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Asian Journal of Animal and Veterinary Advances

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OPEN ACCESS Asian Journal of Animal and Veterinary Advances

ISSN 1683-9919
DOI: 10.3923/ajava.2016.469.476

# Research Article
# Effects of Intravenous Lactated Ringer's Solution in Cows Suffering from Hepatic Disorders

Ken Onda, Chikako Noda, Kazue Nakamura, Reiichiro Sato, Hideharu Ochiai, Sachiko Arai, Hiroo Madarame, Kazuhiro Kawai and Fujiko Sunaga

School of Veterinary Medicine, Azabu University, 17-71 Fuchinobe 1-Chome, Chuo-ku, Sagamihara, 252-5201, Japan

## Abstract

**Background:** This study investigated changes in the blood acid-base balance to determine the effects of Lactated Ringer's Solution (LRS) administration in a steer with liver damage caused by carbon tetrachloride ($CCl_4$) administration and in a cow with a fatty liver caused by a parturient negative energy balance. **Materials and Methods:** The LRS was administered to the $CCl_4$ steer before $CCl_4$ administration and 2, 7 and 11 days after $CCl_4$ administration. The fatty liver cow and a group of control cows were administered LRS once. The initiation of LRS infusion was designated time-point 0. Venous blood samples were collected periodically from time-point 0-360 min thereafter and parameters related to the acid-base balance were measured. **Results:** On day 2, blood pH of the $CCl_4$ steer before LRS administration was 7.26 but it gradually increased after the initiation of LRS administration, before ultimately recovering to within the normal reference range. The $HCO_3^-$ levels decreased transiently just after the administration of LRS on day 7, then rapidly returned normal. Despite the fatty liver cow having severe fat infiltration, there were no substantial differences in parameters related to the blood acid-base balance between the fatty liver cow and the control cows, after LRS administration. **Conclusion:** Even in a steer suffering from liver damage caused by $CCl_4$ administration, lactate was metabolised in the liver and worked as an alkaliser. Therefore, LRS may be a safe extracellular replacement solution when administered at the recommended flow rate and dose (20 mL $kg^{-1}$ $h^{-1}$ and 30 mL $kg^{-1}$, respectively) to dairy cows in clinics.

Key words: Carbon tetrachloride, fatty liver, metabolic acidosis, dehydration, LRS

Received: May 21, 2016 Accepted: July 04, 2016 Published: July 15, 2016

Citation: Ken Onda, Chikako Noda, Kazue Nakamura, Reiichiro Sato, Hideharu Ochiai, Sachiko Arai, Hiroo Madarame, Kazuhiro Kawai and Fujiko Sunaga, 2016. Effects of intravenous lactated Ringer's solution in cows suffering from hepatic disorders. Asian J. Anim. Vet. Adv., 11: 469-476.

Corresponding Author: Ken Onda, Laboratories of Internal Medicine 3, School of Veterinary Medicine, Azabu University, 17-71 Fuchinobe 1-Chome, Chuo-ku, Sagamihara, 252-5201, Japan Tel: +81-42-154-7111

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Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

## INTRODUCTION

Lactated Ringer's Solution (LRS) is widely used in human and veterinary clinics to replace extracellular fluid. In veterinary fields, two types of LRS are available and utilised in clinics. One contains L-lactate only and the other is a racemic mixture that contains L-lactate and D-lactate as sodiumlactate[1,2]. The L-lactate is an intermediate metabolite of glucose and is utilised in glycolysis and fatty acid synthesis via metabolism in the liver. In contrast, D-lactate is rarely used in healthy animals and it is believed that mammals metabolise it slowly. However, recent studies have provided evidence that mammals are able to metabolise D-lactate more efficiently than originally suggested[3]. When L-lactate is administered to animals, it is metabolised mainly in the liver and produces an equimolar amount of bicarbonate ion ($HCO_3^-$) as an alkaliser. In addition, L-lactate metabolism requires thiamine as a coenzyme and an oxygen supply. Therefore, LRS administration in animals suffering from severe liver damage may induce or facilitate lactic acidosis[4].

