

## Case report #2

# Enhancement of performance of a race horse with salicylic acid

1578 Words

### Introduction

It was questioned by a horse trainer if a horse detected with 1250 µg/mL of salicylic acid in urine and 10.4 µg/mL in plasma could have received doping medication and if its racing performances could have been enhanced. For confidentiality reasons, no detail about the condition of sampling (training, race,...) was given by the trainer.

### Problem list

- Regulatory considerations
- Possible origin for salicylic acid detected in the horse
- Performance enhancing capacity of salicylic acid
- Origin likelihood of salicylic acid concentrations found in this horse
- Ability of salicylic acid concentrations to enhance performance

### Regulatory considerations

Salicylic Acid (SA) is a prohibited drug for horses taking part to races or competitions. However, since SA is a substance arising from plants traditionally grazed or harvested as equine feed, horses may compete with the presence of SA in plasma or urine under a threshold fixed by the European Horserace Scientific Liaison Committee at 625 µg/mL in urine and 5.4 µg/mL in plasma. So, if the horse considered here has taken part to a meeting the day of the sampling, the owner and the trainer are outlaw but it does necessarily not mean that the presence of SA is the consequence of a doping medication and that the performances of the horse have been enhanced.

### Possible origin for salicylic acid detected in horse urine and plasma

Salicylic acid (SA) is a phenolic phytohormone involved in plant defence against pathogens. SA was reported to be naturally occurring in grasses, clover, legumes and other plants and could be of dietary origin in horses. For example, hydrolysed alfalfa hay were found to contain as much as 485 µg SA/g (Beaumier, Fenwick et al., 1987).

Moreover, discovery of salicylic alcohol/salicylic acid as active principles in the early 19<sup>th</sup> century led to the use sodium salicylate as the first synthetic non-steroidal anti-inflammatory drug (NSAID) in 1875 and then to the marketing of the acetyl ester of salicylic acid (ASA or aspirin) in 1898. As ASA administered to horses undergoes rapid metabolism to salicylic acid via deacetylation, it could not be

easily concluded that salicylic acid in plasma and urine of this horse could come either from diet or from ASA or salicylic acid medications.

### Performances enhancing capacity of salicylic acid

ASA is a NSAID that has antipyretic, analgesic and potent antiplatelet properties. Salicylic acid is not as potent as ASA for analgesic or anti-inflammatory effects because of the rapid loss of the acetyl group by esterase activity, which is able to acetylate key proteins covalently. In contrast to ASA, salicylic acid does not bind to COX, even if it can inhibit prostaglandin synthesis in intact cells (Higgs, Salmon et al., 1987). A recent explanation of the inhibition of prostaglandin and the anti-inflammatory effect of salicylic acid was that it was able to reduce the transduction of COX-2 in inflamed tissues (Wu, Sanduja et al., 1991).

It is quite unlikely that antipyretic and antiplatelet properties of ASA or salicylic acid can enhance performance. Indeed, indications for anti-thrombotic activity in horses are laminitis, endotoxaemia and thromboembolic colic and it can be supposed that a horse with such diseases would not participate in a race. However, the relief of pain by salicylic acid or its precursor ASA can induce better performance especially if the horse exhibits pain like lameness before administration. If the horse exhibits no pain, it is quite unlikely that the performance is improved by salicylic acid.

### Likely origin of salicylic acid concentrations found in this horse

#### *Treated animals (ASA or SA)*

Salicylic acid can be found in topical formulations licensed for use horses and absorption of the drug through the skin of the horse could be suspected. Indeed, a study reported that the topical administration of 8.4 g of methyl salicylate (7.6 g SA) on 3000 cm<sup>2</sup> per horse led to peak urine and plasma concentrations of salicylic acid of around 1000 and 10 µg/mL, respectively (Beaumier, Fenwick et al., 1987). However, for this horse, absorption of salicylic acid after topical application can be excluded because the recommended maximal quantity of salicylic acid applied on the skin for the licensed products (Table 1) is far lower than in the study of Beaumier et al. and because the sampling would have to have been performed at the time of peak concentrations, which was probably not the case. Moreover, some remaining evidence of such application would likely have been detected.

