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Medication Migration: The Charles Town Naproxen Experience and Why It Matters to All Racing Jurisdictions

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Medication Migration: The Charles Town Naproxen Experience and Why It Matters to All Racing Jurisdictions

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Therapeutic medications are critical to the health of humans and animals alike, and racehorses are no exception. To expect horses to perform at high levels without the benefit of modern therapeutic medication is both unrealistic and inhumane. All industry stakeholders agree that medication that impacts performance or masks lameness at the time of competition needs to be restricted, but turning back the clock to the time before we understood the benefits of anti-inflammatory medication in counteracting the rigors of high-intensity performance is wrong for the industry as well as for the health and welfare of the horse.

Collateral damage from the aggressive push of industry regulators to limit the use of therapeutic medications has included the loss of any number of medications previously in common use. Among those medications with valuable applications in racehorses that have been unrealistically restricted are isoxsuprine, methocarbamol and naproxen.
GETTING TO KNOW NAPROXEN

For many years, Equiproxen was available as an FDA-approved, safe and effective nonsteroidal anti-inflammatory (NSAID) for horses. Like humans, not all horses respond similarly to all NSAIDs, and the availability of different FDA-approved formulations allowed access of appropriate anti-inflammatories for horses in need of alternatives to phenylbutazone or flunixin. For that matter, while it has not been available to the market in a number of years, Equiproxen remains an FDA-approved medication for horses.

Despite Equiproxen’s lack of availability, veterinarians and horsemen alike have continued to use naproxen, the FDA-approved human formulation, for those horses in need of this alternative NSAID. In some jurisdictions, such as Kentucky, warnings have been issued to avoid such use because traces of naproxen can be detected for weeks after a relatively short course of treatment.

Naproxen is usually recommended for back pain and relief of muscle cramping in cases in which typical treatments like methocarbamol are ineffective alone. Additionally, naproxen is prescribed to horses with sore feet to avoid injections of the coffin joints and navicular bursae, procedures that concern practitioners when required repeatedly. To provide the best possible care for the high-level athletes under their care, veterinarians reach for naproxen in these specific instances in which other NSAIDs are not therapeutically effective.

LOGIC OF IDENTIFYING NAPROXEN AT LOW LEVELS

Naproxen can be identified in horses for up to 47 days after the last administration if the horse remains stabled in the same stall in which it was administered the medication (Wennerlund et al., 2000). More important, the amount of naproxen identified in a horse that was never given naproxen but stabled in the stall of a horse given naproxen can be indistinguishable from a horse actually given the drug. Although logic would dictate that the amount of medication that can be recycled in a horse from urine contamination cannot impact a horse’s physiology in any way, these trace blood levels can be detected and may be called a positive in some jurisdictions. Common sense and logic occasionally seem absent from the regulation of horse racing.

HORSEMEN’S ALERT ABOUT NAPROXEN

The likelihood of environmental contamination from naproxen causing a positive test has not been lost on the National Horsemen’s Benevolent and Protective Association, and the following alert was published in its book, World Rules for Equine Drug Testing and Therapeutic Medication Regulation: 2012 Policy of the National Horsemen’s Benevolent and Protective Association, by Dr. Thomas Tobin, Dr. Kimberley Brewer and Kent Stirling:

Naproxen is an oral medication. The dose is large, and naproxen seems to be chemically stable in the environment. Testing can be highly sensitive, and traces of naproxen have been detected for long periods after the last nominal administration, most likely associated with its environmental presence and resulting in inadvertent re-exposure. In April 2006, Kentucky recommended “horsemen, veterinarians and owners to discontinue use of naproxen AT LEAST 120 hours before the race in which the horse is entered.”

