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AN EXAMPLE OF THE INFLUENCE OF PHENYLBUTAZONE ON ENDOTOXEMIA AND THE CLINICAL PICTURE OF JEJUNAL COMPLICATIONS IN HORSES

P. KRULJC

Key words: veterinary medicine; intestinal complication; intestinal ulcus; endotoxemia; phenylbutazone; horse

During a clinical examination of a stallion on the day after a race, symptoms were established that could not be logically connected, so a more extensive examination and treatment at our clinic were proposed. A blood sample showed changed blood parameter values. The stallion was brought to the clinic five hours later. On the basis of the clinical picture, intestinal complications were suspected, but the horse's condition did not improve even after an opioid analgesic and supportive therapy were administered. The stallion died only one hour after arriving at the clinic.

The pathological, histological and toxicological examination showed complications: jejunal necrosis and ulcers, pulmonary edema and a dilated heart, the failure of which was the immediate cause of the horse's death. Toxicological analysis showed the presence of phenylbutazone in the blood. This masked the clinical picture of endotoxemia which had a decisive effect on the damage to the heart and its failure. Immediately before arriving at our clinic, the stallion also received an infusion of calcium preparations, which had an additional toxic effect on the already weakened heart.

PRIMER VPLIVA FENILBUTAZONA NA ENDOTOKSEMIJO IN KLINIČNO SLIKO ZAPLETA JEJUNUMA PRI KONJU

Ključne besede: veterinarska medicina; zaplet jejunuma; črevesni ulkus; endotoksemija; fenilbutazon; konj

Pri kliničnem pregledu žrebca smo dan po tekmovanju ugotovili simptome, ki jih med seboj ni bilo mogoče logično povezati, zato smo predlagali obsežnejši pregled in zdravljenje na naši kliniki. Odvzeti krvni vzorec je pokazal spremenjene vrednosti krvnih parametrov. Pet ur kasneje je bil žrebec pripeljan na kliniko. Na podlagi klinične slike smo posumili na zaplet črevesa, vendar se stanje kljub danemu opioid-

Received: August 4, 1999.
Address of author: Dr. Peter Kruljc, Ass., DVM, Equine Clinic, Veterinary Faculty, Gerbičeva 60, 1000 Ljubljana, Slovenia.

nemu analgetiku in terapiji ni izboljšalo. Žrebec je poginil le uro po prihodu na kliniko.

Patološka, histološka in toksikološka preiskava je pokazala zaplet jejunuma z nekrozo in čiri, edem pljuč in razširjeno srce, katerega odpoved delovanja je bila neposredni vzrok pogina. Toksikološka analiza je v krvi dokazala fenilbutazon. Le-ta je zakril klinično sliko endotoksemije, ki je odločilno vplivala na okvaro in odpoved delovanja srca. Tik pred prihodom na kliniko je žrebec z infuzijo prejel še kalcijeve pripravke, kar je učinkovalo negativno na že prizadeto srce.

Medical history

We were able to establish from the medical history that a little less than three weeks earlier the stallion had been transported from abroad together with another stallion in a special trailer for the transport of horses. The trip lasted several days and was strenuous for the animals. The stallions were often restless, especially during delays at border crossings. A few days after its arrival, the stallion in question was entered in a difficult harness race. A week later it raced again, but was unable to complete the race. As was found out later, the horse was studded to a mare immediately after the race in spite of its condition. The next day, the stallion was examined and immediate transfer to our clinic was proposed due to the very serious condition of the animal.

Clinical picture

During the examination at his home stable, the animal was excessively quiet, apathetic and tired, and paid no attention to its surroundings. Very rapid and shallow breathing drew our attention. The measured heart rate was 23 beats per minute, while the pulse was weak and unpronounced. The breathing frequency was 40 breaths per minute and its body temperature was 37.8 °C. Two blood samples were taken, and it was noticed that the blood was very thick. The colour of the visible mucous membranes was unchanged and the skin was cold and unelastic, with marked signs of dehydration. The clinical picture and medical history did not provide all of the data required for a more accurate diagnosis, therefore immediate transfer of the animal to the clinic was recommended for additional tests and treatment.