Table 1 : Licensed drugs for horse containing salicylates

Trade name	Form of salicylate	Concentration of salicylic acid in the final product	Recommended dosage
Compagel® cream	Hydroxyethyl salicylate	38 mg/g	Max 50g cream/j = 1.9 g SA/j
Dermaflon® cream	Salicylic acid	0.06 mg/g	No data
Dermaflon® solution	Salicylic acid	0.37 mg/mL	No data

There are no labelled drugs for the systemic administration of ASA or salicylic acid in horses. However, extra-label or fraudulent use cannot be excluded. After intravenous administration, the half-life of ASA has been reported to be less than 0.6 h (Lees, Ewins et al., 1987; Broome, Brown et al., 2003) in horses because of a rapid metabolism to salicylic acid. Salicylic acid has also a short half-life (3.7 h) due to a rapid elimination in alkaline urine of horses. After IV administration of 19 or 20 mg/kg ASA, the concentrations of salicylic acid were below 10 µg/mL between 6 h and 10 h after the administration (Lees, Ewins et al., 1987; Broome, Brown et al., 2003) indicating that if the horse had received an IV dose of ASA lower than 20 mg/kg, the administration would have to have been done within few hours before the control.

ASA can also be administered to the horse orally but is poorly absorbed from the gastrointestinal tract of horses. The bioavailability after intragastric administration is 6% (Broome, Brown et al., 2003). After an intragastric administration of 20 mg/kg ASA, the mean plasma concentrations of salicylic acid reached a maximum at 4 h and were below 10 µg/mL at 8 h. Here again, the horse should have received ASA within few hours before the control.

#### *Untreated animals*

A study reported that urine and plasma concentrations of salicylic acid in horses fed with alfalfa hay ranged from 33 to 627 µg/mL and from 0.41 to 3.99 µg/mL respectively (Beaumier, Fenwick et al., 1987). These concentrations are in agreement with the international doping thresholds and are fifty percent lower than those in this horse. As these thresholds have been determined statistically to have less than one not medicated horse among 10,000 tested positive (Toutain, 2010), it is unlikely that the concentrations detected in the present horse originate only from food.

#### Ability of salicylic acid to enhance performance regarding SA concentrations

Toutain et al. (Toutain & Lassourd, 2002) proposed to determine irrelevant plasma concentrations which guarantee the absence of any relevant drug effect by dividing the effective drug concentrations by a safety factor. As plasma salicylic acid concentrations of 50 µg/mL were described to be necessary to produce analgesic effects (Davis, 1980), the irrelevant plasma concentration would be of 0.1 µg/mL salicylic acid with a safety factor of 500. So, it cannot be excluded that the horse with plasma concentrations of salicylic acid of 10.4 µg/mL benefited from analgesic effects even if the concentrations were less than maximal at the sampling time. However, the salicylic acid concentrations of 10.4 µg/mL could be the consequence of an ASA administration few hours before the sampling that could have induced peak plasma concentrations higher than 50 µg/mL with high analgesic effects. It can be supposed that there was a high analgesic effect a few hours before sampling but that this did not last very long due to the very short half-life of the drug and the regeneration of COX rapidly overcoming the inhibition (with the exception of platelets). This means that the horse's performance could only have been enhanced for a few hours after the putative ASA administration and before sampling. If the horse had taken part in a race in this period, performance enhancement could not be excluded.

If salicylic acid comes from the diet or from local application, it is impossible that performance of the horse is or would be enhanced because in these cases, it is quite impossible that plasma concentrations of salicylic acid will reach analgesic concentrations of 50 µg/mL at any time.

### Conclusion

This horse had 1250 µg/mL of salicylic acid in urine and 10.4 µg/mL in plasma, concentrations two times higher than the international threshold fixed by European Horserace Scientific Liaison Committee and accidental contamination from food can be excluded. This horse must have been treated either with ASA or salicylic acid.

Regarding performance, this could not have been enhanced by local application of ASA or salicylic acid. If the horse had been treated extra label with systemic ASA or salicylic acid, the concentrations detected would correspond to administration a few hours before the control. As the half-life and effects of ASA and salicylic acid are short, performance would have been enhanced by the analgesic effects, on an inflamed joint, for example, for only few hours. If the horse had taken part in a race just before the control, this would have been considered as doping. If the horse was just training and if the administration was not repeated, it is very unlikely that the performance of this horse would further be enhanced given that the concentrations would rapidly decrease to values far lower than the legal threshold due to the short half-life of this drug.

### References

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