Naproxen is a classic stall/environmental substance in the horse. It is a high-dose oral NSAID used in both humans and horses. The dose to a horse is 5-10 mg/kg or more administered orally once or twice a day, so the total daily dose can be as high as 10 grams/day. By modern analytical standards, this is an amount that a chemist will trip over, making naproxen readily detectable in post-race plasma and urine samples. Additionally, naproxen is unusual in that it is a relatively small molecule; one gram of naproxen actually contains 33 percent more naproxen molecules for the chemist to detect than one gram of phenylbutazone.

\[\text{Footnotes:} \quad ^{1}\text{Nick Metinnis, DVM, personal communication}\]

\[\text{Footnotes:} \quad ^{2}\text{Mark Cheney, DVM, personal communication}\]
INADVERTENT ENVIRONMENTAL EXPOSURE

The importance of inadvertent stall/environmental exposure as a source of trace-level identifications was abruptly brought to the attention of the racing world in Cambridge, England, in 2000, and naproxen was a charter member of this first group of identified stall-contaminating medications. At the International Conference of Racing Analysts and Veterinarians (ICRAV) that year, no fewer than four papers were presented showing that the therapeutic medications flunixin, naproxen, meclofenamic acid and isoxsuprine were all significant stall contaminants, to the extent that a clean horse put into a post-treatment stall immediately went “positive” just from exposure to the post-treatment stall environment. In a paper from Hong Kong, it was shown that cobwebs in a treatment stall contained the medication, immediately explaining a number of unexpected isoxsuprine identifications. Since that time, myriad papers in different journals have come to the same conclusion: Horses can trigger readily identifiable positive tests in post-race samples from urine contamination of their hay and bedding, even if the tested horse was never administered the medication.

In fact, looking back with the wisdom of hindsight, our Canadian colleagues had much earlier—around 1985 or so—seen the unusually long time required for horses to “clear” naproxen after the nominal last administration, showing that by 120 hours post-dosing plasma naproxen concentrations had bottomed out at about 200 ng/ml or so and then leveled out, not declining further. What was actually happening, of course, was that the naproxen in the stall was re-contaminating the horses, and what our Canadian colleagues were most likely measuring was evidence of the presence of naproxen in the stalls of these horses, as pointed out by our Swedish colleagues some 15 years later in their Cambridge 2000 ICRAV paper.

NAPROXEN ISSUES AT CHARLES TOWN

Fast-forward another 15 years to Charles Town Races in West Virginia in 2015, when Industrial Laboratories took over the state’s testing. When the Association of Racing Commissioners International’s Controlled Therapeutic Medication Schedule was introduced, the threshold for all substances not on the schedule went to zero tolerance, and the contract laboratory was changed from Truesdail to Industrial Laboratories. Attendant with this change was a sudden sporadic pattern of identification of low-concentration naproxen positives. They were being reported at a rate of about one a month in plasma, with concentrations ranging from 6 ng/ml to 160 ng/ml. The first question that springs to mind is this: Where were these low-concentration plasma naproxen identifications coming from?

Preliminary review of the data showed that one early plasma positive was at 4,000 ng/ml, fully consistent with a recent full dose naproxen administration. There were no further high-concentration naproxen identifications, suggesting a lesson learned. All of the other naproxen identifications, however, were much lower concentrations, the highest at 161 ng/ml and the balance below 100 ng/ml, with most below 50 ng/ml and one as low as 6.3 ng/ml, a very low plasma concentration of naproxen.

An initial look at the low-concentration plasma identifications suggested that they were associated with “ship-ins,” so the first theory was that the ship-in stalls at Charles Town were contaminated with naproxen. Responding to this possible explanation, the West Virginia Racing Commission reportedly sampled the ship-in stalls and had the samples analyzed, but to our knowledge the results of this testing have never been released.

We must also note that sampling a stall is one approach to this question but that a more relevant, definitive and defensible approach is to simply put a clean horse in the stall for a day or two and then take a blood and urine sample from the horse. As suggested by the considerable scientific literature on the subject, if the stall is actually significantly contaminated, the horse will test positive for the medication in question, and a horse sniffing around the stall in question for 24 to 48 hours is a much more definitive and defensible test than simply “spot sampling” the stall with samples that may or may not pick up what the horse will pick up and immediately transfer to his blood and urine.

Our next step was to review all of the individually claimed naproxen identification information with the able assistance of Maria Catignani, executive director of the Charles Town HBPA. When working on the data files, we first looked at the jurisdictions from which the affected horse had shipped in to Charles Town. It soon became apparent that a preponderance of these
horse had shipped in from the Mid-Atlantic states, which, it also soon became apparent, had very different regulatory policies regarding naproxen compared to West Virginia’s.

