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FACTORS AFFECTING 'DETECTION TIMES' AND 'WITHDRAWAL TIMES' FOR NSAIDS

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Definitions:

Detection Times:
These are times post administration during which particular agents can be detected.

Withdrawal Time Guidelines:
The estimated time prior to racing that a therapeutic medication should be withdrawn so as to reduce or avoid the possibility of a chemical identification.

Clearance Time:
This is an undefined term in racing chemistry. It is used for the theoretical time it takes an agent to completely 'clear' a horse. 'Clearance' is a well defined but an entirely different concept in pharmacokinetics (where clearance of a drug is defined as the rate of elimination by all routes normalised to the concentration of the drug in a biological fluid).

Threshold:
A 'threshold', or 'limit', or 'cut-off', or 'decision level', or 'reporting level' is any defined drug or drug metabolite concentration in a biological fluid that determines whether regulation should take place or not. In racing, concentrations greater than the stipulated threshold initiate regulatory action, while those below threshold do not.

Detection Time data is authenticated (published) data on the period post administration during which a drug, or medication, or a metabolite thereof, has been reported to have been detected in the blood, urine or other body fluid of the horse. It is usually based on experiments with small numbers of horses that are not racing or in training. The analytical methods used may not be authenticated or appropriate. The dosage used may not be the full therapeutic dose or schedule.

Withdrawal Time guideline is generally longer than the longest reported or published 'detection time' for the agent. The suggestion of a withdrawal time is best the province of the treating veterinarian, who is most familiar with the horse, the history of the horse and any other concurrent treatments. The vet should be familiar with local testing 'sensitivity' and should have a feel for the appropriate level of risk for the circumstance. I always make clear that a suggestion is simply my best professional opinion and that there are no guarantees in life.

Factors Affecting Withdrawal Times:

Dose:
Agents at gram doses cannot be missed by the analytical chemist and agents in a greater than 50mg dose are not difficult to detect. At doses of less than 5mg, agents become quite challenging to detect and at less than 1mg/horse are very challenging.
As a result of the typical doses of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) used in horses, analytical detection of these agents is generally not a problem. NSAIDs are highly protein bound in plasma and readily detected in plasma or serum. Their regulatory control in the US tends to rely on detection, in plasma or serum, usually with defined quantitative regulatory limits.

Sensitivity of testing:
This factor is critical with increased sensitivity resulting in longer detection and withdrawal times. ELISA testing is 100 to 1000 times more sensitive than Thin Layer Chromatography (TLC) testing. If an ELISA test is developed for an agent, the old withdrawal time guidelines may become obsolete overnight. With TLC technology, Flunixin had a 48 hour detection time in urine. With the introduction of an ELISA test for Flunixin, urinary detection time went from 2 to 14 days. This resulted in multiple identifications in some jurisdictions

Local testing procedures:
Testing methods are far from standardised. In Canada for example there is 'Limited Sensitivity Testing' so that Canadian detection time data must be interpreted with care. Canadian withdrawal time guidelines may be shorter than other withdrawal times.
Regulatory limits currently vary widely between states and countries.

Urine pH:
The Trapping Rule: Acidic agents trap in basic urine, basic agents trap in acidic urine.
There can be up to a 10,000-fold range between acidic and basic urines. This is not something you can influence, but it is something to be aware of and can explain some unexpected urinary 'identifications.
Example 1: Oxyphenbutazone (acidic) traps 200-fold more in basic urine than acidic urine.
Example 2: Lignocaine (basic) traps 1000-fold more in acidic urine.
The full extent of this effect is not known for most agents, but it is always useful to know the pH of the urine sample when interpreting forensic data.

Frequency of administration:
If an agent is highly lipid soluble, it will tend to accumulate after repeated doses. A classic example is THC in humans. Other examples include isoxsuprine in the horse as well as phenylbutazone, which shows dose dependent kinetics. Acepromazine, promazine and related antipsychotics are found in the urine for months after the last dose in humans.
Route of administration:
Oral administration can prolong withdrawal times. It can take up to 5 days for ingesta to pass through a horse. Slow dissolution tablets can stay in the gastrointestinal tract for up to 5 days. There is considerable data on phenylbutazone to suggest that its absorption is delayed by food or hay in the GIT.

Sustained release preparations:
These are often oral medications, which can remain in the gastrointestinal tract for 5 days. The urine will contain the agent for at least 5 days and possibly longer.

Time of last meal:
On a theoretical basis, food intake can interfere with the absorption of medications, delay time to peak plasma concentration and extend withdrawal times. The last dose given to a horse should therefore be IV.

