Phenylephrine-induced epistaxis in a six-year-old Quarter horse with nephrosplenic entrapment

Neusbloeden bij een zesjarig paard na fenylefrinebehandeling voor een dorsale colonverplaatsing over de milt-nierband

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ABSTRACT

Left dorsal displacement of the large colon is a common cause of colic in horses. Treatment consists of surgery, rolling the horse under general anesthesia or intravenous administration of phenylephrine. Treatment with phenylephrine, an α1-adrenergic drug, is often associated with sweating and trembling. Especially in horses of more than 15 years old, fatal hemorrhage may occur due to hemothorax or hemoperitoneum. Therefore, phenylephrine treatment is generally not given in horses over 15 years of age. In this report, severe epistaxis in a six-year-old Quarter horse is described after intravenous administration of 22.5 µg/kg BW phenylephrine, and it is highlighted that hemorrhage may also occur in younger horses.

SAMENVATTING

Een dorsale verplaatsing van het colon over de milt-nierband is een vaak voorkomende oorzaak van koliek bij het paard. Behandeling kan gebeuren door chirurgie, het rollen van het paard onder algemene anesthesie of door toediening van fenylefrine. Een behandeling met fenylefrine, een α1-adrenerge stof, geeft vaak aanleiding tot beven en zweten. Uit de literatuur blijkt dat vooral paarden ouder dan 15 jaar het risico lopen op een fatale bloeding in thorax of abdomen. Uitgaande van de veronderstelling dat het gebruik enkel risicovol is bij paarden ouder dan 15 jaar, wordt het product voornamelijk bij jongere paarden ingezet. In deze casuïstiek wordt echter een ernstige epistaxis bij een zes jaar oude Quarterhorse beschreven na intraveneuze toediening van 22,5 µg/kg LG fenylefrine.

INTRODUCTION

Nephrosplenic entrapment of the large colon, also known as a dorsal displacement of the left colon, is a malposition of the left colon. The left colon moves along the left body wall to the area dorsal to the nephrosplenic ligament and becomes entrapped in the nephrosplenic space (van Harreveld et al., 1999; Hackett, 2013).

Mild or more severe clinical signs may occur depending on the occurrence of a total obstruction of the lumen, the orientation of the colon, accumulation of gas, obstruction of small intestines and presence of nasogastric reflux (van Harreveld et al., 1999; Eades and Waguespack, 2006; Hackett, 2013).

The diagnosis should be made by the combination of the clinical signs, rectal examination and transabdominal ultrasound (Santschi et al., 1993; van Harreveld et al., 1999; Hackett, 2013). On ultrasonographic examination of the left flank, gas reverberation is detectable (van Harreveld et al., 1999), the left kidney may not be visible (Santschi et al., 1993 in Hines, 2010; Hines, 2010) and the dorsal part of the spleen is pushed medially by the left colon. The stomach is often displaced ventrally.

A nephrosplenic entrapment can be treated with a combination of lunging exercise (jogging or walking) and the administration of phenylephrine intravenously, rolling the horse under general anesthesia or surgical correction.

Phenylephrine administration and exercise

This conservative treatment involves the administration of 45 µg/kg BW (bodyweight) of phenylephrine HCl in 1 litre of 0.9% sodium chloride (administered over 15 minutes, 3µg/kg/min) intravenously and at the same time jogging the horse (van Harreveld

and Gaughan, 1999; Eades and Waguespack, 2006; Hackett, 2013). The aim of the phenylephrine administration is to decrease the splenic volume due to a splenic contraction and the vasoconstrictive effect of phenylephrine (Hardy et al., 1994; Frederick et al., 2010; Baker et al., 2011). However, the use of phenylephrine may be accompanied by hypertension, second-degree atrioventricular block, premature ventricular contractions, atrial fibrillation and the risk of fatal hemorrhage in horses over 15 years of age (Hardy et al., 1994; van Harreveld et al., 1999; Frederick et al., 2010; Compostella et al., 2012; Fultz et al., 2013). Even if this type of non-surgical treatment is less expensive and avoids risks associated with general anesthesia, the disadvantages mentioned above should be considered when a treatment is chosen.

Rolling under general anesthesia

This procedure may be combined with the administration of phenylephrine (3-6 µg/kg/min in 15 min) before induction of general anesthesia (Hardy et al., 1994; Blikslager, 2010). The horse is positioned in right lateral decubitus and slowly lifted into dorsal recumbency. In order to allow repositioning of the colon, the abdomen is balloted during lifting (Eades and Waguespack, 2006) or rocked back and forth (Kalsbeek, 1989 ; Blikslager, 2010; Hackett, 2013). Subsequently, the horse is further rolled towards left lateral recumbency and then allowed to recover (Kalsbeek, 1989; Blikslager, 2010; Hackett, 2013).

