Spontaneous bilateral epistaxis associated with the administration of phenylbutazone in a horse

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SUMMARY
A 15-year-old male Selle Français horse was presented because of some episodes of spontaneous mild bilateral epistaxis lasting for 7 days. No history of recent trauma was reported, and decrease in exercise performance and respiratory symptoms both at rest and during exercise was not observed. Nasal discharge between episodes of epistaxis was neither seen. The horse had received phenylbutazone at therapeutic doses for three weeks in order to be treated for chronic lameness (osteoarthritis). Physical examination was quite normal but blood analysis revealed a mild anaemia, hypoproteinemia, hypalbuminemia and increased prothrombin time and activated partial thromboplastin time. Endoscopy of the respiratory airways evidenced ulcers in the nasal cavity and in the pharynx. Clinical signs disappeared after removing phenylbutazone therapy and epistaxis was not longer observed. This case indicates that although gastrointestinal ulceration and renal papillary necrosis are the most common clinical alterations due to the toxicity of the non-steroid anti-inflammatory drugs in horses, other symptoms associated with coagulopathies such as ulcers in the respiratory airways might appear.

Keywords: Coagulopathy, epistaxis, horse, phenylbutazone, cyclooxygenase.

RÉSUMÉ
Epistaxis bilatérale spontanée associée à l’administration de phénylbutazone chez un cheval
Un cheval Selle Français de 15 ans a présenté une epistaxis bilatérale spontanée pendant 7 jours. Aucun événement traumatique récent n’a été reporté et aucune diminution des performances physiques à l’exercice ou aucun symptôme respiratoire au repos ou à l’exercice n’ont été constatés. De même, aucun écoulement nasal entre les épisodes d’épistaxis n’a été observé. Cependant, ce cheval a reçu des doses thérapeutiques de phénylbutazone durant 3 semaines afin de traiter une boiterie chronique (ostéoarthrose). L’examen clinique s’est avéré complètement normal alors qu’une analyse sanguine a mise en évidence une anémie modérée ainsi qu’une hypoprotéinémie, une hypalbuminémie et une augmentation des temps de prothrombine et de thromboplastine partiellement activée. Des ulcères dans la cavité nasale et dans le pharynx ont été visualisés par endoscopie des voies respiratoires supérieures. Les signes cliniques ont disparu lorsque le traitement à la phénylbutazone a été interrompu et plus aucune épistaxis n’a été observée. Ce cas montre que, bien que les ulcérations du tractus gastro-intestinal et la nécrose papillaire rénale soient les altérations cliniques dues à la toxicité des anti-inflammatoires non stéroïdiens les plus souvent observées chez le cheval, d’autres symptômes inhérents à des coagulopathies tels que des ulcères des voies respiratoires supérieures peuvent apparaître.

Mots clés : Coagulopathie, cheval, epistaxis, phénylbutazone, cyclooxygénase.

Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) are substances other than steroids that inhibit a component of the inflammatory cascade [12]. They are widely used in equine medicine in order to control acute and chronic pain, inflammation and endotoxaemia, because of their anti-inflammatory, analgesic, antithrombotic and anti-endotoxaemic properties. The most commonly administered NSAIDs in horses are phenylbutazone, flunixin meglumine, ketoprofen, aspirin, carprofen and meloxicam [19].

The synthesis of prostaglandins (PG), mainly PGE2, is pivotal during the process of inflammation, resulting in most of the clinical manifestations, such as heat and erythema [27]. Additionally, they modulate other mediators. PGE2 promote increased capillary permeability with swelling and oedema through histamine and bradykinin, and they make pain receptors more sensitive to mechanical and chemical stimulations. Further, in more advance states of inflammation, PGE2 leads to chemotaxis of leukocytes, which are responsible for the production and activation of a variety of cytokines and other inflammatory mediators. Moreover, fever is a centrally mediated response produced by the endogenous pyrogene stimulation of PG in hypothalamus [27].

PGs are synthesized from the arachidonic acid, obtained from dietary linoleic acid and esterified into cell membrane phospholipids. The enzymatic action of phospholipase A2 on cell membrane phospholipids initiates the arachidonic cascade. Acid arachidonic is metabolized by the cyclooxygenase enzyme to PGE2, prostaglandin I2 (PGI2) and thromboxane A2 (TXA2). The NSAIDs exert their effects through specifically inhibiting the enzyme cyclooxygenase and therefore, the synthesis of PGE2 [13, 16, 30].

Cyclooxygenase exists in two isoforms, named COX-1 and COX-2. COX-1 acts in the maintenance of gastrointestinal
mucosa integrity, platelet aggregation and renal blood flow. It is not induced by inflammation, but is expressed and might have a role in the inflammatory processes. COX-2 has an active role in inflammation and is induced in response to different types of cytokines. Unfortunately, many of the most commonly used NSAIDs in equine clinic are more effective in inhibiting COX-1, thereby affecting the physiological cell functions to a greater degree than the inflammatory process. As a consequence, the administration of NSAIDs can have substantial negative effects, such as gastrointestinal ulceration, papillary renal necrosis, coagulopathies… [12].