The laboratory analysis of the blood sample showed markedly changed blood counts.

The measured blood parameters indicated hemoconcentration (erythrocyte count, hematocrit, Mg) and dehydration (Hb, Ht, Ca, Na), endotoxemia (leukocytes, lymphocytes), impaired functioning of the gastrointestinal tract (serum proteins, Ca), impaired kidney function (total serum proteins, urea, creatinine, Ca, P, Mg, Na, K) and impaired liver function (total serum proteins, bilirubin).

Table 1: Test results of the blood sample

Parameters	Mesure values	Normally values	Unit of measures
erythrocyte	13.5	6 – 10,43	n x 10^{12}/l
haemoglobin	26.6	10 – 16	g/100 ml
hematocrit	0.598	0,35 – 0,48	v 1/1
leukocytes	5.1	6 – 12	n x 10^{9}/l
neutrophils	4.0	3 – 6	n x 10^{9}/l
lymphocytes	0.96	1,5- 5	n x 10^{9}/l
monocytes	0.1	0 – 0,6	n x 10^{3}/µl
total serum proteins	54	52 – 79	g/l
urea	7.57	1,83 – 4,49	mmol/l
creatinine	258	35,36 – 194,48	µmol/l
bilirubin total	87.07	0 – 54,73	µmol/l
Ca	0.13	2,54 – 3,34	mmol/l
aP	3.36	0,48 – 1,52	mmol/l
Mg	1.9	0,58 – 0,95	mmol/l
Fe	21	12,54 – 25,07	µmol/l
Na	123	128 – 142	mmol/l
K	5.6	2,9 – 4,6	mmol/l
AP	254	20 – 350	U/l
CK	141	60 – 330	U/l
AST/GOT	23	160 – 412	U/l
χ-GT	7	9 – 25	U/l
LDH	693	141 – 460	U/l

Six hours after the examination at his home stable, the stallion was brought to the clinic. The clinical picture of its general condition at that time differed dramatically from the one seen upon the first examination. The formerly excessively quiet animal was strongly agitated upon arrival. The stallion could not move in a coordinated manner and could not stand on its own, so it was brought to the clinic premises. It was placed on the floor lying on its flanks, and the animal's agitation was increasing visibly. Its neck and body muscles were tense, it was thrashing its head about and its legs were paddling as if it was trying to gallop. The intensity of these signs was such that access to the animal was risky and dangerous for the staff. In spite of this, we succeeded in administering an opioid analgesic, butorphanol (Torbugesic®) and rehydration was begun (physiological saline, glucose).

Prior to its transport to the clinic, the stallion was examined his home stable by a field veterinarian who noticed that the animal was strongly dehydrated. He decided on rehydration with physiological saline and calcium preparations (Vetacalcin®). Soon after the beginning of the described therapy, the stallion responded with signs of intense agitation similar to those witnessed upon its arrival at the clinic.

Due to the suspicion of intestinal complications, preparations were immediately begun for an abdominal surgical procedure under general anesthesia, but it could not be performed because of the extremely poor condition of the patient, especially its extremely high heart rate, which could not even be measured. Even introduction into general anesthesia would have constituted an excessive and fatal stress for the patient

in such a condition. Less than an hour after its arrival at the clinic and 6 hours after the clinical examination in the field, the stallion died in severe cramps and with protracted cries in spite of attempts to stabilise its general condition.

After its death, the cadaver was sent for pathoanatomical and histological examination and analysis and bacteriological tests due to the unclear clinical picture and the course of the disease, as well as the circumstances. The blood sample taken upon the first clinical examination in the field, at the owner's premises, was sent to the Institute of Forensic Medicine of the Ljubljana Faculty of Medicine, primarily due to a suspicion of the presence of substances in the blood that could mask the true clinical picture and change the course of the disease, even though the medical history of the patient did not mention any previous therapy.