In calves with diarrhoea, metabolic acidosis occurs frequently via L-lactate and D-lactate accumulation and the main goals of treatment are rehydration and the alleviation of acidosis via a high dose of bicarbonate[5]. The LRS administration to calves with immature hepatic function may exacerbate lactic acidosis. Domestic adult cows undergo various types of stress resulting from the secretion of large amounts of milk or excessive meat production and are known to suffer from hepatic disorders including fatty liver. It is debatable whether LRS administration to cows suffering from liver disorders is advisable. There is little information available on whether LRS administration to adult cows suffering from metabolic acidosis facilitates acidosis by adding excess lactate and the actual grade or level of liver damage permitting safe LRS administration is also not clear.

This study observed changes in the blood acid-base balance to determine the influence of LRS administration in a steer with liver damage caused by carbon tetrachloride ($CCl_4$) treatment and in a cow with a fatty liver caused by a parturient negative energy balance.

## MATERIALS AND METHODS

**$CCl_4$-administered steer:** This part of the study was performed in July 2004, with the approval of the Animal Care and Use Committee of the Azabu University School of Veterinary Medicine (Approval No. 040512-1). A 13 months old castrated male jersey cow weighing 270 kg was administered $CCl_4$. Before $CCl_4$ administration, no clinical or blood abnormalities were found. The $CCl_4$ Wako, Tokyo, Japan was orally administered at 0.03 mL $kg^{-1}$ b.wt., 8.28 mL per head, which is a lower dosage than was used in two former studies[6,7] using a nasogastric tube and 8 L of water. Clinical signs were recorded after $CCl_4$ administration.

The LRS administration and the accompanying tests were performed four times; before $CCl_4$ administration and 2, 7 and 11 days after $CCl_4$ administration. The LRS used in this study contained 28 mEq $L^{-1}$ L-lactate, 131 mEq $L^{-1}$ $Na^+$, 4 mEq $L^{-1}$ $K^+$, 3 mEq $L^{-1}$ $Ca^{2+}$ and 110 mEq $L^{-1}$ $Cl^-$ (Sollact, Terumo, Tokyo, Japan). Eight litres (30 mL $kg^{-1}$) of LRS was administered for 90 min (20 mL $kg^{-1}$ $h^{-1}$) to the animal, in accordance with a previous report[8]. The initiation of the infusion was designated as time-point 0. Venous blood samples were collected at time-point 0 and 15, 30, 45, 60, 90, 120, 150, 180, 240, 300 and 360 min thereafter. At each collection time-point, heart rate, respiratory rate and rectal temperature were recorded. Blood samples were collected aerobically in heparinised syringes and the tips of the syringes were capped after collection. Immediately after collection, the blood samples were analysed via an automatic gas analyser (AVL OPTI-Critical Care Analyzer, AVL Medical Instruments AG, Schaffhausen, Switzerland). Values were corrected according to each animal's rectal temperature. An aliquot of each blood sample was used to determine haematocrit (Ht) values via the microhaematocrit method. Other aliquots had the protein component removed immediately were centrifuged and then stored at -80°C until blood L-lactate analyses were performed using a fluoroscopic method[9].

Blood samples were collected from the jugular vein every day after $CCl_4$ administration. Samples for complete blood counts were treated with 5 mg $mL^{-1}$ ethylenediaminetetraacetic acid disodium salt. Samples for blood chemistry were incubated at 37°C to allow clotting, centrifuged at 1200×g for 20 min at 4°C, then the isolated serum was stored at -80°C prior to analysis. Serum concentrations of urea nitrogen, creatinine and total bilirubin, as well as the activities of aspartate aminotransferase (AST), lactate dehydrogenase (LDH), g-glutamyltransferase (GGT), alkaline phosphatase (ALP) and creatinine kinase (CK) were determined via an automated blood chemical analyser (Cobas Integra, Roche Diagnostics Japan, Tokyo, Japan). Serum ornithine carbamoyltransferase (OCT) activity was measured using a commercial kit (OCT-Test Wako, Wako Pure Chemical Industries, Osaka, Japan). Liver tissues were biopsied before $CCl_4$ administration and 3, 8 and 12 days thereafter (the day after each LRS administration) using a Silverman's

needle inserted from the right side, between the 10 and 11th ribs with sedation and local anaesthesia. Tissues were fixed in a 10% neutral phosphate buffered formalin solution. Paraffin sections were prepared and stained with haematoxylin and eosin.

