

ACID-BASE, BLOOD GAS AND HAEMOCOAGULATION CHANGES IN HALOTHANE-ANAESTHETIZED HORSES, SUBMITTED TO ABDOMINAL SURGERY

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Summary

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The changes in acid-base balance and haemocoagulation under halothane anaesthesia without and with abdominal surgery were investigated in six horses in a cross-over design study. During its first phase, the animals were submitted to an anaesthetic schedule using halothane, and during the second phase (one month later) - to the same anaesthesia and abdominal operation. It was concluded that halothane anaesthesia resulted in the development of a compensated respiratory acidosis and when combined with abdominal surgery – in a non-compensated respiratory acidosis, contributing to the tendency towards hypercoagulability. The abdominal surgery intensified the tendency towards hypercoagulability, manifested by shortened APTT and TEG parameters – reaction (r) and coagulation (k) times.

Key words: abdominal surgery, acid-base balance, halothane anaesthesia, horses, thromboelastography

INTRODUCTION

Haemocoagulation and acid-base balance, being two principal components of systemic homeostasis, are subject of a reciprocal influence and interaction (Raevskii, 1984; Weiner, 1988). The changes in one of them, depending on their direction and degree, result in adequate, but sometimes disproportionate changes in the other. Thus, metabolic acidosis stimulates blood coagulation system, but often fibrinolytic system as well (Umanskii, 1971).

The changes in haemocoagulation are directly related to the extent and the type of surgical intervention as well as to the anaesthetic schedule (Mistakopulo and Zhukovskaya, 1983; Kelly et al., 1985; Mihailova, 1985; Lisichkov, 1987). They influence acid-base balance as well (Go-

lemanov, 1989; Golemanov et al., 1989; Kelly et al., 1985).

The importance of the information about the dynamics of acid-base balance and blood coagulation and their changes under the influence of anaesthesia and surgical intervention motivated the present study in horses. It aimed to establish the changes occurring in acid-base balance and haemocoagulation under halothane anaesthesia without and with abdominal surgery.

MATERIALS AND METHODS

Animals

The experiments were performed in six male local breed horses, aged 5-12 years,

weighing 350 ± 18 kg. The animals were fasted for 18 hours prior to anesthesia but had free access to tap water. They were included in a cross-over design study with 2 phases: phase I – anaesthesia without surgery and phase II: anaesthesia with surgery, performed after a 4-week wash-out period.

Anesthesia

The schedule of anesthesia included i.v. premedication with diazepam (Diazepam®, Sopharma) at 0.1 mg/kg followed after 10 minutes by i.v. xylazine (Rometar®, Spofa) at 2.2 mg/kg. The induction was performed with ketamine hydrochloride (Imalgen® 1000, Rhône Mérieux) at 2.2 mg/kg.

After orotracheal intubation, anesthesia was maintained with halothane 3-4 vol% (by means of a Flutec Mark III vaporizer – large animal circuit system with soda lime absorption) and oxygen flow of 5 l/min.

Abdominal operation

The abdominal surgery was a median celiotomy, enterectomy of a segment of the jejunum, enteroanastomosis (Gambee-Lambert suture) and closure of the abdominal cavity. The operation was done within hours 1 and 2.5 h after the induction of anesthesia.

Blood sampling

Prior to and during the different stages of the inhalation anesthesia - premedication, induction, maintenance (hour 1) and recovery (hour 2.5) and the corresponding stages of the abdominal surgery (laparotomy – min 15, enterectomy – hour 1, enteroanastomosis – hour 2, skin closure – hour 2.5), blood samples were obtained from the jugular vein. Thromboelastographic parameters were also assessed at hour 2 of deep anaesthesia (phase I) and

at hour 5 after the induction i.e. 2.5 h after the extubation (both phases).

Assays

- acid-base status and blood gases: pH, partial oxygen pressure (pO_2 , mmHg), partial carbon dioxide pressure (pCO_2 , mmHg), actual bicarbonates (HCO_3 , mmol/l), oxygen saturation (SAT, %), oxygen content (O_2CT , vol%), actual base excess (ABE, mmol/l) were measured with an acid-base analyser (ABL-3, Radiometer, Denmark);
- prothrombin time (PT) and activated partial thromboplastin time (APTT) were assessed on a coagulation monitor (Ciba Corning 512);
- the parameters of thrombodynamics – reaction time (r), coagulation time (k), maximum amplitude time (t) and maximum amplitude (ma) were directly measured on thromboelastogrammes obtained with a haemocoagulograph (ГКГМ4-02, Russia).