In this report, the case of a horse with spontaneous bilateral epistaxis associated with laboratory evidence of coagulopathy after prolonged use of phenylbutazone at therapeutic doses for the treatment of chronic muscle-skeletal pain (osteoarthritis) was described.

Case report

HISTORY

A 15 year-old Selle Français gelding horse, weighing 470 kg, used for jumping competition, was remitted to the Equine Sport Medicine Center of the University of Córdoba in order to be evaluated for a spontaneous bilateral epistaxis lasting for 7 days, although he was not bleeding at the presentation. According to the information provided by the owner, the epistaxis appeared in both nostrils, although it was more intense in the left. The intensity of the epistaxis was mild, and it did not appear to be increased by exercise or by changes in head position. No history of recent trauma was reported by the owner. The horse was usually in a box and he was trained for about 1-2 hours every day, 5-6 days/week. Since the bilateral epistaxis appeared, the owner neither did notice a decrease in performance nor other respiratory symptoms, such as cough nor laboured breathing at rest or during exercise. Nasal discharge between episodes of epistaxis was not seen neither.

The horse was properly vaccinated against influenza, tetanus and rhinopneumonitis and dewormed. He was fed with a concentrate source for sport horses, supplemented with Se and vitamin E, hay and forage. At the moment of the presentation, he had received phenylbutazone per os at 1g/day for three weeks in order to be treated for chronic lameness (osteoarthritis).

PHYSICAL EXAMINATION

Physical examination was unremarkable. Heart rate was 40 beats/minute (usual range: 36-44 beats/minute), respiratory rate was 12 breaths/minute (usual range: 12-24 breaths/minute) and rectal temperature was 37.4°C (usual range: 37.0-38.5°C). The mucosa membranes were slightly pale and the hydration status of the horse was adequate. There was no difference in airflow between both nostrils. Auscultation of the thorax and abdomen did not reveal significant abnormalities. No other clinical signs compatible with systemic coagulopathies, such as petechial and ecchymotic haemorrhages of mucosal membranes were observed in the physical examination.

COMPLEMENTARY BLOOD ANALYSES

A jugular venous blood sample revealed a mild anaemia (haemoglobinemia: 60 g/L, (usual range: 111-115 g/L), a low packed cell volume (PCV) (32%, usual range: 35-45%) coupled to hypoproteinemia (55 g/L, usual range: 60-75 g/L) and hypalbuminemia (23 g/L, usual range: 25-35 g/L). Fibrinogen concentrations were within the usual range (3 g/L, usual range: 1-5 g/L). No other abnormality in haematology and clinical biochemistry was found.

Platelet number was within the usual range (119x10⁹/L, usual range: 100-500x10⁹/L). A laboratorial bleeding profile was performed. The prothrombin time (PT) was 12.9 seconds (usual range: 9.0-11.0 seconds) and the activated partial thromboplastin time (APTT) was 56.8 seconds (usual range: 30-55 seconds).

RESTING ENDOSCOPY OF THE UPPER RESPIRATORY AIRWAYS

An endoscopy of the upper respiratory airways was made in order to investigate the origin of the bilateral epistaxis.

**Figure 1A and 1B:** Ulcers in resolution (arrows) located at the end of the ventral meatus of the nasal cavity in the presented horse.
Endoscopy revealed ulcers in the nasal cavity and in the pharynx (figures 1 and 2). No active bleeding was found at that moment. No other source of haemorrhage was observed in the upper respiratory airways and in the trachea.

CASE EVOLUTION

The medication of the horse with phenylbutazone was interrupted. A telephone follow-up was made and the owner informed that the horse did not bleed again.

Discussion

Epistaxis is a clinical sign which occurs with a wide range of disorders of the equine upper and lower respiratory tract as well as in systemic coagulopathies. Determination of the source and cause of the haemorrhage is essential, in order to differentiate potentially life-threatening conditions from those which are likely to be self-limiting. A complete history, together with the clinical examination and the endoscopy might provide enough information to the clinician to diagnose the aetiology of the haemorrhage. The main differential diagnoses of epistaxis are facial and sinonasal trauma, progressive ethmoidal hematoma, neoplasia, foreign bodies, guttural pouch mycosis, rupture of the longus capitis and rectus capitis ventralis muscles, exercise-induced pulmonary haemorrhage, haemorrhagic pleuropneumonia, and systemic clotting diseases [2, 4, 7, 8, 14, 24, 25].

