HEPATIC LIPIDOSIS: DIAGNOSTIC TOOLS AND INDIVIDUAL AND HERD RISK FACTORS

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1. INTRODUCTION

Over the last decades intense genetic selection, improved nutrition and cow management increased annual milk yield of HF dairy cows significantly. Unfortunately, the increase in the genetic merit of milk yield is only partly associated with an increase in maximal feed intake (Veerkamp *et al.* 2000). Thus, a negative energy balance (NEB) is a common feature in high yielding fresh cows due to a high initial milk yield in face of delayed increase of dry matter intake. In order to adjust to the imbalance in nutritional energy intake and energy expenditure for maintenance and milk yield low plasma concentrations of insulin, IGF-1 and thyroxin and high plasma levels of glucagon, growth hormone and Cortisol allow increased hepatic gluconeogenesis and mobilization of lipids and protein from adipose and muscular tissues, resp. In consequence high plasma levels of nonesterified fatty acids (NEFA) are measured in cows during early lactation (Baumann & Currie, 1980; Hart, 1983; Vernon & Sasaki, 1991; Ingvartsen & Andersen, 2000).

Fatty liver develops when the hepatic availability of lipogenic and glucogenic products is imbalanced. Thereby the oxidation capacity of fatty acids is exceeded and since hepatic secretion of lipids is inherited low excess hepatic lipids are stored as triacylglycerol (TAG) in the liver tissue (Katoh, 2002; van Knegsel *et al.* 2005). Fatty liver occurs predominately in the first month of lactation. Approximately 15% of dairy cows develop severe and 35% moderate fatty liver. Fatty liver is associated with decreased health status, well-being, milk yield, reproductive performance and reduced immune response. Therefore fatty liver is a major risk factor for decreased average life time of cows (Gerloff *et al.* 1986; Rehage *et al.* 1996; Wensing *et al.* 1997; Zerbe *et al.* 2000).

2. CLINICAL PATHOLOGY

Classical parameter of clinical biochemistry, such as plasma activities of liver enzymes, bilirubin or bile acid concentrations do not allow a reliably discrimination between mild (< 50 mg TAG/g FW) or moderate (50-100 mg TAG/g FW), moderate and severe (> 100 mg TAG/g FW) and even not between mild and severe fatty liver (Rehage *et al.* 1999). The degree of hepatic lipidosis can only be diagnosed by taking liver biopsies with subsequent histological or biochemical examination for

total fat or TAG content. As a non-invasive technique sonographic examination of the liver may be promising in this regard (Bobe *et al.* 2004).

Recent studies showed that there is no linear relationship between liver function and the liver fat content. The majority of cows even with severe fatty liver showed in tests of clinical biochemistry no indication of impaired liver function. However, the risk of liver failure increased fivefold in cows with severe fatty liver compared to cows with mild fatty liver. Studied tests included hepatic excretion (Bilirubin subfractioning by HPLC, BSP clearance, bile acids, ammonia), hepatic production capacity (proteins, clotting factors, cholesterol, gluconeogenesis) and homeostasis (amino acids, acid base) (Rehage, 1996; Rehage *et al.* 2001; Mudron *et al.* 2004).

While high hepatic fat content was identified as a significant risk factor for the development of liver failure there was no indication that this is also true for low hepatic glycogen content (Rehage, 1996; Rehage *et al.* 2001). However, peroxidative processes were detected in the liver tissue due to low vitamin E availability and were assumed to contribute to the development of liver failure in cows with fatty liver (Mudron *et al.* 1997; Mudron *et al.* 1999).

The imbalance in the amino acid homeostasis and ammonia concentrations in plasma and cerebro spinal fluid (CSF) in cows with clinically obvious liver failure (no feed intake and ataxia, recumbency and coma) indicated that in cows the syndrome of hepatic encephalopathy occurs. In cows with hepatic encephalopathy plasma and CSF levels of aromatic amino acids (tyrosine, phenylalanine) increase, while levels of branched chain amino acids (lysine, isolysine, and tyrosine) decrease. Additionally, tryptophane and glutamine accumulate in the CSF which is also assumed to contribute to the development of clinical signs of hepatic encephalopathy (Rehage, 1996; Rehage *et al.* 2001).