Statistical analysis

Data are presented as mean $\pm$ SEM. Statistical analysis of results was done using one-way ANOVA (Statmost for Windows) at $p < 0.05$ level of significance. *Post hoc* comparisons were done by the least significance difference (LSD) test.

RESULTS

The data for acid-base and blood gas parameters in anaesthetized horses without surgery (phase I) are presented in Tables 1 and 2. They showed that halothane anaesthesia resulted in a classic primary compensated respiratory acidosis.

The initial pH values (7.371 ± 0.010) decreased gradually being statistically significantly different than baseline during all observed periods: 7.297 ± 0.097 after the intubation ($p < 0.05$); 7.215 ± 0.071

Table 1. Changes in acid-base parameters in halothane-anaesthetized horses (n=6) without operation (phase I) and with abdominal operation (phase II)

Parameter	Prior to anaesthesia ¹ (n=12)	Phase I (n=6)	After intubation	Deep anaesthesia (1-2 h)		Extubation (2.5 h)
		Phase II (n=6)	After intubation and celiotomy	Enterectomy (1 h)	Enteroanastomosis (2 h)	Skin closure (2.5 h)
pH	7.371 ± 0.010	Phase I (n=6)	7.297* ± 0.039	7.215*** ± 0.029		7.178*** ± 0.028
		Phase II (n=6)	7.283 ± 0.007	7.229*** ± 0.008	7.195*** ± 0.023	7.153*** ± 0.037
pCO ₂ , mmHg	50.3 ± 1.1	Phase I (n=6)	66.2* ± 2.0	82.9*** ± 4.8		87.1*** ± 5.6
		Phase II (n=6)	65.6* ± 2.1	73.6** ± 3.6	86.4*** ± 7.0	95.2*** ± 11.0
HCO ₃ , mmol/l	28.7 ± 0.7	Phase I (n=6)	32.0 ± 2.5	33.0* ± 0.8		32.1* ± 0.7
		Phase II (n=6)	30.5 ± 1.1	30.7 ± 0.7	31.6 ± 1.1	31.9 ± 0.8
TCO ₂ , mmol/l	29.0 ± 1.6	Phase I (n=6)	31.5 ± 4.0	32.6 ± 3.4		31.8 ± 3.8
		Phase II (n=6)	32.5 ± 1.1	32.2 ± 1.4	34.3 ± 1.4	34.9 ± 1.1
ABE, mmol/l	3.0 ± 0.7	Phase I (n=6)	4.3 ± 2.7	2.9 ± 1.1		0.9 ± 1.3
		Phase II (n=6)	2.5 ± 0.9	1.1 ± 1.0	1.5 ± 0.4	0.1 ± 1.3

¹ mean values, determined during the analysis prior to phases I and II; * p<0.05; ** p<0.01; *** p<0.001 vs baseline

Table 2. Changes in blood gas variables in halothane-anaesthetized horses (n=6) without operation (phase I) and with abdominal operation (phase II)

Parameter	Prior to anaesthesia ¹ (n=12)	Phase I (n=6)	After intubation	Deep anaesthesia (1-2 h)		Extubation (2.5 h)
		Phase II (n=6)	After intubation and celiotomy	Enterectomy (1 h)	Enteroanastomosis (2 h)	Skin closure (2.5 h)
pO ₂ mmHg	46.3 ± 3.1	Phase I (n=6)	107.4** ± 17.3	136.8*** ± 33.3		123.8** ± 24.5
		Phase II (n=6)	51.9 ^a ± 3.9	61.9 ^b ± 9.2	63.0* ^b ± 8.0	57.8 ^a ± 7.1
SAT, %	80.0 ± 3.0	Phase I (n=6)	95.3* ± 1.2	97.9*** ± 0.5		96.8*** ± 1.3
		Phase II (n=6)	83.2 ^b ± 2.5	84.5 ^b ± 3.4	85.8 ^b ± 3.8	88.5 ^a ± 3.0
O ₂ CT, vol %	12.5 ± 0.9	Phase I (n=6)	13.3 ± 0.6	15.1* ± 0.6		15.4* ± 0.9
		Phase II (n=6)	12.8 ± 0.7	11.8 ^b ± 0.6	12.1 ± 2.5	14.5 ± 1.7

¹ mean values, determined during the analysis prior to phases I and II* p<0.05; ** p<0.01; *** p<0.001 vs baseline; ^a p<0.05; ^b p<0.01 between phases.

during stable anaesthesia ($p < 0.001$) and 7.178 ± 0.069 at the end of anaesthesia ($p < 0.001$).