Diagnosis of these disorders can be made by different imaging modalities, such as endoscopy, radiography, computed tomography, magnetic resonance imaging, and scintigraphy, together with cytology studies, such as bronchoalveolar lavage or BAL. Respiratory endoscopy was the key diagnostic technique for ascertaining the source of haemorrhage in this case. By means of the endoscopy, it was found in the present case that the haemorrhage source was the presence of ulcers distributed through the whole nasal cavity and pharynx. Although this imaging technique permitted to rule out other causes of epistaxis, the potential presence of exercise-induced pulmonary haemorrhages cannot be completely excluded. Even though epistaxis in this horse was not associated with exercise, a BAL would have helped to rule out exercise-induced pulmonary haemorrhage or other types of pulmonary haemorrhages.

A blood analysis, particularly with the measurements of haemoglobinemia and PCV is pivotal in order to assess the intensity of the anaemia during/or after epistaxis episodes. The low values of PCV, haemoglobinemia, total proteins and albumin were consistent with blood loss. Unfortunately, an endoscopy of the gastrointestinal tract was not performed in order to check whether active haemorrhages and ulcers existed. It has been reported that gastrointestinal ulcers associated with NSAIDs lead to loss of blood, with decrease in PCV and proteins [18, 20, 21, 31]. The prothrombin time (PT) measures the activities of extrinsic and common coagulation pathways [3, 5] and is considered a sensitive indicator of misuse of anticoagulants [3-5], whereas the activated partial thromboplastin time (APTT) evaluates the function of coagulation factors in the intrinsic and common pathways and it is a useful screen for the function of several clotting factors [3-5]. In the present case, both PT and APTT were mildly elevated, revealing a systemic clotting disorder.

Congenital haemostatic defects were not considered because of the age of the horse (15 years). The most common differential diagnoses of acquired haemostatic defects are thrombocytopenia, acquired coagulation factor deficiencies and platelet dysfunctions [4]. Thrombocytopenia was not observed in this case. Acquired coagulation factor deficiencies and platelet dysfunctions appear with different disease conditions, such as metabolic diseases (uraemia, liver failure, hyperproteinemia, and severe anaemia), liver failure (acute hepatitis, necrosis, chronic cirrhosis,…), vitamin K deficiency (choléstasis disease and vitamin K antagonist toxicity), disseminated intravascular coagulation (systemic inflammatory syndromes, neoplasia and severe tissue injury) and drugs (NSAIDs) [15, 23, 28]. Metabolic, liver and other systemic diseases, such as neoplasia, were ruled out in the present case as not clinical and laboratorial evidences were found. The owner did not report the uptake of vitamin K antagonist. Some drugs inhibit platelet activation and aggregation by a variety of different mechanisms. Thus, NSAIDs act by inhibiting the intraplatelet cyclooxygenase, leading to impaired production of TXA2 and diminished platelet response to other agonists [32, 33].

As indicated before, toxicity of NSAIDs is derived from the inhibition of COX-1 and PGs. In the gastrointestinal tract, the main PG function is to regulate the motility, secretion, blood flow and to assure mucosal protection [17, 26, 29]. NSAIDs induce gastrointestinal ulceration via inhibition of these protective PGs. In small animal medicine, the use of more selective COX-2 inhibitors has diminished the occurrence of gastrointestinal side effects [10]. To the authors’ knowledge, the published data in relation to these drugs in horses are scarce [1]. Similarly, renal complications of NSAIDs are also related to the inhibition of basal PG production. During vasoconstriction induced after release of angiotensin, norepinephrine and vasopressin, the subsequent reduction in kidney blood flow leads to a feedback loop, releasing PGs. Thus, there is a vasodilatation and a return to normal kidney blood flow [9]. Moreover, PGs also have regulatory functions at the
tubular level. In the present case, neither laboratorial nor clinical signs compatible with kidney failure were found. It is considered that, when used at proper doses in non dehydrated patients, the occurrence of renal side effects is low, whereas in the face of a mild dehydration, the detrimental effects can be dramatic [11].

Other toxicities associated with these drugs include hepatocellular toxicity [18], blood dyscrasias, bronchoconstriction and local effects, such as cellulitis, thrombophlebitis, tissue necrosis and clostridia myositis [20]. Although systemic coagulopathies are rarely reported in horses receiving NSAIDs therapy, they have been described when the patients are subjected to other simultaneous medications, such as anticoagulant therapy [6]. The horse of the present report was not receiving other types of medications and the ingestion of anticoagulants was improbable. The reason of the appearance of ulcers in the upper respiratory airways in this horse in association with phenylbutazone therapy is unknown.

Conclusion

The administration of phenylbutazone, and probably of other NSAIDs which blocked not specifically the cyclooxygenase-2 enzyme might lead to clinical and laboratorial evidences of coagulopathies. Although uncommon, these coagulopathies might appear as spontaneous bilateral epistaxis as a consequence of coagulopathies. Although uncommon, these coagulopathies are rarely reported in horses receiving NSAIDs therapy [6]. The horse of the present report was not receiving other simultaneous medications, such as anticoagulant therapy butazone therapy is unknown.

References

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