**Fatty liver cow and control cows:** This part of the study was performed from August, 2010-October, 2010 with the approval of the Animal Care and Use Committee of the Azabu University School of Veterinary Medicine (Approval No. 100818-3). A Holstein cow was hospitalised at the Veterinary Teaching Hospital of the Azabu University, School of Veterinary Medicine and diagnosed with severe fatty liver. The main symptoms of this cow were anorexia, low vitality and low milk production (18 kg day$^{-1}$). The cow was primiparous, 2 years and 5 months old, 438 kg b.wt. and had calved 10 days before the LRS experiment. Four control cows were used in the study and all were non-lactating and non-pregnant healthy Holstein cows maintained at the Azabu University, School of Veterinary Medicine for the purposes of student education.

The LRS was administered to each cow once, via the same procedures that were used for the $CCl_4$-administered steer. Blood samples were also collected using the same procedures as for the $CCl_4$-administered steer and parameters pertaining to the acid-base balance and L-lactate were measured with a portable i-STAT blood analyser (Fuso Pharmaceutical Industries, Osaka, Japan).

Blood tests were performed once before LRS administration, in the same manner as for the $CCl_4$ steer. Serum Total Protein (TP) concentrations were measured via refractometry. Non-esterified fatty acid (NEFA) (NEFA C-test Wako, Wako Pure Chemical Industries, Osaka, Japan) and b-hydroxy butyrate (BHBA) (Ketone Test B Sanwa Liquid, Sanwa Kagakukenkyusyo, Nagoya, Japan) were also measured in the fatty liver cow. Liver biopsies were taken the day after LRS administration and histochemistry was performed on the samples. Hepatic triglyceride content was also measured in the fatty liver cow and the four control cows[10].

## RESULTS

### $CCl_4$-administered steer

**Clinical symptoms, blood tests and histopathology:** Eight hours after $CCl_4$ administration, the steer became lethargic and lost its appetite. The animal avoided standing and movement of the rumen was not audible on day 1. Anorexia and lethargy continued until day 3. On day 4 after $CCl_4$ administration, appetite and rumen movement had improved a little. By day 8, activity, dietary intake and movement of the rumen had recovered to the same levels as before $CCl_4$ administration.

Table 1: Blood chemistry results from a $CCl_4$-administered steer

| | Pre | Day 2 | Day 7 | Day 11 |
|---|---|---|---|---|
| Urea nitrogen (mg/100 mL) | 11.40 | 12.20 | 7.70 | 8.00 |
| Creatinine (mg/100 mL) | 0.80 | 1.30 | 0.80 | 0.80 |
| Total-bilirubin (mg/100 mL) | 0.111 | 1.689 | 0.381 | 0.173 |
| AST (IU L$^{-1}$) | 61.00 | 14241.00 | 323.00 | 107.00 |
| LDH (IU L$^{-1}$) | 2567.00 | 22826.00 | 7186.00 | 5155.00 |
| GGT (IU L$^{-1}$) | 19.00 | 149.00 | 125.00 | 96.00 |
| ALP (IU L$^{-1}$) | 163.00 | 822.00 | 309.00 | 190.00 |
| OCT (IU L$^{-1}$) | 10.00 | 7063.00 | 79.60 | 15.90 |
| CK (IU L$^{-1}$) | 169.00 | 311.00 | 123.00 | 144.00 |

Pre: Before $CCl_4$ administration, days 2, 7 and 11: Time-points after $CCl_4$ administration, AST: Aspartate aminotransferase, LDH: Lactate dehydrogenase, GGT: G-glutamyltransferase, ALP: Alkaline phosphatase, OCT: Ornithine carbamoyltransferase, CK: Creatinine kinase

The blood test results are shown in Table 1. On day 2, increases in the serum concentrations of urea nitrogen and creatinine were mild. Severe liver injury was observed on day 2, as indicated by the total bilirubin concentration in serum and the activities of AST, LDH, GGT, ALP and OCT. The high values of these parameters gradually decreased, returning to approximately baseline levels by day 11. The CK activity was increased on day 2, likely because the cow remained unstanding for a long period and its muscles may have been injured.

