLOOD LEVELS OF XYLAZINE IS APPARENTLY COMPLETE WITHIN 1.5 HOURS. THE TIME AT WHICH THE HORSE IS APPARENTLY BACK TO "NORMAL"

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Table 3. Serum concentrations (mean \pm standard deviation and rangeTable 4. Pharm
tration at 1 mg/

PLASMA HALF-LIFE OF XYLAXZINE AFTER RAPID IV ADMINISTRATION, SEMILOG PLOT OUT TO 5 HOURS

THE DIAMONDS SHOW THE DECLINING PLASMA CONCENTRATIONS OF XYLAZINE POST IV ADMINISTRATION OF 1M/KG OF XYLAZINE IN 4 HORSES. THE ESTIMATED TERMINAL PLASMA HALF-LIFE IS 61 MINUTES AND THE LAST TIME POINT IS AT 240 MINUTES. **Di Salvo et al, 2014.**

Medication	Threshold	Withdrawal Guideline	Dosing Specifications	Reference Notes	Note
Penicillin <i>(Administration must be as directed to Commission)</i>	25 nanograms per milliliter of plasma or serum	Following entry to race	Intramuscular	RMTC – reference notes online	Mandatory surveillance of horse at owner's expense 6 hours before racing
Triamcinolone acetonide	100 picograms per milliliter of plasma or serum	7 days	Total dose of 9 milligram in one articular space ⁴	<i>Equine Veterinary Journal</i> , 10.1111/evj.12059 (2013)	Applicable analyte is triamcinolone acetonide in plasma or serum
Xylazine	0.01 nanogram per milliliter of plasma or serum	48 hours	Intravenous		Applicable analyte is xylazine.

RMTC XYLAZINE “SCHEDULE”

1/ NO REFERENCE/NOTES, NO SPECIFIED DOSE !!!

**2/ REGULATORY THRESHOLD 0.01 NANOGRAMS/ ML
OR 10 PICOGRAMS/ML IN PLASMA/SERUM.**

**3/ 10 PICOGRAMS/ML THRESHOLD [SOUNDS A LOT LIKE A
METHOD LIMIT OF DETECTION/QUANTIFICATION??].**

**4/ IMPRESS RACING COMMISSIONERS [?], BUT AS FAR AS
YOUR SPEAKER IS CONCERNED, THIS LOOKS RATHER
LIKE A “WBG” STATEMENT. [WBG = *WE BE GUESSIN*].**

XYLAZINE CLINICAL USE

. WASHINGTON STATE STORY

- 1/ XYLAZINE, 200 MG IV, FOR A DENTAL PROCEDURE >52 HOURS PRIOR TO POST.**
- 2/ TRUESDAIL REPORT STATED THAT XYLAZINE “*ABOVE THE THRESHOLD*”.**
- 3/ LOUISIANA COULD NOT QUANTIFY THAT LOW, SO SPLIT SAMPLE TO INDUSTRIAL LABS → 0.0977 NG/ML.**
- 4/ VET ACCUSED OF ADMINISTERING MEDICATION WITHIN 24 HOURS; WATERMAN TESTIFIED CITING “NEW” STUDY.**

XYLAZINE, WASHINGTON STATE

1/ TRAINER [30 YEAR CLEAN RECORD] GOT \$250 FINE, LOSS OF PURSE, 7 DAY SUSPENSION.

2/ I REVIEWED THE MATTER AT MARYANN'S REQUEST.

3/ VERY LIKELY NO DATA TO SUPPORT THE RMTC THRESHOLD THAT WASHINGTON WAS RELYING ON.

4/ FROM LITERATURE, A CALCULATED "NO EFFECT THRESHOLD" IS 76 PICOGRAMS/ML, I SUGGESTED A MORE CORRECTLY CALCULATED 300 PG/ML FOR WASHINGTON, SENT LETTER TO Dr. MACOMBER.