Results of tests

Pathoanatomical results

The autopsy of the stallion showed jejunal complications with consequential hemorrhagic congestion of the intestinal wall and the omentum, with two ulcers in the jejunal wall. The right ventricle was strongly dilated; blood congestion and pulmonary edema were established. The liver, kidneys, spleen and the meninges were also congested. Hemorrhagic edema of the subcutaneous tissue was established in the laryngeal region. Hemorrhages were found in pelvic muscles. Under the hepatic capsula as well, there were several smaller calcinated foci which were the result of parasite infestation.

The intestinal wall was hemorrhagically congested, with congestion in the submucosal veins. The peritoneum was acutely inflamed. The mesenteric veins were congested with blood and thrombosed. The kidneys, spleen, brain and meninges were congested with blood. Hemorrhages were also found under the endocardium and the splenic capsule. The hepatic capsule was thickened and fibrosis of interlobular hepatic tissue was present. Pathohistological examination of the jejunum showed that the jejunal ulcers were a pathological process only a few days old.

Bacteriological results

α and β hemolytic streptococci and *E. coli* were found in the kidneys, spleen and lungs.

Forensic toxicology examination

The Institute of Forensic Medicine of the Ljubljana Faculty of Medicine used a combination of gas chromatography and mass spectrometry (GC-MS) to prove the presence of phenylbutazone in the serum.

Discussion

Horses in which these complications occur and cause obstruction of the small intestine usually exhibit severe colicky pain 3 to 4 hours later. These complications may also last a longer period of time and even though a part of the intestine is subject to necrosis, the affected animals do not show signs of colicky pain, or this pain is insignificant. The apparent listlessness, apathy and standing with lowered heads and a complete lack of interest in the environment are associated with severe endotoxemia which is often misunderstood by owners as an improvement of the animal's condition (1).

In this stallion, the complications in the small intestine caused a complete interruption of blood flow in the affected part of the intestine, due to which the venous blood was not drained and the entire venous vasculature was filled with blood. This resulted in severe circulatory changes (hypovolemic shock). The endothelium of the blood vessels became more permeable and the plasma passed into the tissue. It is known that degeneration of the blood vessel epithelium progresses rapidly and results in the passage of the blood from dilated blood vessels into the tissue (venous infarction) (1). Due to a lack of oxygen, the epithelial cells of the intestinal villi become necrotic and 4 to 5 hours later the entire mucosal epithelium is necrotic. After 6 to 7 hours, the degenerative process spreads to the outer muscular layer of the intestinal wall. Damage to the muscular barrier enables intestinal bacterias and endotoxins to reach the lamina propria and submucosa and further on to the blood vessels. Less than 6 hours are necessary for bacteria and toxins to penetrate through the serosa into the peritoneal cavity, from which they are immediately absorbed and cause severe intoxication of the entire body. The released toxins strongly affect the animal body, and especially impair the cardiac function (1, 2).

The clinical picture of acute complications in the small intestine is manifested in permanent colicky pain, which, however, the stallion did not exhibit in its home stable. This type of pain cannot be eliminated, or can be alleviated only temporarily with analgesics. The heart rate becomes increasingly higher, and the quality of the pulse decreases, but this was not established in this case. Both parameters are important criteria for the assessment of the condition of a patient with colic, as well as endotoxins released, which are absorbed from the intestine. This depends more on hemoconcentration, reduced flow of venous blood in the heart, and the released toxins which are absorbed from the intestine. The heart rate, quality of the pulse and duration of the colic are closely related: the heart rate increases along with the development of endotoxemia (1, 3).

An important indicator of the condition of and prognosis for patients with acute complications in the small intestine is the colour of the visible mucosal membranes (cyanosis) and the capillary filling time, which is as a rule prolonged in these cases, but these changes were not found in our patient. However, an increased breathing frequency was found, which occurred as a result of pulmonary edema and developing metabolic acidosis. Due to the very rapid progression of this complication, the majority of horses die within 24 to 30 hours, primarily due to irreversible septic (endotoxic) shock and vascular collapse (1).