Drug formulation:
Care should be taken with different oral formulations. It should not be assumed that apparently similar preparations from different manufacturers are equivalent. The last dose prior to competition should always be IV.
Other medications:
There is always a concern that certain individual medications can interfere with the metabolism or elimination of another. For example, recent Canadian experience and the literature on omeprazole suggest that this agent may interfere with the metabolism of diazepam.

Stable and other contamination:
Recent research and field experience has suggested that treating horses in a stable significantly contaminates the stable. The risk of contamination can be quite high if the agent is administered orally, especially if as a powder or a paste. There is also a risk if the medication is administered IV. Dr Auer's suggestion of a designated treatment stable is a good conservative precaution.

The Non-Steroidal Anti-Inflammatory Agents
These are acidic agents and this determines many of their analytical and pharmacological characteristics. They are relatively less potent agents and therefore doses are in the 0.5 to 3 grams per day range. They are highly plasma protein bound and easily detectable in serum or plasma and are also readily detected in urine. NSAIDs are generally therapeutically active for about 24 hours but are excreted for relatively long periods in urine – up to two weeks at maximal testing sensitivity.

NSAIDs are used in supportive treatment for musculoskeletal and soft tissue conditions, because of their antiinflammatory, analgesic and antipyretic effects. Their principal action is to inhibit cyclooxygenase (COX) enzymes and thereby reduce prostaglandin and thromboxane production. There are two forms of cyclooxygenase: COX-1 is a constitutive isoform found in blood vessels, stomach and kidney, while COX-2 is induced in settings of inflammation by cytokines and inflammatory mediators Most older agents inhibit both COX1 and COX2 enzymes, but some newer agents have greater selectivity for COX-2. NSAID toxicities are commonly associated with COX1 inhibitors. COX2 inhibitors should be relatively selective for inflammatory responses and therefore have a better therapeutic index.

Aspirin
Acetylsalicylic acid has a short half life in the horse: approximately 4 hours, and it is rapidly metabolised and excreted in the urine. It has limited pharmacological efficacy. Salicylate is normal in horse urine and is therefore not commonly 'called'. The international threshold for salicylate is 750ug·ml in urine and 6.5ug ml in plasma. Doses of greater than 12g/horse will result in urinary concentrations exceeding the international threshold at 24 hours.
Thiosalicylate has broadly similar pharmacology to aspirin and is easily detectable and distinguishable by the analytical chemist. It may readily give rise to chemical identifications. In Canada it has a 30 hour detection time.

Phenylbutazone
This is the standard medication against which all other NSAIDs are compared. The dose is approximately 1-3g/day, parenterally, or more commonly, orally. The oral absorption characteristics are erratic, so the last administrations prior to competition should be IV. The onset of peak action is at least 4 hours post oral administration. Phenylbutazone seems to act on the inflammatory component of pain and does not directly suppress the perception of pain, unlike the narcotics or local anaesthetics. This is consistent with its mechanism of action via suppression of prostaglandin synthesis. It acts to reduce pain, swelling and inflammation, especially in acute inflammatory responses, and 'normalises' inflamed tissues. Its effects on performance are unclear, but it has been shown, in very limited experimental work, to improve performance in clinically 'normal' horses; which brings into question the definition of a sound horse.

Phenylbutazone was at one time the most popular and economical NSAID used in horses. It has a clinical efficacy comparable with other NSAIDs. It has been claimed that the dose of drug producing analgesia is less than that producing an antiinflammatory effect, so what is the nature of its pharmacological effect? Phenylbutazone is often described in lay literature as a 'painkiller', however when tested in our analgesic model, it did not suppress 'normal' pain perception. It

apparently acts to clear up minor musculoskeletal problems, thereby improving performance. My definition of a sound horse would therefore be a horse declared sound on skilled clinical inspection, which is then given a therapeutic dose of phenylbutazone.

Phenylbutazone is metabolised to oxyphenbutazone and gammahydroxyphenbutazone. The pharmacological actions of phenylbutazone are terminated by this metabolism. Phenylbutazone and its metabolites are readily detected in post-administration urine samples. These metabolites are acidic and therefore concentrate in alkaline urine. There is at least a 200-fold increase in concentration of oxyphenbutazone in alkaline urine. This very significant concentrating effect means that what is commonly detected in post race urine is trace oxyphenbutazone in a horse producing alkaline urine. The latest detection time I am aware of is about 14 days post dosing (Hong Kong). Therefore, I believe blood testing is by far the 'fairest' procedure for detection of phenylbutazone and other NSAIDs.