Hepatic histopathology on day 3 revealed multiple hepatocyte necroses, which were more severe in the centres of the lobules. On day 8, mild-to-moderate hepatocyte fibrosis was observed in the centrilobular and interlobular regions and small-to-medium sized transparent droplets (probably fat droplets) were also evident in the hepatocytes. By day 8, hepatocyte necrosis was no longer evident and the droplets in the hepatocytes had decreased in size and number.

**Changes in blood acid-base balance during LRS administration:** Changes in the blood acid-base balance during LRS administration are shown in Fig. 1. By day 11, the balance had returned to approximately the same levels as prior to treatment. On day 2, before LRS administration the pH was low, then it gradually increased after its initiation, before recovering to within the normal reference range[11] of 7.38-7.46 at 360 min after the initiation of LRS administration. The L-lactate concentration on day 2 was extremely high, but it decreased markedly with LRS administration. Moreover, L-lactate was mildly increased during LRS administration in the tests before treatment and on days 2, 7 and 11.

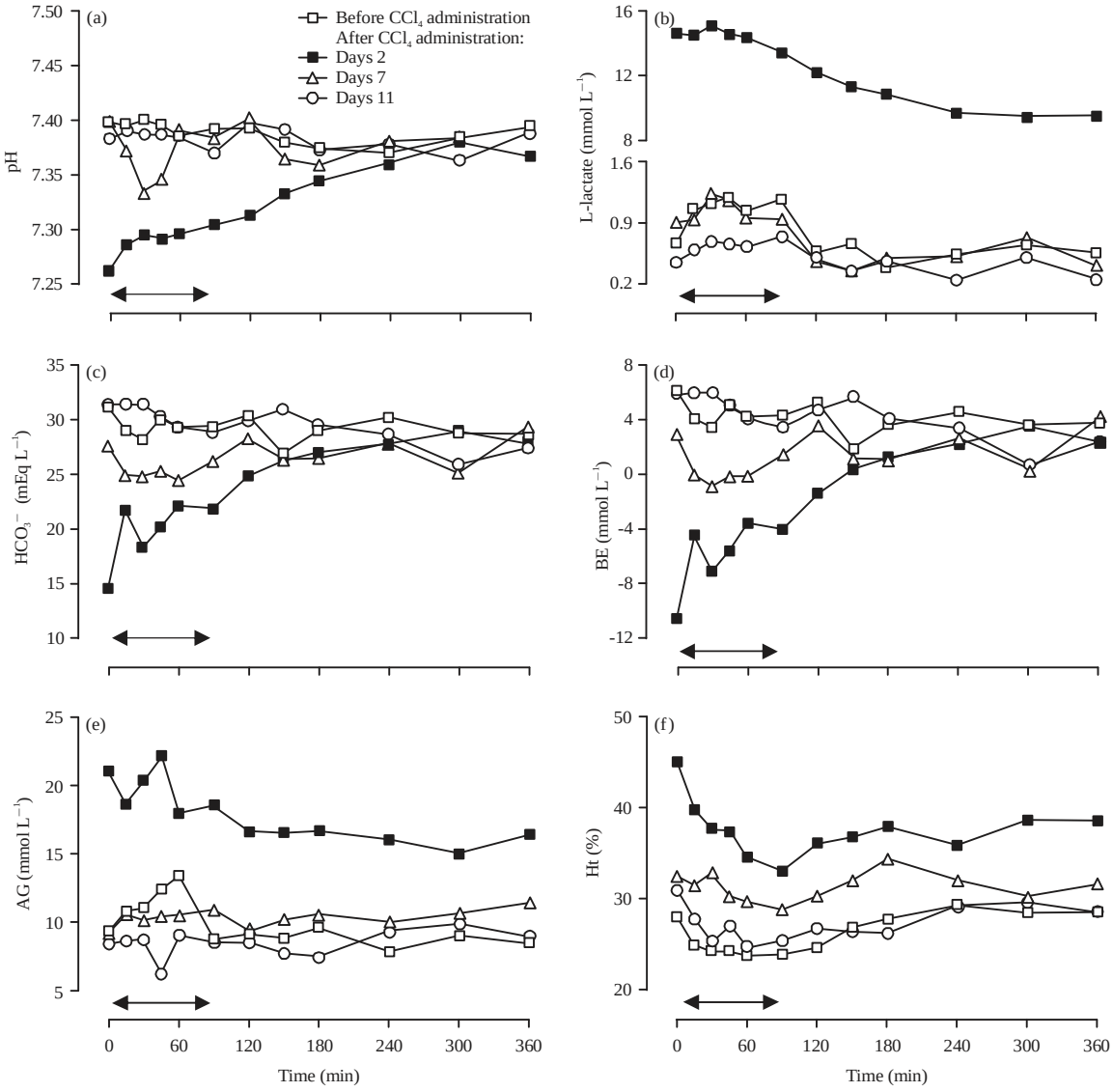


Fig. 1(a-f): Changes in the acid-base balance of a $CCl_4$-treated steer administered lactated Ringer's solution, (a) pH, (b) L-lactate (c) $HCO_3^-$, (d) BE, (e) AG and (f) Ht values are shown. Arrows indicate the Ringer's lactate administration time-points

