Lotlorièn BV

The acute poorly performing sport horse - CESMAS 2008

A.V. van Weezel Errens MVSc[1], A.H. Werners, DVM, PhD, DECVPT[2] and J. Fink-Gremmels, DVM, PhD, DECVPT[3]
[1]Lotlorièn BV, the Hague, the Netherlands, author of the Equinesports Veterinary Manual.
[2]Department of Equine Sciences and[3] Department of Veterinary Pharmacology, Pharmacy and Toxicology, Faculty of Veterinary Medicine, Utrecht University, Utrecht, the Netherlands.
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"Treating the elite sports horse; can we determine withdrawal times from data available in the literature?"

Take home message

How can we establish 'cut-off' levels for therapeutic substances used in competition horses? Do we have scientifically sound data describing the effects of drugs in horses that participate in competitions? Do we have sound kinetic data to predict the mean residence time and the rate of elimination? Do we have sufficient data to propose the necessary period of retraction, i.e. the period in which a treated horse would not be allowed to start in a competition? The present abstract aims to provide some answers to these questions that rise for every veterinarian who actively is involved in the management of equine athletes.

Introduction

Competition horses need veterinary care if they encounter diseases or are injured. As this may also take place during the competition season, veterinarians might have to take a decision to use a certain drug, with a long residence time, hindering the horse to participate in a competition. Other drugs, which may be less useful, but have a short residency time, may be used and hence confer no risk to the equine athlete to be accused for drug misuse and/or doping. To reach this conclusion, the responsible veterinarian would have to know what time span is required between application of the drug, and the excretion of the drug and its active metabolites to levels, that will not influence the behavior of the animal, and/or its

performance. This research project aims to support veterinarians in their task to evaluate benefits and risks for a certain treatment, taking into account basic pharmacological and pharmacokinetic data and ultimately to estimate withdrawal time for sports, i.e. the EWT(s) (estimated withdrawal period) for therapeutic substances used in the treatment of competition horses.

At this moment there is a 'zero-tolerance' policy for all substances that are able to exert a pharmacological response in the horse, the only exception being certain drugs that are used in the therapy of gastric ulcers. In prescribed doping controls (see FEI regulations) urine or blood samples can be demanded directly after the competition, and the presence of pharmacologically active compounds result in penalties for rider and its trainer. Modern analytical techniques such as liquid chromatography coupled to mass spectrometry can detect drug molecules in concentrations that are unable to cause any significant biological response. Hence therapeutic intervention by a veterinarian, even under the best way of animal health care, can be identified, and the presence of these residual drug amounts will than be considered as doping, regardless of the biological activity of the compound under consideration. This policy was considered necessary to guarantee that in_equine sports a fair competition is conducted, not only in terms of clean sports, but also in consideration of the economic interests involved in performing horses.

Positive doping samples as a result of therapeutic intervention cause negative publicity and a slur on the integrity of equestrian sports. Therefore it is important that regulatory bodies establish procedures that are transparent, but take into account the fact, that 'cut-off' levels exist, below which no biological activity can be observed in horses.

Material and Methods

This evaluation focuses on whether or not existing data regarding the pharmacokinetic and -dynamic parameters of therapeutic substances in horses provide a basis for establishing relevant and irrelevant plasma and urine concentrations (EPC, IPC, IUC). The EPC, IPC and IUC levels are calculated using the model as described by Toutain et al.[1], which links both

pharmacokinetic and -dynamic parameters of a substance based on information retrieved after intravenous administration (independent of administration and formulation).

The evaluation is based on scientific literature (PubMed). Pharmacokinetic and dynamic information published until the summer of 2004 was assessed and the following parameters were used in the equations; total clearance (CL), volume of distribution (V_d), volume of distribution calculated by the area method ($V_{d(area)}$), effective dose (d), the dose-effect relationship Hill factor (H), steady state balance between plasma and urine (R_{ss}), concentration at which 50 % of the maximum effect is reached (EC_{50}) and the effect at a given time point (E%), concentration at time 0 ($C_{(0)}$). When essential pharmacokinetic parameters were not provided, the WinNonlin nonlineair regression analysis programme was used to determine specific data from the calculated concentration-time curves. To calculate EPC, the lowest standard dose and the mean or highest clearance rates were used.