In cows with fatty liver and in particular in those with liver failure substantial insulin resistance was found in studies using hyperglycaemic-hyperinsulinemic and euglycaemic-hyperinsulinaemic glucose clamps (Kaske *et al.* 2001).

3. TREATMENT

Since the pathogenesis of the development of fatty liver is not sufficiently understood therapeutic measures are less causative than symptomatic. A major goal must be to improve feed intake, since negative energy balance and subsequently lipomobilization is one of the major causes of fatty liver (Drackley, 1999; Herdt, 2000). Additionally, cows need to be animated to consume feed and excessive dietary protein must be avoided and sufficient amounts of easily fermentable carbohydrates provided to reduce the ammonia load to the liver (Rehage, 1996).

Reduction of lipomobilization can be achieved by all measures which lead to increased insulin plasma levels, either by insulin administration or by bolus or better by continuous glucose infusions (Bobe *et al.* 2004). Since insulin sensitivity of tissues is reduced during episodes of fatty liver (Kaske *et al.* 2001) continuous glucose infusions should not exceed about 2.0 g glucose/kg BW/24 h. Also oral treatment with glucoplastic substances, such as propionate, propylenglycol, glycerol or glucoplastic amino acids will provide at least small amounts of energy but will also lead to increased insulin plasma levels (Grummer, 1993; Bobe *et al.* 2004). Repeated oral application of sodium propionate or propylenglycol in isoenergetic dosages to continuous glucose infusions appears to be of similar efficacy. However, it must be considered that higher dosages of sodium propionate (bolus of > 250 g) will decrease significantly feed intake and hepatic ureagenesis and will induce metabolic alcalosis (Rehage *et al.* 1994).

Hepatic lipoperoxidative processes are assumed to play a negative role in the pathogenesis of hepatic failure in cows with fatty liver. Thus, administration of high dosages of vitamin E and selenium or other antioxidative substances is recommended (Mudron *et al.* 1997, 1999; Abd Ellah *et al.* 2004).

Although there are promising reports about the application of glucagon in cows with fatty liver in terms of enhancement of hepatic gluconeogenesis and reduction of liver fat content (Hippen *et al.* 1999; Bobe *et al.* 2003), the use in practise is still constricted, since there is still no appropriate galenism available to solve the problem of the short half life time of glucagon and it is at least in Europe not approved as a legal drug.

Dexamethasone is assumed to increase gluconeogenesis, which is concluded from raised plasma glucose levels. However, there are indications that elevated plasma glucose levels are more due to increased peripheral insulin resistance than to enhanced gluconeogenesis. However, recent studies showed several positive effects of dexamethasone in dairy cows with fatty liver: reduction in plasma ketone body levels and hepatic triglyceride content, increased plasma insulin, reduced plasma non esterified fatty acids and ammonia concentrations, and a restoration of plasma amino acid homeostasis (Shigel *et al.* 1996; Rehage *et al.* 2002; Jorritsma *et al.* 2004). In particular the capacity of dexamethasone to decrease plasma ammonia levels and to increase plasma concentrations of branched chain amino acids needs to be emphasized. Ammonia as well as the imbalance in amino acid homeorrhesis is assumed to play an important role in the development of severe clinical CNS signs in cows with liver failure (Rehage *et al.* 2002).

4. PREVENTION

Feeding cows in balanced rations which meet energy requirements and provide sufficient amounts of fiber in order to avoid subclinical ruminal acidosis is an essential precondition in the prevention of fatty liver. In particular obesity of dry cows is a major risk factor for subsequent fatty liver in early lactation. Only feed stuffs of high quality should be offered and enough bunk space and intensive bunk management will allow cows to maximize feed intake and thereby to minimize negative energy balance during early lactation (Drackley, 1999; Kleen *et al.* 2003; Vernon, 2005). Effective prevention of milk fever and early and resolute treatment of all diseases which commonly go along with ketosis and fatty liver, such as abomasal displacement, mastitis, endometritis, and lameness are required (Bobe *et al.* 2004). Avoiding social and environmental stress, clean and comfortable housing conditions, regular exercise and good micro climate conditions are also important measures (Drackley, 1999). Drenching Propylenglycol, oral administration of glycerol or sodium or calcium propionate and provision of sufficient amounts of antioxidative substances in the diet are recommended (Grummer, 1993; Abd Ellah *et al.* 2004; Bobe *et al.* 2004). Efficacy of fat supplements to the ration of dry or lactating cows is discussed controversially (Grummer, 1993, Drackley, 1999; Bobe *et al.* 2004; Vernon, 2005; Van Knegsel *et al.* 2005). Providing antibiotic ionophores such as monensin as feed additives appears to be effective in particular in obese cows (Duffield, 2000; Duffield *et al.* 2003). However, monensin is not approved as a legal drug in the European Union in dairy cows.