The $HCO_3^-$ and Base Excess (BE) values were low on day 2 before LRS administration but gradually increased with the initiation of administration, before ultimately returning to within the normal reference ranges. On day 7, the levels of both decreased transiently just after the initiation of administration, then rapidly returned to normal. The Anion Gap (AG) reflected the rise in L-lactate, which remained high at 360 min despite LRS administration on day 2. The Ht value on day 2 decreased upon LRS administration but remained slightly above normal. The Ht value decreased temporarily with the start of LRS administration before $CCl_4$ administration and on days 7 and 11.

**Fatty liver cow and control cows**

**Clinical symptoms, blood tests and histopathology:** The results of the blood tests from the cow with a fatty liver are shown in Table 2. The high NEFA and BHBA concentrations and low glucose concentration suggest this cow suffered from a negative energy balance.

Histopathology revealed severe fat infiltration into the liver (Fig. 2). After the experiment, displacement of the abomasum occurred in association with the fatty liver. A surgical operation returned this cow to good health and it was ultimately discharged from the animal hospital. Blood tests and histopathological analysis of the four control cows

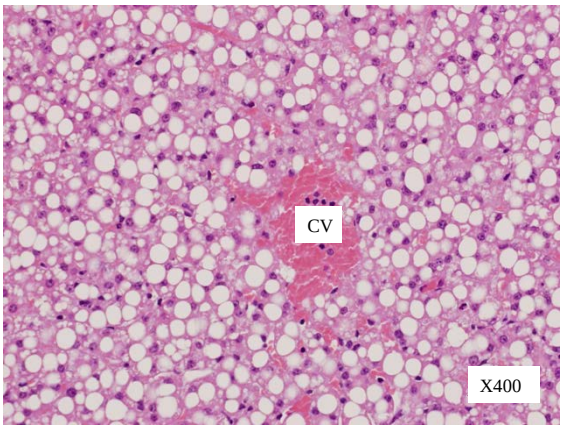


Fig. 2: Liver histochemistry from a cow suffering from a fatty liver. Medium-to-large transparent droplets in the cytoplasm of swelling hepatocytes are diffusely distributed in the hepatic lobule, CV: Central vein