The partial CO_2 pressure increased progressively from a baseline values of 50.3 ± 3.6 mmHg to 82.9 ± 11.7 mmHg and 87.1 ± 5.6 mmHg ($p < 0.001$) at stable anaesthesia and at extubation, respectively. Actual bicarbonates (Table 1) were significantly elevated between hours 1–2 of anaesthesia (33.0 ± 2.0 mmol/l; $p < 0.05$) and at the end of the study (32.1 ± 1.6 mmol/l; $p < 0.05$) compared to initial values (28.7 ± 2.5 mmol/l).

Blood gas parameters (pO_2 , SAT and O_2CT) exhibited an increase that was statistically significant, but at a different extent (Table 2). TCO_2 and ABE remained statistically unchanged during the entire experimental period.

In halothane-anaesthetized horses, submitted to surgery (phase II), acid-base changes were characteristic for a deeper respiratory acidosis without a tendency towards compensation. The changes in pH during the second phase were also manifested by a significant decrease compared to initial values ($p < 0.001$ for all observed periods), characteristic for acidosis. There were no statistically significant differences between both phases.

Oxygen metabolism parameters pO_2 and SAT during this phase were significantly lower compared to all respective periods during the first phase and O_2CT for the period of stable anaesthesia vs enterectomy. At the same time, pCO_2 showed a stable and statistically significant increase compared to baseline, most apparent at the end of operation (95.2 ± 27.0 mmHg at $p < 0.001$).

For the other parameters (HCO_3^- , TCO_2 and ABE) there were no significant changes by respect to baseline as well as between both phases.

The changes in APTT and PT – two parameters of haemocoagulation – are presented in Table 3. When only a halothane anaesthesia was performed, APTT showed a marked decrease. From a baseline value of 72.7 ± 1.7 s it changed statistically significantly in all subsequent periods: after the premedication and intubation (55.1 ± 2.6 s; $p < 0.05$), during stable anaesthesia (44.2 ± 8.7 s; $p < 0.01$) and at the end of anaesthesia (41.6 ± 4.8 s; $p < 0.001$).

During phase II (anaesthesia and abdominal surgery), the tendency of APTT decrease compared to baseline was similar – 53.3 ± 2.3 s at $p < 0.01$ (enterectomy), 58.4 ± 4.8 s at $p < 0.05$ (enteroanastomosis) and 48.7 ± 4.6 s at $p < 0.01$ (closure of abdominal wall).

Prothrombin time did not change significantly during both phases of the experiment.

The results for the direct thromboelastographic parameters: reaction time (r), coagulation time (k), maximum amplitude time (t) and maximum amplitude (ma) are presented in Table 4. The changes in reaction time values in halothane anaesthesia without and with surgery were confined within the period between hours 1 and 2.5 (phase I) and 2.5 (enterectomy-skin closure; phase II) respectively. During phase I, reaction time was reduced from initial values of 7.17 ± 0.17 min to 6.22 ± 0.26 min by hour 1 ($p < 0.05$), 5.22 ± 0.13 min by hour 2 ($p < 0.001$) and 4.45 ± 0.20 min ($p < 0.001$) by hour 2.5. Afterwards, during the 2.5 h of recovery, a stable tendency towards elevation up to baseline values was noticed. The changes during the second phase were characterized with a high statistical significant decrease vs baseline as early as the enterectomy (5.22 ± 0.23 min, $p < 0.001$) without significant inter-phase

Table 3. Changes in activated partial thromboplastic time (APTT, s) and prothrombin time (s) in halothane-anaesthetized horses (n=6) without operation (phase I) and with abdominal operation (phase II)

Parameter	Prior to anaesthesia ¹ (n=12)	Phase I (n=6)	After intubation	Deep anaesthesia (1-2 h)		Extubation (2.5 h)
		Phase II (n=6)	After intubation and celiotomy	Enterectomy (1 h)	Enteroanastomosis (2 h)	Skin closure (2.5 h)
APTT, s	72.7 ± 1.7	Phase I (n=6)	55.1*±2.7	44.2** ± 8.7		41.6*** ± 4.9
		Phase II (n=6)	61.4 ± 4.3	53.3** ± 2.3	58.4* ± 4.8	48.6** ± 4.6
PT, s	11.2 ± 0.3	Phase I (n=6)	11.5 ± 1.1	12.0 ± 1.1		11.3 ± 0.5
		Phase II (n=6)	11.5 ± 0.6	12.2 ± 1.1	11.6 ± 0.9	12.8 ± 1.7

¹ mean values, determined during the analysis prior to phases I and II; * p<0.05; ** p<0.01; *** p<0.001 vs baseline

Table 4. Changes in reaction time (r, min), coagulation time (k, min), maximum amplitude time (t, min) and maximum amplitude (ma, mm) in halothane-anaesthetized horses (n=6) without operation (phase I) and with abdominal operation (phase II)