To verify the position of the large colon after rolling on the recumbent horse, rectal examination (Eades and Waguespack, 2006; Hackett, 2013) and transabdominal ultrasound are recommended. If the position has not changed, the procedure may be repeated during the same anesthesia. According to Eades and Waguespack (2006), rolling under general anesthesia is successful in 70-90% of the cases (Eades and Waguespack, 2006).

The disadvantages of this technique are the possibility to cause a large bowel torsion or an intestinal or vessel rupture, and to aggravate the original displacement. Furthermore, the treatment is inappropriate in case of severe colonic distension and indication of intestinal devitalization (Eades and Waguespack, 2006).

Surgery

Surgery is recommended in severe cases, in which medical treatment has not been successful. It can be performed via a ventral midline approach (Eades and Waguespack, 2006; Hackett, 2013) or a left paralumbal fossa laparotomy. Another possibility is a standing laparoscopy but only in cases without colonic distention and minimal signs of pain (Hackett, 2013).

The prognosis of a nephrosplenic entrapment is good. To prevent displacement, a laparoscopic closure of the area between the left kidney and the spleen can be performed (Blikslager, 2010; Hackett, 2013) by placing a suture between the dorsal splenic margin and the nephrosplenic ligament (Röcken et al., 2005).

CASE REPORT

History

A six-year-old Quarter horse mare (bodyweight 366 kg) was presented with colic signs to the Department of Large Animal Internal Medicine, Faculty of Veterinary Medicine, Ghent University. The signs of colic had started four hours before presentation and intravenous treatment consisted of scopolamine butylbromide and metamizole sodium (5mL/100kg BW, Buscopan® Compositum Ad Us. Vet., Boehringer Ingelheim) and flunixin meglumine (1.1mg/kg BW, Finadyne®, Intervet). Also five litres of paraffin oil had been administered via nasogastric tube. Since the colic signs persisted, the horse was referred.

Clinical findings

At presentation, the horse was dull, but temperature, respiratory rate and hematocrit were normal. The heart rate was slightly increased (54 beats/min). The lumbar reflex was positive. Abdominal auscultation and percussion revealed puddle sounds in the right flank and gas bilaterally. On rectal examination, dorsal displacement of the left colon over the nephrosplenic ligament, left colon impaction and gas in the cecum were detected. On ultrasound examination, the left kidney was not visible but reverberation artefacts were found instead. The dorsal splenic border was pushed medially by the colon. The stomach was displaced ventrally but there was no reflux. The small intestines were mildly dilated but still contractile.

Therapy

At the clinic, 45µg/kg BW phenylephrine hydrochloride (Phenylephrine 15%® eye drops, Théa Pharma) dissolved in 1 L of saline solution (0.9% NaCl, Braun) was administered over 15 minutes while the horse was hand-walked. After receiving half of the dose, the horse started showing bilateral epistaxis, started to cough, to sweat and also started to tremble. On ultrasound examination, comet-tail artefacts were found in the caudodorsal part of the lungs suggesting pulmonary hemorrhage. Phenylephrine infusion was immediately terminated. Intranasal oxygen therapy was started and 10mg/kg BW tranexamic acid (Exacyl®, Sanofi) diluted in 1L of saline (0.9% NaCl, Braun) was administered intravenously. Over the next ten minutes, epistaxis gradually resolved. Over the next two days, the horse received crystalloids, was hand-walked and was not allowed to eat.

On ultrasound examination, one day after phenylephrine treatment, the left kidney could be detected.

Comet-tail artefacts were still present at the level of the caudodorsal lung field. One day later, the rectal examination and abdominal ultrasound were normal. Small amounts of hay were given over the next two days. The hematocrit was checked every four hours after the epistaxis and remained within normal limits. Also the temperature remained normal. Five days after initial treatment, the horse could leave the clinic. It was advised to keep the horse at rest for one month. The horse had a full recovery.

DISCUSSION

There is evidence that the administration of phenylephrine in horses older than 15 years can lead to fatal hemorrhage (Frederick et al., 2010). The current case report highlights however, that also young horses may develop hemorrhage and that this risk should be taken into account when treating horses with nephrosplenic entrapment.

Phenylephrine is an α1-adrenergic sympathomimetic (Baker et al., 2011) used in horses to treat nephrosplenic entrapment of the colon in combination with exercise. The effect of phenylephrine is based on inducing vasoconstriction in vascular beds (Hardy et al., 1994) and a contraction of the spleen (Frederick et al., 2010; Baker et al., 2011). The smaller size of the contracted spleen helps the colon to regain its normal position (Hardy et al., 1994). Side effects include sweating in the cervical area, restlessness, urticaria, bradycardia, hypertension, second-degree atrioventricular block, ventricular premature contractions, atrial fibrillation and the risk for fatal hemorrhage, especially in old horses (Hardy et al., 1994; van Harreveld et al., 1999; Frederick et al., 2010; Compostella et al., 2012; Fultz et al., 2013).