Table 2: Blood tests and chemistry results from a cow with a fatty liver

| Parameters | Values |
|---|---|
| Red blood cells ($\times 10^4$ μL) | 674.00 |
| Hematocrit value (%) | 31.00 |
| White blood cells (μL) | 5700.00 |
| Total protein (g $dL^{-1}$) | 6.80 |
| Urea nitrogen (mg/100 mL) | 10.90 |
| Creatinine (mg/100 mL) | 0.81 |
| Glucose (mg/100 mL) | 54.00 |
| AST (IU $L^{-1}$) | 232.00 |
| LDH (IU $L^{-1}$) | 4186.00 |
| GGT (IU $L^{-1}$) | 37.00 |
| ALP (IU $L^{-1}$) | 77.00 |
| NEFA (μmol $L^{-1}$) | 1265.00 |
| BHBA (μmol $L^{-1}$) | 3320.00 |

AST: Aspartate aminotransferase, LDH: Lactate dehydrogenase, GGT: G-glutamyltransferase, ALP: Alkaline phosphatase

showed no abnormalities. The triglyceride content of wet liver tissue was 214 mg $g^{-1}$ in the cow with a fatty liver and the control cows yielded a mean triglyceride content of 13.6±1.6 mg $g^{-1}$.

**Changes in the blood acid-base balance during LRS administration:** Changes in the blood acid-base balance during LRS administration in the cow with a fatty liver and the control cows are shown in Fig. 3. A small increase in L-lactate and a small decrease in $HCO_3^-$ were observed in association with reduced pH values in both the fatty liver cow and the control group during LRS administration. These parameters returned to their original levels after the cessation of LRS administration and the pH values were within the normal reference range. There was no substantial change in the AG from time-point 0-360 min after the initiation of LRS administration in the cow with a fatty liver or the control cows. The Ht values decreased slightly in the cow with a fatty liver and the control cows, as it did in the $CCl_4$-treated cow.

## DISCUSSION

Originally, the $CCl_4$ study was planned as an isolated investigation. Next experiment was organised 5 years later in an effort to achieve a better understanding of the results of the $CCl_4$ study and to determine whether administering LRS to cows suffering from liver injury is safe. On day 11 after $CCl_4$ administration, activity, appetite and other physical parameters had returned to normal. While some parameters indicating liver injury remained high, the blood acid-base balance was almost the same as it was pre-treatment, so it was speculated that the steer had recovered and regained its acid-base balance.

The LRS administration flow rate in this study was 20 mL $kg^{-1}$ $h^{-1}$, which is half the previously recommended safe flow rate for cows[12]. The $CCl_4$ steer exhibited metabolic acidosis on day 2 as evidenced by low pH and $HCO_3^-$ values of 7.26 and 14.5 mmHg, respectively. The high AG observed was caused by substantially elevated L-lactate and the steer was still suffering fromlactic acidosis on day 2. Moreover, a high Ht value (45%) suggested that the steer was dehydrated. The low pH of 7.26 on day 2 was increased, even after the cessation of LRS administration at 90 min, then, the pH recovered to almost within the normal reference range (7.36) at 360 min after the initiation of LRS administration. The L-lactate had decreased and conversely $HCO_3^-$ had increased at this time-point, meaning that the administered lactate did not facilitate lactic acidosis and accelerated the metabolism of endogenous lactate. The Ht values had decreased from 45-38% at 360 min after the initiation of LRS administration. These findings suggest that the liver may have enough standby capacity to metabolise lactate under this level of liver injury if blood circulation is re-established and supplies enough oxygen to the liver.