In spite of the very poor condition of the patient, a surgical procedure is the only possible solution, but it must be performed within 8 hours of the occurrence of the complications, when the survival rate is up to 80 % (1).

The autopsy showed that the stallion died due to the consequences of complications in the small intestine. This condition, which usually develops very rapidly, can be caused by a series of different factors.

The entire clinical case and the immediate circumstances which caused it from the very beginning up to the animal's death was carefully studied with respect to the pathoanatomical, histological, bacteriological, toxicological and pharmacological findings and analyses. A schema was created with sequences of clinical events and consequences which may have led to the death of the animal.

In addition to the stress factors (straining transport, two competitions, the horse was studded to a mare) there were probably also other reasons which might have contributed to the development of the complications of the small intestine. Most probably, this began a few days before the race. Phenylbutazone was administered by the caretaker probably due to a poor assessment of the stallion's condition – an attempt was made to imptove it with this analgesic, which is confirmed by its presence in the stallion's blood sample in the form of its active substance.

Since the stallion most probably rejected food and water due to pain, the administered phenylbutazone damaged the intestinal wall and caused both intestinal ulcers; these develop faster if the animal receives irregular and smaller meals and its intestine is less filled (4). The histological examination of the initial part of the jejunum showed that the ulcers were only a few days old, which proves that the stallion had health problems a few days before the race, and that the caretaker attempted to eliminate them with phenylbutazone. Intestinal ulcers are a rare occurrence in horses, but they are a characteristic consequence of the use of nonsteroidal antiphlogistics and analgesics. Phenylbutazone is known for being able to cause ulcers in the entire gastrointestinal tract (5). In veterinary medicine, this analgesic is used primarily to alleviate muscular and joint pain. After its administration, the substance stays in the body for a longer period of time binding on plasma proteins (99 %) and it is usually excreted within two months of administration. Activity of phenylbutazone is based on the blockade of prostaglandins formation. It has no direct effect on pain, but reduces excessive sensitivity to it by reducing the inflammatory response. It inhibits endotoxic shock, reduces the body temperature and may increase the heart rate. A sensitive indicator of high toxic doses of phenylbutazone (8-14 mg/kg/day) is a reduction in serum proteins, changes in the plasma such as reduction of nitrogen compounds, Ca and an increase in creatinine and phosphorus (4, 6). All these changes with the exception of the nitrogen content were found in the tested blood sample. Irrespective of the effect of phenylbutazone, the stallion was under its direct analgesic pharmacological influence during the last race, which is inadmissible for sports races.

During clinical examination, the heart rate was 23 beats/min. In spite of the fact that the physiological limits are between 28 and 40 beats/min, it can be even lower than 20 beats/min in older trained horses (7). The body temperature of 37.8 °C did not differ significantly from the physiological values (36.5 to 39 °C) (8). However,

the increased breathing frequency and above all shallow breathing warned of a considerable deviation from the normal values, especially since in the majority of horses the frequency of breathing ranges between 10 and 40/min, and its increase can be a very important indicator of the occurrence of a respiratory disease. Tachypnea in horses can be primarily a result of respiratory diseases associated with hypoxemia or hypercapnia (9). The colour of visible mucosal membranes was unchanged.

Conclusion

Upon clinical examination which took place only 6 hours before death, the stallion was already in a state of sepsis due to the above-mentioned changes. It was strongly dehydrated, with toxic products of the necrotic intestine spread all over its body (endotoxemia) and all of the consequences of impaired heart function. But since the stallion also received a calcium preparation as part of the therapy of dehydration, which increases the contractile power of the heart muscle and altitude the heart's excitability, this strongly excited the heart already weakened from endotoxins, it responded with a very increased heart rate, which could not be measured upon the patient's arrival at the clinic.

The administration of phenylbutazone was not reported in the medical history. Its side effects caused the pathological condition in the form of intestinal ulcers, masked endotoxemia and considerably masked the multilayered clinical picture of an intestinal complication and its consequences for the entire body.

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