$Cl_{total} = Q * E$

$Q_{(mL/kg/min)} = 180\ BW_{(kg)}^{-0,19}$

$t_{½\ elimination} = \ln 2 * V_d / Cl_{total}$

EPC = (standard dose per dosing interval) / (Cl_{total})

IPC = EPC / safety factor

$RA = IPC * V_{d(area)}$

$IUC = IPC * R_{ss}$

$E_{(\%)} = (E_{max} * C_{(t)}^{H}) / (E_{(0)} + EC_{50}^{H} + C_{(t)}^{H})$

$D_{(t)} = C_{(t)} * CL_{total}$

$WT_{(IPC)} = 1,44 * t_{½\ elimination} * (\log (B_{(0)} / IPC)$

$C(0) = A * e^{-\alpha.t} + B * e^{-\beta.t}$

Q = cardiac output

E = extraction ratio

BW = 480 kg

EPC = Effective Plasma Concentration

IPC = Irrelevant Plasma Concentration

IUC = irrelevant Urine Concentration

RA = Residual amount

Secondly, the reliability of the extrapolation of pharmacokinetic and -dynamic from rat to horse was evaluated. For those medicinal products used in horses with sufficient data to calculate EPC, IPC and IUC, the corresponding data in the rat were retrieved from the literature and EPC, IPC and IUC were calculated. Using the first three formulas mentioned above, the values determined in the rat were extrapolated to the horse, assuming that the volume of distribution of the substance was equal in both species. The values determined using the horse data were set at 100% and were compared with the extrapolated data. The reliability of the extrapolation was calculated.

Results and Conclusions

In total 291 articles provided data that could be used in this study. An IPC based on a Hill-factor could be established for only a few substances; the calculated withdrawal times are given in table 1. For ketoprofen, meloxicam and vedaprofen no official Hill factor was reported. Hence the EPC, the IPC and the withdrawal time for the IPC were calculated using only the EC_{50} values (table 2).

Table 1: Calculated IPC and IUC from substances with a known Hill factor

Substance	**Dose (mg/kg)**	**Hill factor**	**EPC (ng/mL)**	**Safety factor**	**IPC (ng/mL)**	**Withdrawal time $WT_{(IPC)}$ (hours)**
Carprofen	0,7	1,56	3663,58	300	12,21	189
Clenbuterol	0,8 mcg/kg b.i.d.	0,32	1,08	700	0,0015	84,24
Clemastine	0,05	3,6	2,64	200	0,0053	56,43
Digoxin	4,6	0,86	0,5	600	0,0008	22,37

	mcg/kg					
Flunixin	1,1	0,89	612,37	600	1,02	18,45
Metocurine	0,01	4,6	80,75	200	0,4	29,25
Phenyl-butazone	4,4	1,03	4440	500	10	55,6

Table 2: Calculated IPC and IUC values for substances of which the Hill factor was not reported but tha EC_{50}.

Substance	**Dosis (mg/kg)**	**EC_{50} (ng/mL)**	**EPC (ng/mL)**	**Safety factor**	**IPC (ng/mL)**	**Withdrawal time $WT_{(IPC)}$ (hours)**
Ketoprofen (S)	1,1	33	120,76	500	0,24	14,52
Ketoprofen R/S	2,2	57 +/- 9	308,6	500	0,62	6,7
Meloxicam	0,6	200	730	500	1,5	101
Vedaprofen	2	630 (94,5%)	250,7	500	0,50	30

The highest no effect level (HNEL) was reported in 7 substances (table 3)

Table 3: Substances with reported HNEL values

Substance	**Dosis (mg/kg)**	**HNEL (ng/mL)**	**Safety factor**	**IPC (ng/mL)**	**Withdrawal time $WT_{(IPC)}$ (hours)**
Caffeine	2	2000	10	200	50,92
Carprofen	0,7	1500	10	150	120,7

Dimethyl sulfoxide	0,1			1000 (FEI)	65,15
Ibuprofen	10	200	10	20	8,58
Ketoprofen	1,1	400	10	40	5,14
Salicyclic acid				540 (FEI)	66,67
Theophylline	4,5 PO b.i.d.	10600	10	1060	35,13

During the literature search it became evident that very little complete information had been published on pharmocokinetics and -dynamics of therapeutic substances in horses. Therefore calculation of withdrawal times and establishing 'cut-off' values was possible in only 10 of the 700 substances that were evaluated. Extrapolation from rat to horse resulted large variations, hence adequate extrapolation of the elimination time of a substance form one species to another does not help us in the establishment of 'cut-off' values for prohibited substances.

Rules and regulations should allow veterinarians to perform their jobs properly. The use of cut-off levels would allow for treating veterinarians to adequately aid injured or diseased horses and still enables these horses to compete. In order to adopt the use of 'cut-off' levels of therapeutic substances it is essential that not only more research is initiated into the pharmacokinetics and -dynamics of medicinal products, but also on the influences of exercise and feed-stuffs on these parameters.

Information regarding pharmacokinetic and dynamics of therapeutic substance in sport horses has recently been published in the Equinesports Veterinary Manual. The manual enables veterinarians to estimate a (scientifically based) time post-treatment a horse should not be entered in competition, i.e. EWT(s). The EWT(s) is the minimum elimination time (MET) plus a safety margin, to allow for differences between horses such as breed, age, gender, size, metabolism, degree of fitness, nutraceuticals, other medications, recent illness etc.

References

1. Toutain, P. L. Lassourd, V. *Pharmacokinetic/pharmacodynamic approach to assess irrelevant plasma or urine drug concentrations in postcompetition samples for drug control in the horse.* Equine Vet. J. 2002 34 (3) 242-9.