On day 7 after $CCl_4$ administration, blood pH, lactate and other parameters returned to approximately pre-administration levels; thus, the steer's reactions to LRS administration were different from its reactions pre-administration and on day 11. Blood pH decreased immediately after LRS administration and reached 7.33 at 30 min, it subsequently increased and had returned to 7.39 at the 60 min time-point. The L-lactate had increased to pre-administration level at this time-point however and the AG was unchanged. Moreover, the BE decreased upon the initiation of LRS administration, depending on $HCO_3^-$ consumption. This suggested that the steer was under the

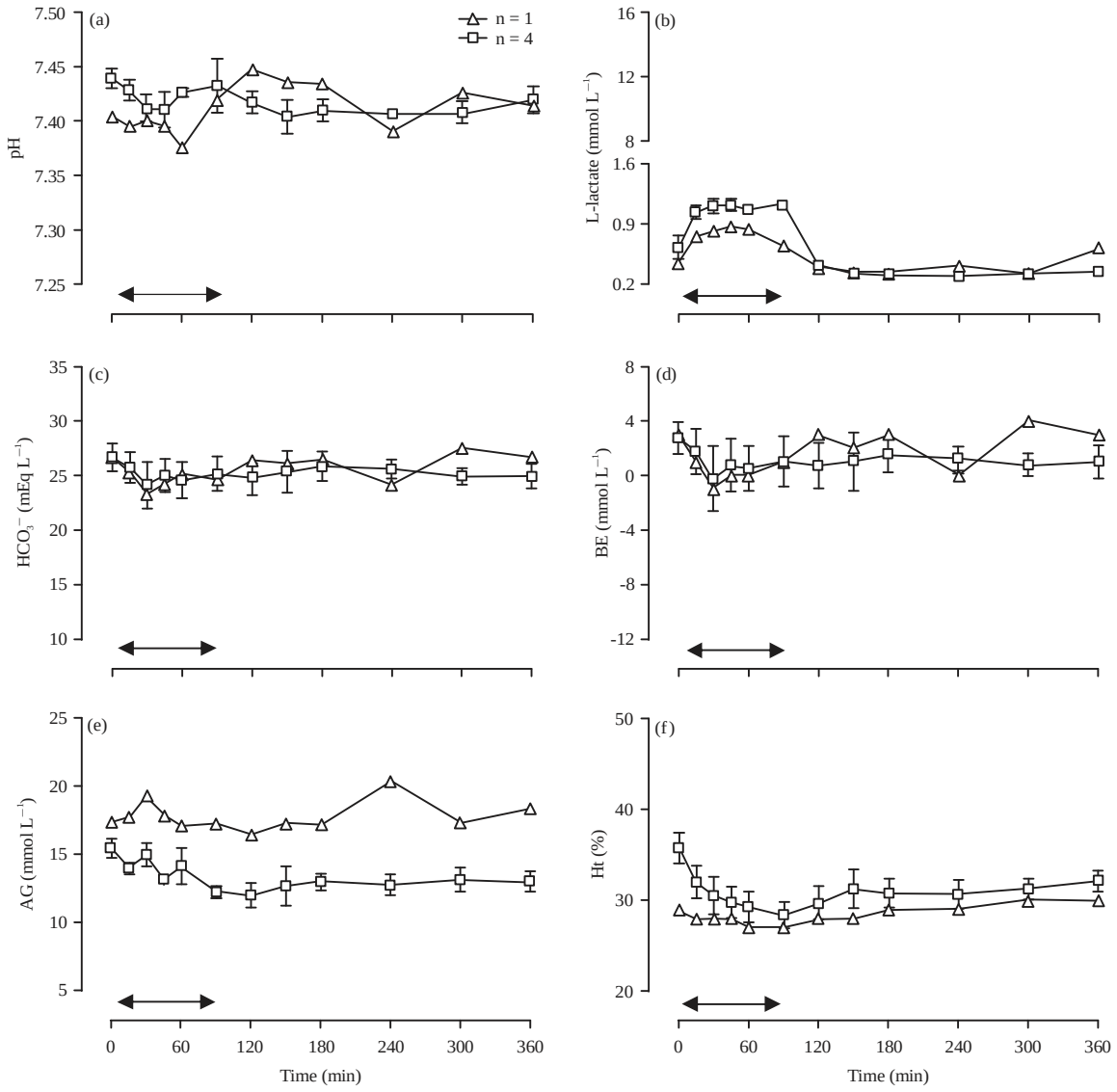


Fig. 3(a-f): Acid-base balance changes in a cow with a fatty liver (n = 1) and clinically healthy cows (n = 4) administered lactated Ringer's solution, (a) pH, (b) L-lactate, (c) $HCO_3^-$, (d) BE, (e) AG and (f) Ht values are shown. Arrows indicate the Ringer's lactate administration time-points

