Guest Editorial

Control of medication in horses: Detection time, withdrawal time and beyond

One of the most difficult tasks for a veterinarian when treating a competition horse is to decide a withdrawal time (WT), in other words to recommend an appropriate delay between the end of a treatment for the horse under his/her medical responsibility and the possibility for that horse to return to competition. The review by Professor Tom Tobin of the Maxwell H. Gluck Research Center at the University of Kentucky, and his colleagues, published in this issue of The Veterinary Journal and entitled ‘A clinician’s guide to factors affecting withdrawal times for equine therapeutic medications’ comprehensively addresses the most critical factors that a veterinarian should integrate before advising trainers and owners (Tobin et al., 2013).

In their introduction, Tobin et al. (2013) briefly address the most important concepts that a veterinarian should not confuse when making a recommendation, namely, what is a detection time (DT) versus a WT? I would like to emphasize that there is a clear distinction between the European and US perspectives here because, in Europe, only DTs, and not WTs are issued by the racing authorities. The European Horserace Scientific Liaison Committee (EHSLC) is the organization emanating from the racing authorities of Britain, France, Ireland, Italy, Germany and the Scandinavian countries (Sweden, Norway and Finland) and is charged with harmonizing the screening limits (SLs) of analytical techniques used for medication control amongst its members and to release corresponding DTs.1

For the EHSLC, a DT is an observation and not a recommendation. More precisely, the DT is the first observed time point at which urine and/or plasma samples collected from all horses (generally n = 6) in a study conducted according to specific recommendations (a given medicinal product, manufacturer’s recommended dosage regimen, etc.) are negative. Thus, the concentrations in the plasma and/or urine are below the harmonized SL of the analytical technique. It should be understood that according to the EHSLC, a DT is only a piece of information without any statistical protection that is released by racing authorities to assist veterinarians in subsequently recommending their own WT. This explains why a WT recommended by a veterinarian for horses competing in Europe should be longer than the EHSLC’s DT in order to avoid the risk of a positive control. Veterinarians should transform a DT by taking into account the impact of all possible sources of animal variability (age, sex, breed, training, racing history, etc.) and those of the medicinal product actually administered (formulation, route of administration, dosage regimen, duration of treatment) as extensively discussed by Tobin et al. (2013) and previously by Barragry (2006).

Disturbing evidence for all players in this field is the large differences existing amongst jurisdictions in terms of issued WTs/DTs and a possible confusion between a DT and a WT. The recent example of firocoxib is illustrative. Firocoxib is a recently launched COX-2 selective non-steroidal anti-inflammatory drug (Equi-ox, Merial). For the product Equi-ox, the EHSLC issued a DT of 15 days for an oral dose of 100 μg/kg for 7 days. In the meantime, using exactly the same experimental data set, the Racing Medication and Testing Consortium (RMTC),2 which is the US counterpart of the European EHSLC, published in its list of ‘Controlled Therapeutic Medications’, a WT (not a DT) for plasma of 14 days for the same oral dosing.3 In addition, the RMTC qualified the plasma level (20 ng/mL) associated with this WT. At first glance, a layman could conclude that the EHSLC’s DT and the RMTC’s WT are equivalent. Actually, this is not the case as the RMTC computed a statistically protected WT (R. Arthur, personal communication) using the statistical definition that is commonly used to compute a WT for drug residues with the computational method used for milk.4 This means that the WT computed by the RMTC for firocoxib is the time when the upper one-sided 95% tolerance limit for the plasma concentration is below 20 ng/mL with 95% confidence, or more simply, if a jurisdiction uses a plasma level of 20 ng/mL, observing a delay of 14 days would guarantee (with a risk of ≤5%) that at least 95% of the horse population is under the specified level of firocoxib.

To offer such a population guarantee with a WT of a ‘reasonable’ duration of 14 days, the RMTC was obliged to select a relatively high plasma concentration level with respect to the effective plasma concentrations of firocoxib in horses (about 100 ng/mL). In other words, the considered plasma level was tuned by the RMTC to enable a 14-days population WT to be computed. The priority in this approach is the protection of the owner/trainer against the risk of a positive control. Indeed, in the US, horse owners, trainers and veterinarians are very committed within the regulatory process which is why the US approach is to avoid positive tests even at the sacrifice of the principles of drug free racing. In doing so, the US organizations implicitly accept that by actually observing the 14-days WT of firocoxib in a horse population, some slow administration, dosage regimen, duration of treatment) as

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1 See the EHSLC website: https://www.ehslc.com/ (accessed 26 August 2013).


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metabolizing horses actually race under the residual influence of the drug (20 ng/ml) while other more rapid metabolizers are totally free of the drug after an interval of 14 days.