Parameter	Prior to anaesthesia ¹ (n=12)	Phase I (n=6)	After intubation	Deep anaesthesia (1 h)	Deep anaesthesia (2 h)	Extubation (2.5 h)	5 h
		Phase II (n=6)	After intubation and celiotomy	Enterectomy (1 h)	Enterotomosis (2 h)	Skin closure (2.5 h)	5 h
r, min	7.17 ± 0.17	Phase I (n=6)	7.17 ± 0.34	6.22* ± 0.26	5.22*** ± 0.13	4.45*** ± 0.2	6.83 ± 0.25
		Phase II (n=6)	7.05 ± 0.3	5.22*** ^b ± 0.23	4.05*** ^b ± 0.28	3.78*** ± 0.22	6.33* ± 0.25
k, min	4.08 ± 0.15	Phase I (n=6)	3.28** ± 0.18	2.78*** ± 0.13	2.45*** ± 0.18	2.22*** ± 0.17	3.95 ± 0.28
		Phase II (n=6)	3.50* ± 0.18	2.83*** ± 0.15	2.22*** ± 0.22	2.00*** ± 0.20	4.12 ± 0.20
t, min	24.3 ± 1.6	Phase I (n=6)	25.8±2.5	21.9 ± 2.9	22.3 ± 2.4	21.4 ± 2.2	23.5 ± 2.1
		Phase II (n=6)	24.5 ± 2.3	20.7 ± 2.3	22.3 ± 2.0	25.5 ± 1.9	27.0 ± 1.4
ma, mm	26 ± 1	Phase I (n=6)	36*** ± 2	28 ± 2	27 ± 2	20* ± 2	24 ± 2
		Phase II (n=6)	29 ^b ± 2	24 ± 1	22 ^a ± 1	23 ± 2	25 ± 2

¹ mean values, determined during the analysis prior to phases I and II;

* p<0.05; ** p<0.01; *** p<0.001 vs baseline; ^b p<0.01 between phases.

differences, excepting by hours 1 and 2.

There was a decrease in coagulation time during both phases that began after the administration of ketamine hydrochloride ($p < 0.01$ at induction; $p < 0.05$ at celiotomy) and became more pronounced ($p < 0.001$) during the subsequent periods of observation. However, there were no significant differences between phases. In the period of recovery, the tendency towards restoration of pre-experimental values was apparent.

The changes in maximum amplitude time (t) were insignificant despite the observed intra- and inter-phase variations for all periods. The changes in maximum amplitude (ma) were similar for both phases with significant differences vs baseline only during phase I (anaesthesia). The peak maximum amplitude was registered after the intubation and induction of anaesthesia – 36 ± 2 mm ($p < 0.001$ vs baseline).

DISCUSSION

The analysis of data for acid-base balance and blood gas changes suggested that they were primarily due to the used combination of anaesthetics and in a lesser extent – to performed surgical intervention: bicarbonate values did not change considerably during the operation and $p\text{CO}_2$ continued to increase. At the end of anaesthesia this was probably due to hypoventilation (Golemanov, 1989; Golemanov et al., 1989), and its escalation during the operation was probably related to the dorsal recumbency, as observed by De Moor and Desmet (1974) and Hall (1981) in left lateral recumbency fixation. From the other side, the changes have to be interpreted according to the type of surgery. It is known that small intestine disorders usually result in metabolic acidosis and large intestine lesions – in metabolic al-

kalosis (Datt and Uzenik, 1975). In our experiment, the surgery was performed on small intestines, that could further contribute to observed changes.

The evaluation of blood coagulation system status must take into account several factors, a most important one being the synergy anaesthesia-operation (Raevskii, 1984). The data for the influence of general anaesthetics upon haemocoagulation are contradictory because the influence of the type of anaesthesia (single or combined, non-inhalation or inhalation) that have to be considered in every particular case (Horn et al., 2001). Thus, according to the authors, single anaesthesia does not have an impact upon coagulation, whereas after the introduction with isoflurane, APTT increases significantly. The application of sevoflurane produced no changes in APTT, thus evidencing the various effect of inhalation anaesthetics upon haemocoagulation system.

The type of operative intervention also influences blood coagulation system. The follow-up of thromboelastogrammes, APTT and PT after castration of stallions (Hubenov et al., 1994) showed that they do not change significantly, probably because castration is a "peripheral" operation. Similar results are reported by Law et al. (2001) in humans with head and neck surgery.