5. SUMMARY

Fatty liver and ketosis are closely related and occur predominately during early lactation as the major metabolic disorders in high producing dairy cows. Even mild fatty liver is associated with a decrease in animal production, reproductive performance and immune competence. With increasing hepatic fat content the risk of developing liver failure is increasing steadily. Liver failure is associated with increased oxidative stress in liver tissue. Treatment of fatty liver and ketosis includes continuous or bolus infusions of glucose, single shots of corticosteroids, Vitamin E,

Selenium or other antioxidative substances. Repeated oral applications of sodium propionate or propylenglycol in isoenergetic dosages compared to continuous glucose infusions appear to be of similar efficacy. Preventatives include avoidance of obesity of cows, early treatment of any diseases such as mastitis or endometritis, balanced dietary intake of high quality feed stuffs during the dry and lactation period, stress free environment and excellent bunk management and housing conditions with a high level of cow comfort.

6. KEYWORDS

Cattle, fatty liver, ketosis.

7. RESUME

La stéatose hépatique et la cétose sont étroitement liées et surviennent principalement en début de lactation, comme troubles métaboliques majeurs de la vache laitière. Même une légère stéatose hépatique s'accompagne d'une baisse de production, de problèmes de reproduction et de désordres immunitaires. Le risque d'insuffisance hépatique s'accroît avec l'augmentation des dépôts adipeux dans le foie. L'insuffisance hépatique est liée à l'augmentation du stress oxydatif dans le parenchyme hépatique. Le traitement de la stéatose hépatique et de la cétose repose sur l'administration, continue ou par bolus, de glucose, et sur des injections uniques de corticoïdes, vitamine E, sélénium et autres antioxydants. La répétition de plusieurs administrations orales de propionate de soude ou de propylène glycol à doses iso-énergétiques est aussi efficace que l'infusion de glucose en continu. La prophylaxie repose sur la prévention de l'obésité chez la vache et le traitement précoce des mammites ou des endométrites, sur une ration alimentaire équilibrée et de haute qualité pendant le tarissement et la lactation, sur un environnement sans stress et sur un excellent entretien de la litière et du logement avec un haut niveau de confort.

8. MOTS CLES

Bovins, stéatose hépatique, cétose.

9. ZUSAMMENFASSUNG

Leberverfettung und Ketose treten in der Regel in der Frühlakation gemeinsam auf und zählen zu den häufigsten metabolischen Gesundheitsproblemen bei hochleistenden Milchkühen. Leberverfettung entsteht als Folge übermäßiger Lipidmobilisation in Phasen negativer Energiebilanz und unausgewogener hormoneller Adaptation. Mit zunehmendem Fettgehalt in der Leber steigt das Risiko einer Leberinsuffizienz. In Fällen einer Leberinsuffizienz ist das Lebergewebe erhöhtem oxidativem Stress ausgesetzt. Selbst bei geringgradiger Leberverfettung sind Leistungsfähigkeit, Fruchtbarkeit und Immunkompetenz beeinträchtigt. Die Behandlung beinhaltet Bolus- oder kontinuierliche Infusionen von Glucose, Corticosteroide, Vitamin E, Selen oder andere antioxidative Substanzen. Zu den wichtigsten Präventivmaßnahmen zählen Vermeidung übermäßiger Verfettung, Minimierung der negativen Energiebilanz in der Frühlaktation durch Maximierung der Futteraufnahme (qualitativ hochwertige und ausgewogen rationierte Futtermittel, gutes Trogmanagement), stressfreie U mgebung, Optimierung des Kuhkomforts und frühzeitige und entschlossene Behandlung jedweder Erkrankungen.

10. SCHLÜSSELWORTE

Leberverfettung, Leberfunktion, Ketose

11. REFERENCES

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