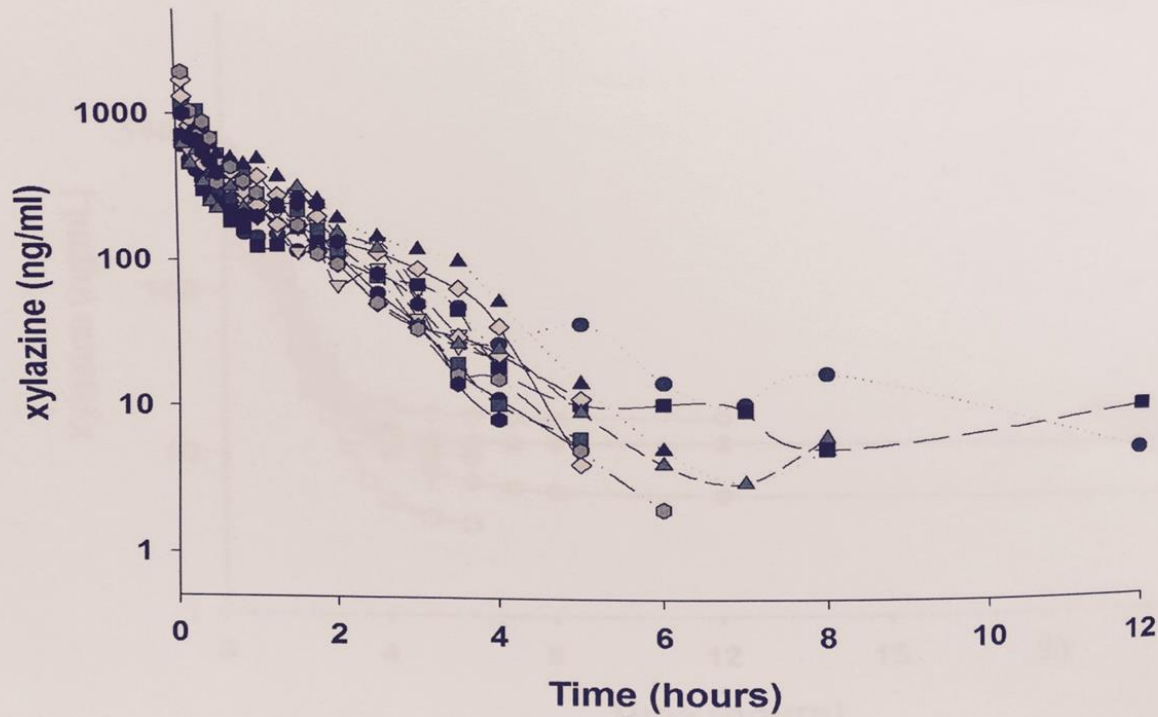
XYLAZINE, WASHINGTON STATE

1/ I ALSO E-MAILED DR. GLENYS NOBLE, CHARLES STURT UNIVERSITY, WAGGA WAGGA, AUSTRALIA, ASKING FOR ANY XYLAZINE DATA SHE HAD ACCESS TO.

2/ DATA ARRIVED DAY AFTER I WROTE THE MACOMBER LETTER.