Based on discussions with veterinarians, chemists and other colleagues and a review of testimony in those Mid-Atlantic cases, it was found that many if not all of the Mid-Atlantic states have had a long-standing regulatory threshold for naproxen of 1,000 ng/ml in plasma, a threshold that is apparently still in place in these states.3

This finding immediately pointed to an additional possible source for these low-concentration plasma identifications of naproxen, namely that they were irrelevant trace-level residues of therapeutic administrations that “hung over” in horses racing in the Mid-Atlantic when they shipped in to Charles Town. None of these 161 ng/ml or less plasma residues identified in the Charles Town positives would have raised an eyebrow in the Mid-Atlantic states. Additionally, the range of values in these Charles Town ship-in identifications was sufficiently low enough that their origins could reasonably be attributed to trace residues of naproxen associated with inadvertent or unknowing stall exposure to traces of the medication. In lay terms, horses in the Mid-Atlantic states are racing with pharmacologically insignificant traces of naproxen in their plasmas. The concentrations are well below where the Mid-Atlantic drug testing radar is set for naproxen, but those concentrations have the potential to trigger a trace-level identification positive in the now zero tolerance for naproxen at Charles Town.

So, with regard to naproxen, it appears that Charles Town is a border jurisdiction with horses from the Mid-Atlantic shipping in that are clean by Mid-Atlantic levels but testing positive for traces of naproxen by Charles Town’s new regulatory standards. Given this circumstance, the most practical approach to this matter is to set a screening limit of detection for naproxen in Charles Town that recognizes that horses from the Mid-Atlantic states will occasionally tend to test above 6 ng/ml in plasma and to set an upper limit on this screening limit of detection that accommodates the needs of these Charles Town ship-in horses.

3 George Maylin, DVM, personal communication

**SETTING A SCREENING LIMIT FOR NAPROXEN**

Taking this approach, we therefore reviewed the statistical spread of the trace-level Charles Town plasma identifications and calculated the concentrations at which “soft” and “hard” outliers of the trace-level naproxen identification population occurred. This analysis placed the “hard” outlier concentration at close to 250 ng/ml, which we selected as our recommended screening limit of detection for the Charles Town authorities in this naproxen matter.

We also reviewed how this proposed screening limit of detection compared with the current list of regulatory thresholds for the RCI-controlled therapeutic medication thresholds. Our analysis showed that this proposed screening limit of detection for naproxen fell within the broad range of the RCI-controlled therapeutic medication thresholds, confirming its suitability for use in circumstances such as the Charles Town situation.

A detailed copy of this analysis, with extensive supporting documentation and the proposed screening limit of detection solution, was presented to the West Virginia Racing Commission as it reviewed these naproxen identifications. The outcome was that a significant number of these identifications were rescinded, although it is unclear at this time precisely what the new screening limit of detection for naproxen in West Virginia is or will be.

That brings us to one final matter raised by these Charles Town events, which is the status—or more correctly at this time the non-status—of naproxen as an RCI-controlled therapeutic medication. Naproxen has a long international history and an excellent safety record as a controlled therapeutic medication as evidenced by the 1985 Canadian research and the 2000 Swedish research, as well as its 30-year history as a controlled therapeutic medication in the Mid-Atlantic states and its status as an FDA-approved medication in horses. Given these circumstances, it may well be appropriate to recommend to regulatory authorities outside of the Mid-Atlantic region that the decades-long historical threshold for naproxen of 1 ug/ml be included in the RCI list of controlled therapeutic medications based on its long-established worldwide history of use as a safe and effective equine therapeutic medication.

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**CONCLUSION**

Rational thresholds for therapeutic medications need to be considered in all jurisdictions to allow the reasonable treatment of our precious athletes. The limitation of a practitioner’s armamentarium to an arbitrary 28 or 30 medications, with limited scientific basis for the thresholds, is at the very least unrealistic and at worst endangers the health and welfare of the horse. The West Virginia Racing Commission took the high road in the case of naproxen, choosing a reasonable threshold, and other jurisdictions should take notice. In a recent case in Kentucky, both the absolute insurer rule and the arbitrary threshold for methocarbamol were successfully challenged. Racing commissions across the country need to pay attention and follow the lead of West Virginia. Rational regulation of therapeutic medications avoids costly legal battles and allows our regulators to get back to the business of promoting horse racing and fighting the real threats to the integrity of our sport.