APTT is a parameter characterizing the intrinsic route of blood coagulation and combined with PT – the common route. According to our results, during abdominal surgery under halothane anaesthesia, APTT exhibited a significant decrease but PT – insignificant changes. It is believed that low APTT values are accompanying all cases of factor XII activation, that occurs not only during surgical intervention, but also during systemic endotoxin challenge (Morrison and Co-

chrane, 1974; Deldar et al., 1984).

In our experiments, blood coagulation changes became more pronounced after the celiotomy and the manipulations of intestines, most probably because of the influx of thrombogenic substances from damaged tissues into the circulation, taking into account the extensive absorption capacity of peritoneum. The hypercoagulability could also be related to the development of acidotic conditions in venous blood, since acidosis is one of the commonest causes for the occurrence of disseminated intravascular coagulation (DIC) syndrome (Lisichkov, 1987; Badilak et al., 1988; Slappendel et al., 1988; Weiner, 1988).

One of the principal methods for functional study of hemostasis, presenting a graphic information for its three principal phases, is thromboelastography (TEG). This method provides valuable information for the diagnostics of coagulopathies, accompanying surgical interventions (Moriwaki et al., 1992).

Otto et al. (2000) interpret TEG data together with study of APTT, PT, antithrombin III and fibrinogen, concluding that the clinical signs of thrombosis or phlebitis predominate during a viral enteritis, simultaneously with laboratory data for hypercoagulopathy without evidence for DIC syndrome. Those changes are manifested by a significant increase in TEG amplitude, decreased antithrombin activity, prolonged APTT and no change in platelet counts.

A decreased fibrinolytic activity following aseptic laparotomy combined with intestinal resection is observed 24 h after the intervention (Hau et al. 1979) – another cause for a more intense hypercoagulability. In our experiments, the increased potential for haemocoagulation was manifested by TEG parameters, espe-

cially by changes in reaction and coagulation times, confirming the clear tendency towards increased functional activity of haemocoagulation system in operated animals.

CONCLUSIONS

Halothane anaesthesia resulted in the development of a compensated respiratory acidosis and when combined with abdominal surgery – in a non-compensated respiratory acidosis, contributing to the tendency towards hypercoagulability.

The abdominal surgery intensified the tendency towards hypercoagulability, manifested by shortened APTT and TEG parameters – reaction (r) and coagulation (k) times.

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Abstract: The evaluation of the toxic effect of the triazole fungicide disiconazole (Sund S 2WP) on rabbits was carried out following up the changes in blood activities of aspartate aminotransferase (ASAT), alanine aminotransferase (ALAT), alkaline phosphatase (AP), lactate dehydrogenase (LDH) and cholesterol (Chl). The studies were performed in one control and three experimental groups, treated orally via a gastric tube with increasing doses of disiconazole (0, 0.5, 1.0 and 1.5 g/kg body weight).

Blood for analysis of studied activities was sampled at hours –48, –24 and 0 prior to the treatment and hours 2, 4, 6, 8, 10, 12, 24, 48 and 72 after the treatment from all animals.

It was observed that the triazole fungicide disiconazole had a toxic effect manifested by increased ASAT, ALAT and LDH activities, decreased AP activity and no changes in Chl.

Key words: alanine aminotransferase, alkaline phosphatase, aspartate aminotransferase, cholesterol, disiconazole, lactate dehydrogenase, Sund S 2WP, triazole fungicide.

INTRODUCTION

It is known that the toxic effect of triazole fungicides is accompanied with changes in activities of several enzymes. Data in this respect have reported about the effect of cyproconazole, fluconazole, 1,2,4-triazole and propiconazole in mice, rats and human (Bachew, 1993; Baytan (Iridimov), 2000 – in cattle (Markelov and Shabanov, 1994) and pigs (Dinev, 2000); of tri (propiconazole) – in rats following intraperitoneal administration (Kurumbayev et al., 1995); of flutrypholazole – in mice (Grischen and Muller, 1999) and in rats (Gopal et al., 1998a; Parfi et al., 1998b). These studies evidenced that depending on the amount of the toxic sub-

stance, the blood activities of aspartate aminotransferase (ASAT), alanine aminotransferase (ALAT) and lactate dehydrogenase (LDH) increased while data about the levels of alkaline phosphatase (AP) and cholesterol (Chl) were contradictory.

In previous studies of ours upon the acute intoxication with the triazole fungicide disiconazole in rabbits, the changes in the clinical signs (hypothermia, tachycardia, polyuria) and some haematological changes (thrombocytopenia, erythrocytic, haemoglobin, haematocrit, haemoglobin, haemoglobin, haemoglobin and slower erythrocyte sedimentation rates) were described (Dinev, 2001). Here