3/ DATA SHOWS THAT FROM 6 to 12 HOURS POST ADMINISTRATION THE DECLINE IN THE PLASMA CONCENTRATIONS IS VERY SLOW

Plasma xylazine alone, 400 mg/horse



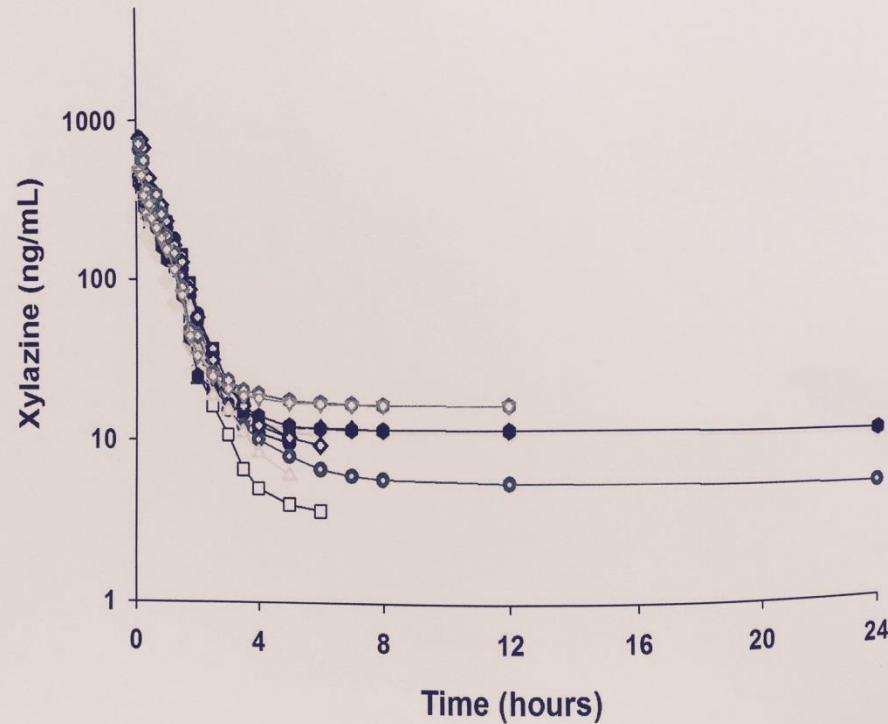
XYLAZINE I/V 400 MG/HORSE

NOTE THAT POST SIX HOURS THE PLASMA LEVELS APPEARS TO FLATTEN OUT, AND BETWEEN SIX AND TWELVE HOURS POST ADMINISTRATION THERE IS NO APPARENT DECLINE IN PLASMA CONCENTRATIONS OF XYLAZINE. THIS INCREASE IN THE PLASMA-HALF LIFE IS NOT UNUSUAL, BUT IN THIS CASE THE TERMINAL PLASMA HALF-LIFE MAY BE VERY LONG INDEED

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Plasma xylazine combination

Dose, 250 mg/horse



XYLAZINE CONCENTRATIONS WHEN COMBINED WITH BUTORPHANOL

NOTE THAT POST SIX HOURS THE PLASMA HALF-LIFE APPEARS TO FLATTEN OUT, AND BETWEEN SIX AND TWENTYFOUR HOURS POST ADMINISTRATION THERE IS NO APPARENT DECLINE IN PLASMA CONCENTRATIONS OF XYLAZINE. THIS INCREASE IN THE PLASMA-HALF LIFE IS A LITTLE SURPRISING, AND IT SEEMS THAT IN THIS CASE THE TERMINAL PLASMA HALF-LIFE MAY BE VERY LONG INDEED

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XYLAZINE, WASHINGTON STATE

1/ SENT THE ABOVE MATERIALS TO MARYANN TO COMMUNICATE TO DR. MACOMBER.

2/ PENALTY CHANGED TO NO LOSS OF PURSE, \$1,500 FINE AND 7 DAY SUSPENSION.

3/ WASHINGTON STATE HAS CHANGED THE XYLAZINE THRESHOLD FROM 10 TO 200 PG/ML

“Xylazine - ((0.01)) 0.2 ng/ml”

4/ AS NEAR AS I CAN TELL, THIS IS STILL A “WBG” APPROACH, BUT I WOULD LIKE TO THINK THAT THIS NEW RULE IS BEING APPLIED VERY CAUTIOUSLY.

TAKE HOME MESSAGES

1/ BE VERY CAREFUL WITH XYLAZINE CLOSE TO RACING SINCE THE PUBLISHED RMTC/ARCI THRESHOLD IS AT BEST NOT WELL SUPPORTED.

2/ BE PARTICULARLY CAREFUL IF YOU ARE USING XYLAZINE IN COMBINATION WITH BUTORPHANOL, SINCE BASED ON THE WAGGA WAGGA DATA YOU MAY BE AT CONSIDERABLY INCREASED RISK OF EXCEEDING THE RMTC/ARCI PLASMA THRESHOLD FOR XYLAZINE.