As an injectable phenylephrine pharmaceutical formulation is not available in some countries, epinephrine (adrenaline) (α1-, α2- en β- adrenergic agonist) has been used to induce contraction of the spleen and has proven to be efficient (Deniau et al., 2013). In contrast to phenylephrine, adrenaline shows α- and β-adrenergic activity. It induces a stronger vasoconstriction (Palm and Hellenbrecht, 1992 in Venner et al., 2001; Venner et al., 2001), an increase in arterial blood pressure and, due to the effect on β-receptors, also vasodilatation of the arterioles of the muscles and bronchodilation (Bentz, 1982). According to Venner et al. (2001), the effect on blood vessels in the muscle is beneficial in horses with colic because of a decreased bloodflow in the muscle due to shock. Negative side effects of adrenaline administration are the occurrence of second-degree atrioventricular block, ventricular premature contractions, sweating and tachycardia (Venner et al., 2001).

In the study of Frederick et al. (2010), phenylephrine administration in horses older than 15 years of age showed per year of age a 1.4 times increased risk to develop hemorrhage compared to younger horses (Frederick et al., 2010). Four of the five horses with hemorrhage immediately following phenylephrine treatment died or were euthanized. The clinical signs included epistaxis, cough or even hemoptysis, weakness, shaking, sweating and collapsing (Frederick et al., 2010). On necropsy, large volumes of blood could be found in the thorax or abdomen but only in one case the ruptured blood vessel (a. uterina) was found (Frederick et al., 2010).

Epistaxis also occurred in the horse mentioned in this case report and seemed to be related to pulmonary hemorrhage. The bleeding probably occurred in the caudodorsal part of the lungs, the same location as in exercise-induced pulmonary hemorrhage (EIPH) in athletic horses, as numerous comet-tail artefacts were found on ultrasound of this region. EIPH occurs especially in racehorses, due to the increased transmural pressure between the alveolar lumen and the inside of the capillaries (Hinchcliff, 2014).

As phenylephrine treatment is mainly known to have a higher risk in horses older than 15 years (Frederick et al., 2010; Blikslager, 2010), this treatment is still used in younger horses. However, Compostella et al. (2012) described a case of a nine-year-old mare, which was treated with phenylephrine and developed an acute hemoperitoneum after treatment. The horse was treated with a 20 mg phenylephrine in 500 ml sodium chloride solution over 30 minutes, which corresponds to about 45µg/kg, and was lunged for 20 minutes. Forty-five minutes after returning to the stable, the horse was extremely painful even though the displaced colon had returned to its normal position. On ultrasound examination, free swirling heterogeneous fluid was visible in the ventral abdomen. An exploratory laparotomy confirmed hemoperitoneum but the origin of the bleeding could not be found.

In human medicine, the use of phenylephrine has been avoided in patients with arteriosclerosis, possibility of pre-existing myocardial disease and peripheral and cerebral vascular disease, which include a fragile peripheral vascular system that isn't able to handle the increase in blood pressure induced by phenylephrine (Compostella et al., 2012). Age-related arteriosclerosis and decreased vessel compliance play an important role. Similar aged-related vascular changes might explain phenylephrine-induced vascular rupture in horses although the effect of ageing on the equine vasculature has not been defined yet (Frederick et al., 2010). It has been reported that older mares have a higher risk to develop fatal hemorraghe because of rupture of the external iliac, middle uterine or utero-ovarian arteries (Sellon, 2004). On histological examination, the uterine arteries of aged and multiparous mares show smooth muscle cell atrophy with fibrosis (Ueno et al., 2010). Grüninger et al. (1998) mentioned the occurrence of perivascular and intimal sclerosis in the vessels of older maiden mares, which appeared to be equal to "pregnancy-sclerosis" in other species. This includes atrophy in the media, elastosis and fibrosis in the media, intima and adventitia, calcification in the media and disruption of the

membrana elastica interna (Grüninger et al., 1998).

Age-related vascular wall changes may lead to impaired adaptation to a sudden increase in blood pressure and an increased risk of rupture. This could be an explanation for the occurrence of hemorrhage after treatment with phenylephrine. Non-invasive (ultrasound) techniques to assess arterial wall stiffness are applied in human patients and should also be developed for horses.

The horse in this study was treated with tranexamic acid, a lysine analogue that inhibits plasminogen activator, decreasing plasmin formation, and stimulates the release of alfa2-antiplasmin from endothelial cells. As such, hemorrhage is prevented or stopped by inhibiting the breakdown of clots after they have formed.

CONCLUSION

Despite the young age of the horse described in this case report, phenylephrine-induced hemorrhage occurred. Although conservative therapy of a left dorsal displacement of the large colon by phenylephrine administration is often successful, one should be aware of an associated risk for hemorrhage. Although especially old horses (>15 years) present an increased risk for vascular rupture, on rare occasions, it may also be seen in younger animals.

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