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The Effect of Gentamicin Sulfate on Plasma Glucose Concentrations Post Suckling of Milk in Holstein Calves

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Abstract: The purpose of this study was to determine the effect of gentamicin sulfate on plasma glucose concentrations after suckling of 2 L of whole cow milk in healthy calves. Five male Holstein-Friesian calves (3 to 7 days of age) were given one of the following treatments in random order: Control, 2 mL of NaCl IM; gentamicin, 6.6 mg kg^{-1} IM and gentamicin, 4.4 mg kg^{-1} IM. Serial plasma glucose concentrations were measured at baseline and during 8 h after suckling. During the first 30 min plasma glucose concentrations was lower in gentamicin ($p<0.05$) group compared to placebo. We proposed that the lower glucose concentrations after gentamicin administration is due to slowing the abomasal emptying rate, post normally consumed milk. Most of diarrheic calves with hypoglycemia have stasis in gastrointestinal motility and gentamicin may be of no benefit as part of treatment and probably exacerbates critical condition in them.

Key words: Gentamicin sulfate, whole milk, glucose, calf

INTRODUCTION

Few studies have measured abomasal emptying rate of normally consumed whole cow milk while evaluating the effect of delaying abomasal emptying on glucose concentrations. Impaired abomasal motility is suspected to play a major role in the development of abomasal disorders in adult cattle, such as left displaced abomasum in lactating dairy cows and abomasal tympany in calves (Constable *et al*., 1992). Feed lot cattle severely affected with pneumonia or foot rot has decreased reticuloruminal motility and is likely to have abomasal hypomotility (Nouri and Constable, 2006). Any factors such as hypocalcaemia (Madison and Troutt, 1988), endotoxemia (Vlaminck *et al*., 1985), alkalemia (Poulsen and Jones, 1974) and hyperglycemia (Holtenius *et al*., 1998; Sen *et al*., 2006) decrease abomasal emptying rate in cattle are believed to have effects on it. In addition to these factors some antibiotics such as gentamicin sulfate that decrease the horse's colon peristaltic response (Lees and Percy, 1981) and inhibits spontaneous cow's myometrium contraction may also have the same effect on abomasal smooth muscles. At present time clinicians by correcting disorders causing abomasal hypomotility treat the affected cows and calves.

Gentamicin is an aminoglycoside antibiotic effective against most gram negative and some gram positive bacterial infection and has been used as part of the treatment of sick neonatal calves with septicemia or calf diarrhea (Constable, 2004). Gentamicin is therefore commonly administered to critically ill calves that are suspected to have abomasal hypomotility and hypoglycemia. However, gentamicin decreases the peristaltic response of the horse colon (Lees and Percy, 1981) and decreases the contractility of the isolated rat uterus (Paradelis, 1982) and bovine uterine smooth muscle strips (Ocal *et al*., 2004). Because the smooth muscle in the calf's abomasum may be similarly sensitive to the effects of gentamicin as uterine smooth muscle, we were concerned that parenterally administered gentamicin might decrease the abomasal emptying rate in the calf and finally leading to the reduction of plasma glucose level. Accordingly, the objective of this study was to determine whether altering abomasal emptying in calves by gentamicin could have any effect on glucose absorption after milk is suckled. Contractory inhibition of cow isolated uterus myometrium by gentamicin sulfate has recently been reported (Ocal *et al*., 2004). There is not any study according to the literatures to show if gentamicin can do the same on abomasal muscle contraction,

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therefore the present study seems to be the first investigation to consider the effect of gentamicin sulfate on glucose blood levels after whole cows milk was suckled by calf.

MATERIALS AND METHODS

Animals: Five healthy male Holstein-Friesian colostrum-fed calves were obtained from local farms within the first week of life. Mean body weight of these calves was 40 kg (range, 31 to 48 kg). Calves were kept unrestrained in individual stall and fed twice a day (10% of body weight) with fresh cow's milk.

At the day of experiment an intravenous catheter was placed in the jugular vein and secured to the neck. Calves had access to fresh water at all times that weren't under experiment.