Phenylbutazone has a t-½ of approximately 6 hours in the horse. It appears however, that oxyphenbutazone may act to inhibit the metabolism of phenylbutazone. This gives rise to 'dose dependent kinetics' for phenylbutazone in the horse, which is when as the blood concentrations of phenylbutazone rise, it inhibits its own metabolism and its half life therefore gets longer. Phenylbutazone has a narrow therapeutic range in the horse and the dose dependent kinetics readily give rise to toxic blood concentrations. Signs of toxicity include anorexia, depression and oral and gastrointestinal ulceration. Toxic effects include protein losing enteropathy, neutropenia, renal papillary necrosis and death from hypovolaemic shock. Therefore, care must be exercised with longer term dosing with phenylbutazone. If phenylbutazone is withdrawn early, then the prognosis is good. If it is not withdrawn, then death is likely and may be delayed up to 50 days post dosing.
There is no ARCI classification for phenylbutazone because this agent was closely regulated with thresholds before the ARCI classification system was developed. The US threshold is 5ug ml in plasma. With a typical dosing regimen, the detection time is 48 hours or more. Single IV doses of phenylbutazone yield blood concentrations unlikely to exceed the 5ug/ml threshold at 24 hours post dosing.

Flunixin (*Finadyne*)
This is another very commonly used NSAID in the United States, which is overtaking phenylbutazone in both market share and clinical acceptance. Flunixin is listed as an analgesic, antiinflammatory and antipyretic and is available in oral paste, parenteral solution and granule form. It is well absorbed (80%) after oral administration, with blood concentrations peaking rapidly. The duration of its pharmacological action is approximately equivalent to that of phenylbutazone, about 24 hours. Its therapeutic efficacy is at least equivalent to that of phenylbutazone and clinical reports suggest that it may be fractionally better.

Flunixin is very quickly 'cleared' from the blood. The beta phase half-life is quite rapid at about 1.6 hours. The half-life of the third or terminal phase is much slower and this is presumed to result in the approximately 24 hour duration of the pharmacological effect of flunixin. Unlike phenylbutazone, flunixin does not appear to saturate and doses do not tend to accumulate with repeated administration. The plasma clearance of flunixin is significantly faster than that of phenylbutazone, and flunixin can become undetectable in blood in as little as 6 to 8 hours. In urine, flunixin is generally undetectable by TLC by 48 hours post dosing, however ELISA testing can enable chemists to detect traces of flunixin in urine for up to 14 days after the last dose. Like phenylbutazone, the best regulatory technology for flunixin is via quantitative blood testing. There are different thresholds for flunixin in different states in the US: the threshold in California, for example, is 0.5ug/ml, in Ohio is 0.1ug ml and in Pennsylvania is 0.01ug ml.

Ketoprofen (Ketofen)
Ketoprofen is an analgesic and antiinflammatory, available as tablets, capsules and parenteral solution. It is well absorbed after oral administration and has a relatively short plasma half-life. Ketoprofen inhibits the cyclo-oxygenase enzymes and in some circumstances has been reported to inhibit the lipoxygenase pathway (leukotriene production) as well. This may give it an added therapeutic benefit. The plasma clearance is 24 hours and urinary detection time is thought to be at least 72 hours. Plasma thresholds vary from AHSA, 0.25ug/ml and Ohio, 0.1ug/ml, to California 50ng/ml.

Dipyrone
Regulatory limits: Jockey Club of Brazil: 1000ng/ml plasma. Canada: repeated dosing, 120 hours. AEVA: 10g sid, 72 hours, Europe 120 hours.

Indomethacin
Regulatory limits: Jockey Club of Brazil: 50ng/ml plasma, Canada: repeated dosing, 120 hours, AEVA 10g sid, 72 hours, Europe 120 hours.

Meclofenamic Acid
Regulatory limits: Ohio: 1000ng/ml, plasma. Canada: repeated dosing, 48 hours. AEVA 20g sid, 72 hours.

Naproxen
Detection time: Canada, repeated dosing 120 hours, urine

Piroxicam
Detection time: Canada, 100mg, 72 hours urine

Sulindac
Detection time: Canada, 1g, orally, 96 hours, urine

Zomepirac
Detection time: Canada, 1g, 3 days, orally 96 hours, urine

NSAIDs - Summary

- Not classic 'pain-killers', simply act to inhibit the inflammatory component of pain.
- Actions are confined to the inflamed area.
- Have no effect on 'normal' pain perception.
- Have a duration of action in the area of about 24 hours.
- Are readily detectable in plasma and serum.
- May be detected in urine for a prolonged period, and, for phenylbutazone at least, urine levels can be highly variable.
- The best, fairest, most forensically reliable approach is limits or thresholds in blood and this approach is becoming well established for these agents in the US.

Further Reading:
Equine Drugs and Vaccines: A Guide for Owners and Trainers. Eleanor M Kellon, VMD (Breakthrough Publications, 1995).
Drugs and the Performance Horse. Thomas Tobin (Springfield IL, Charles C Thomas, 1981)