3/ WE ARE WORKING ON GETTING A COMMUNICATION ON THESE MATTERS SUBMITTED FOR PUBLICATION.

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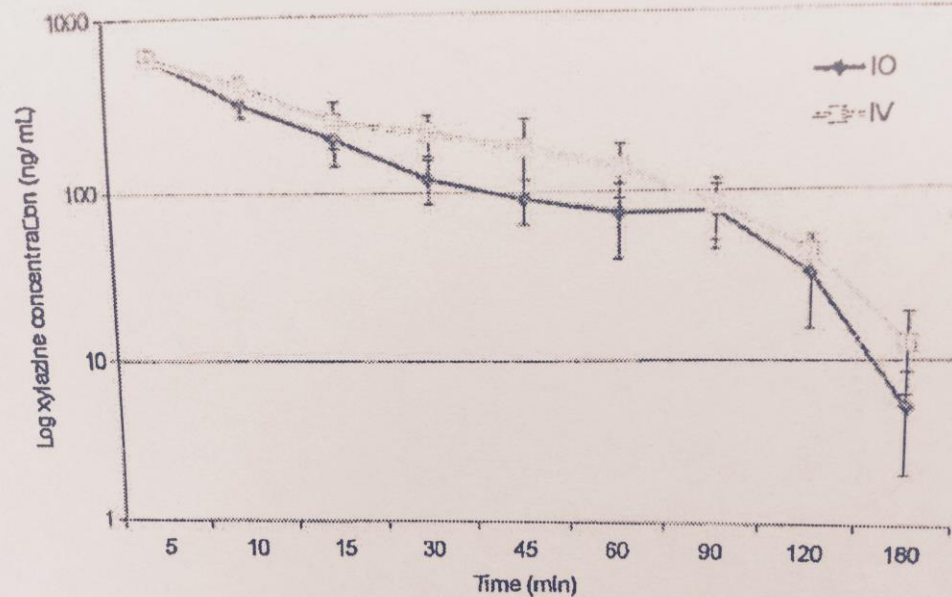


Fig. 4. Semi-log graph of mean and 95% confidence interval of serum xylazine concentration over time in the i.v. and IO groups. There was no statistical difference between the i.v. and IO groups.

during the subsequent IO administration. However, if the

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XYLAZINE CONCENTRATIONS FROM THE WATERMAN CITED STUDY

NOTE THAT THE PLASMA CONCENTRATIONS ONLY GO 3 HOURS POST ADMINISTRATION; THESE DATA GAVE A PLASMA HALF LIFE OF 31 MINUTES, MUCH LESS THAN THE SIXTY MINUTE HALF-LIFE FIGURE ALREADY IN THE LITERATURE WHEN THIS PAPER WAS PUBLISHED/PRESENTED. THE AUTHORS WERE APPARENTLY APPROACHING THIS MATTER FROM A CLINICIAN'S POINT OF VIEW, WHICH WOULD ACCOUNT FOR THE THREE HOUR CUT-OFF. NOTE ALSO THAT THE HORIZONTAL AXIS IS MISLEADING IN THAT IT IS NOT ARITHMETIC. THESE DATA ARE FOR SOME REASON PRESENTED IN AN UNUSUAL AND BASICALLY INCORRECT FORMAT AND ARE IN NOT IN MY OPINION IN ANY "NEW" WAY RELEVANT TO A 48 HOUR THRESHOLD.[DOSE 0.6 MG/KG]

THIS RESEARCH WAS MADE POSSIBLE BY SUPPPORT FROM

- 1/ The National Horsemen's Benevolent and Protective Association.**
- 2/ The Florida Horsemen's Benevolent and Protective Association.**
- 3/ The Ohio Horsemen's Benevolent and Protective Association.**
- 4/ The Indiana Horsemen's Benevolent and Protective Association.**
- 5/ The Kentucky Horsemen's Benevolent and Protective Association.**
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