influence of dilution acidosis caused by LRS administration. Acidosis caused by LRS administration on day 7 differed from the high AG acidosis caused by excess L-lactate on day 2. Hartmann and Senn[13] developed LRS containing lactate to partially replace $Cl^-$ in order to prevent dilution acidosis when Ringer's solution and saline solution are administered rapidly. However, the $CCl_4$ cow exhibited dilution acidosis because a reserve base such as $HCO_3^-$ was not fully supplied. The Ht values on day 7 during LRS administration were slightly higher than pre-administration and on day 11, therefore, insufficient kidney function caused by mild dehydration may have been related to this transient dilution acidosis on day 7. In fact, the pH values of the cow with a fatty liver and the four control cows decreased slightly, however, they stayed within the normal reference range.

The LRS administration to cows with severe liver damage and lactic acidosis should be avoided, due to the possibility of exacerbating lactic acidosis. Acetated Ringer's Solution (ARS) administration is becoming more common in bovine clinics, for various reasons. Acetate is metabolised by peripheral tissues, not just the liver and is metabolised immediately. Lactate differs in these respects[1]. However, the superiority of ARS over LRS as an alkaliser is not always demonstrated. Nakagawa *et al.*[14] reported that ARS was superior to LRS for the

treatment of experimentally induced metabolic acidosis in calves. On the other hand, Kasari and Naylor[15] reported that acetate and lactate had similar alkalising effects on the acid-base balance in calves with diarrhoea. Cohen suggested that LRS administration to a patient with a liver dysfunction and acidosis is not deteriorated in logic[16]. In dogs, LRS administration after disrupting hepatic blood flow and they were able to metabolize the lactate quite well[17]. There are other similar studies and LRS is generally considered safe in humans, even with severe hepatic disease[18,19]. However, some studies reported different results. The LRS infusions can be deleterious to patients with cirrhosis[20] and liver dysfunction caused by prolonged shock[21]. These discrepancies remain unsolved.

In the present study, important information was obtained about LRS administration in cows with liver damage. Though general symptoms were worst and hepatic enzymes measured were the highest on day 2 in the $CCl_4$ steer, the administration of LRS at the flow rate and dosage used in this experiment did not exacerbate lactic acidosis in this animal. Moreover, improved circulation resulting from LRS administration rendered the pH appropriate for metabolising excess lactate. Though the pH of the cow had recovered by day 7, dilution acidosis was observed transiently in conjunction with LRS administration. The pH findings in association with LRS administration observed on days 2 and 7 were not observed on day 11, by which time the steer had recovered clinically and hepatically, at least as indicated by histopathological parameters.

In general, a hepatic triglyceride content of over 30 mg $g^{-1}$ of tissue is diagnosed as fatty liver in cows[22,23] and the cow with the fatty liver in the present study was diagnosed as having severe fat infiltration. However, the blood acid-base balance parameters of this cow did not differ substantially from those of the control cows. Therefore, LRS can be a safe extracellular replacement solution when administered to dairy cows at the recommended flow rate and dosage (20 mL $kg^{-1}$ $h^{-1}$ and 30 mL $kg^{-1}$) in clinics.

Acetate in ARS can be metabolised in the muscle, kidney and other organs when the liver has lost all function. However, if the liver maintains its original function, most of the acetate is probably metabolised in the liver. Even in a steer suffering from liver damage caused by $CCl_4$ administration and in a cow suffering from severe fatty liver, in the present study lactate was metabolised by the liver and worked as an alkaliser. The LRS should be used more as a general alkaliser and for extracellular fluid replacement in cows in clinical practice.

## ACKNOWLEDGMENTS

This study was supported in part by a Grant-in-Aid to KO from the Ministry of Education, Culture, Sports, Science and Technology of Japan (No. 25450457) and a research project grant awarded by the Azabu University Research Services Division.

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