Study design: Each calf was given the following 3 treatments in randomized order: gentamicin (Gentamicin sulfate 80 ®, Alborz Daru); 6.6 mg kg^{-1} IM. gentamicin, 4.4 mg kg^{-1} IM and control, 2 mL of NaCl IM. Calves were fed 2 L of whole cow milk 30 min after treatment was administered. Treatments were initiated 30 min before feeding because maximal plasma concentrations of gentamicin occur at 45 min after IM administration in cattle (Haddad *et al.*, 1986). The dosage protocol for gentamicin was based on pharmacokinetic studies in calves and adult cattle (Clarke *et al.*, 1985; Haddad *et al.*, 1986, 1987). At least 36 h elapsed between each study in order to ensure an adequate wash out period. During this time calves were fed cow's whole milk (Sen *et al.*, 2006).

Blood analysis: Venous blood samples for determination of plasma glucose levels were obtained at -30, 0, 15, 30, 45, 60, 90, 120, 150, 180, 240, 300, 360, 420 and 480 min relating to the start of suckling cow's whole milk. Plasma was separated immediately after finishing the study and frozen at -20°C until analysis. Plasma glucose levels were measured using an Élan autoanalyzer (Eppendorf, Germany).

Statistical analysis: Plasma measurement data were entered into a Microsoft Excel spread sheet and analyzed with statistical software (SPSS 9.0). Friedman ANOVA was used to compare treatment groups with control. Follow up paired comparisons were carried out using Wilcoxon matched pairs test. $p<0.05$ was considered statistically significant. Data are expressed mean±standard error of mean (SEM).

RESULTS

There were no significant difference between the mean base line (before drug infusion, time = -30) of plasma glucose levels for placebo, low dose gentamicin and high dose gentamicin groups, which were 58/80±15/45, 54/40±14/36 and 59/4±19/50 mg dL^{-1} (mean±SEM), respectively (Fig. 1).

Using Friedman ANOVA test, significant ($p = 0.006$) difference was shown for all groups 30 min after the calf suckled milk. Follow up post-hoc comparison tests with Wilcoxon matched pairs test revealed that the two treatments had significant difference versus controls ($p = 0.043$). No significant ($p = 0.500$) difference was shown when the treatment groups (Gentamicin 4.4 mg kg^{-1} and gentamicin 6.6 mg kg^{-1} were compared. A highly significant ($p = 0.000$) difference was shown for all groups in area under the plasma glucose-time curves

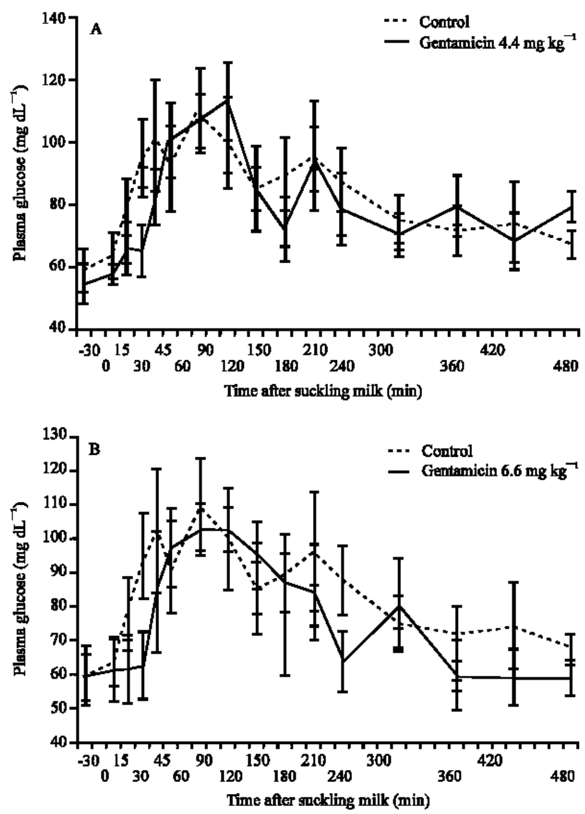

Fig. 1: Effects of gentamicin and NaCl injections on plasma glucose. Glucose concentration after gentamicin injection in doses 4.4 mg kg^{-1} (A) and 6.6 mg kg^{-1} (B) is significantly lower than the control at 30 minutes after suckling whole milk in 5 healthy calves. Mean±SEM, Error bars represent SEM. * $p<0.05$ vs. placebo