In addition, it should be kept in mind that the US does not use SLs. The 20 ng/ml firocoxib level is actually a plasma regulatory threshold (RT), not a SL. Accordingly, a laboratory would need to add a measurement uncertainty calculation to the RT and, due to the contentious legal challenge of laboratory results, a laboratory would be very unlikely to report a firocoxib level below 25–30 ng/ml in plasma. Finally, to add a further layer of complexity, it should be acknowledged that the RMTC is not a national US Authority and each US State is free to adopt or not the suggested RMTC WT. This leads to a range of published WTs for firocoxib from 24 h (New Mexico) to ‘not permitted at any level’ (Florida) with several States at 14 days (e.g. Arizona, California). In Canada, a WT of 14 days is also reported.

For the EHSLC, the method of obtaining a DT is exactly the opposite to the US approach for a WT. The SL is first determined without any consideration of the possible DT/WT because the EHSLC priority is animal welfare and the selected SL should guarantee a total lack of residual drug effect for the vast majority of horses. Thus, a SL from EHSLC for firocoxib in plasma would be lower than 20 ng/ml (actually the operational EHSCL SL is for urine). Then, the EHSCL merely releases the longest observed DT in the considered experimental data base, in this case 15 days. Here, the risk is no longer for a horse that is racing under the masking influence of firocoxib but the risk for the owners/trainers of having a horse for which the depletion curve of firocoxib is slower than the slowest observed by the EHSCL.

Facing this kind of situation, a veterinarian can rapidly be lost and it is easy to understand why international harmonization is so difficult. The International Federation of Horseracing Authorities (IFHA) encourages international harmonization through the use of internationally agreed SLs and published ‘Detection Times’ (rather than RTs due to the technical requirements for using RTs as compared to SLs). To achieve this goal, a prerequisite is to be certain that the same values are shared amongst organisations by explaining what is the priority of medication control? Is it horse welfare, fairness of racing, institution reputation, confidence of punters, breed selection, legalistic considerations, convenience/horse trading, etc.? The same consolidated definitions must then be used when considering the DT vs. the WT.

A supplementary step to facilitate international harmonization would be to adopt the same procedure to determine an SL and a DT even if all roads may lead to Rome. To the best of our knowledge, only the EHSCL has an explicit procedure that follows the well-established principles of risk analysis to determine an SL and a DT with the three sequential steps, namely risk assessment (RA), risk management (RM) and risk communication (RC) (Toutain, 2010b). During the RA step, the so-called irrelevant plasma concentrations (IPC) and irrelevant urine concentrations (IUC) are estimated using standard pharmacological concepts (Toutain and Lassourd, 2002), irrespective of the possible DT/WT and the sensitivity of analytical techniques. Computation of IPC and IUC was the historical option selected by the EHSCL for medication control to replace the so-called ‘zero tolerance’ approach that was no longer acceptable when considering the high level performances of some analytical methods (Smith, 2000) that are now able to track certain substances (such as phenylbutazone) to much lower concentrations than the pharmacologically established IPC or IUC. Thus, this first RA step is purely a scientific one and it is probably the easiest to harmonize if the same values are shared by stakeholders, i.e. if it is accepted that science cannot be violated even to achieve a short DT/WT as was the case for phenylbutazone for several jurisdictions.

During the RM exercise, an SL is then selected taking into account not only the scientific evidence resulting from the previous RA step but also real world constraints (cost, capability, convenience and, above all, harmonization of the SL that is the ultimate goal of any international harmonization). The last step of the RC consists in issuing a DT, and unlike the SL that is by essence a genuine drug parameter, many possible DTs can be released from a single SL taking into account all possible local variability in drug usage (such as formulation, route of administration, dose level, and breed).

For the future, a tremendous advance would consist of performing international population kinetics in order to measure quantitatively the influence of the main factors of variability that impact a WT, as reviewed by Tobin et al. (2013), and that are mainly of biological origin (breed, sex, age, exercise, disease, etc.). Population kinetics is becoming more and more popular in veterinary medicine and is not out of reach for the racing industry even if several hundred horses needed to be investigated to build a relevant population model. Using Bayesian approaches, an individual typical WT for a given horse could be estimated using published population parameter estimates conditional on the demographic characteristics of the horse in question by the computation of so-called ‘Empirical Bayesian Estimate’. This Bayesian approach is now well-established in other fields of therapeutics and is beginning to attract the attention of the horse industry (McGree et al., 2013).

In most instances, such an individual WT would be shorter than the one computed by the population definition of a WT as used by the RMTC for firocoxib and could replace the currently precautionary approach that involves applying some more or less conservative safety factors to estimate a WT from a DT as released by the EHSCL (Toutain, 2010a).

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References


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