(AUC) by Friedman ANOVA test. Follow up post-hoc comparison tests with Wilcoxon matched pairs test revealed that two treatment had also significant difference versus controls (p = 0.022) at time 45 and 60 min after calf suckled milk. During the first 45 and 60 min, the mean AUC were significantly smaller after gentamicin 4.4 mg kg^{-1} (2994.9±670 mg min^{-1} dL^{-1} p = 0.043, 3845.4±840.6 mg min^{-1} dL^{-1} p = 0.043, respectively) and gentamicin 6.6 mg kg^{-1} (2941.5±928.9 mg min^{-1} dL^{-1} p = 0.043, 4299±1300.5 mg min^{-1} dL^{-1} p = 0.043, respectively) when they compared to that of placebo (3844±999 mg min^{-1} dL^{-1} 5295±1486 mg min^{-1} dL^{-1}, respectively).

DISCUSSION

This study investigated the effect of gentamicin on blood glucose concentrations in healthy calves. As it was shown in our previous study, gentamicin delayed abomasal emptying in healthy calves (Omidi *et al*., unpublished data). Results of this study confirmed immediately effect of gentamicin on abomasal emptying rate. The study showed that gentamicin can change blood glucose level during first 1 h. after injection (Fig. 1). Gentamicin has been used as part of the treatment of sick neonatal calves with Gram-negative infections, septicemia or calf diarrhea (Constable, 2004).

Endotoxemia causes a profound inhibition of gastrointestinal motility and the whole gut collapses owing to the release of some mediators by endotoxins (Morris *et al*., 1986). Hypoglycemia is common in prolonged or severe endotoxemia (Spitzer *et al*., 1989) and in calves has been recorded as a concurrent problem with diarrhea which could be secondary to the interference with digestion and absorption of carbohydrate and glucose (Radostits *et al*., 2000).

After challenging the calf with *Escherichia coli* STa (Heat-stable) enterotoxin orally, migrating myoelectric complex decreases and therefore could reduce abomasal emptying (Roussel *et al*., 1992,).

The entry of glucose into the circulation is influenced by the rate at which carbohydrates empty from the stomach. Delaying emptying of a meal will delay absorption of carbohydrate in the small intestine and may result in less postprandial hyperglycemia. (Gonlachanvit *et al*., 2003).

In conclusion, this study demonstrated that, gentamicin sulfate tended to decrease abomasal emptying rate and lowers blood glucose concentrations in healthy calves. Because of inhibitory effect of gentamicin on gastrointestinal motility, its use may exacerbate critical condition of sick calf with the gut collapse (Fig. 2).

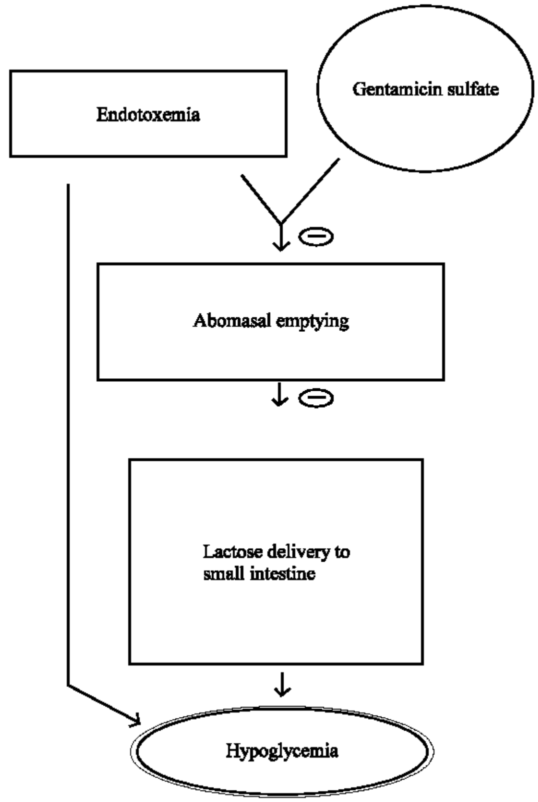

Fig. 2: Synergetic inhibitory effect of gentamicin and endotoxemia on abomasal emptying and inducing hypoglycemia

It remains to be determined whether alteration in abomasal emptying rate and blood glucose level by gentamicin occurs in sick calves (as it was occurred in healthy calves in this study) and whether this effect of treatment is clinically important.

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