Effect of 2-methyl-2-phenoxy propionic acid on serum lipid profile and ovarian activity in dairy cows

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ABSTRACT: Hepatic lipidosis and ketosis are frequent metabolic disorders in dairy cows during the transition period. The 2-methyl-2-phenoxy propionic acid (MFPA) is an activator of energy metabolism. The objective of this study was to evaluate the effect of administration of MFPA 10 days prepartum to day 36 postpartum on serum lipid profile, ovarian reactivity, and milk yield. Fifty seven multiparous Holstein cows were divided into four groups. The groups 1 (n = 14) and 2 (n = 14) had body condition score (BCS) above 4; BCS of the groups 3 (n = 15) and 4 (n = 14) was between 3.25 and 3.75 at calving. The solution containing 10 mg/kg MFPA was injected intramuscularly (IM) to cows of groups 1 and 3, 10–7 days prepartum and 6 h postpartum. The groups 2 and 4 received 50 ml of 0.9% NaCl as placebo in the same way. Blood samples for serum lipid profile were collected from all cows 10 days before calving without treatment, 2 days after the first administration of MFPA and postpartum at days 2, 10, and 21 after the second administration of MFPA. At days 21, 24, 27, 30, 33, and 36 postpartum, blood samples were obtained for plasma progesterone determination. Milk yield was registered daily during 60 days postpartum. Prepartum free fatty acids (FFA) were mildly increased without difference among all the groups ($P > 0.05$). β-hydroxybutyrate (BHB) was increased only at day 10 after calving in cows of group 1 treated with MFPA ($P < 0.05$) due to higher number of postpartum diseases. In cows from groups 3 and 4 (BCS normal), BHB was mildly increased, not indicating subclinical ketosis. The serum concentrations of triacylgycerols, cholesterol, albumin, activities of aspartate aminotransferase and creatine kinase were within the limits of reference values, indicating adequate liver integrity and function. Cows of normal BCS treated with MFPA presented better milk production but without significant difference among four groups ($P > 0.05$). Ovarian reactivity was present at day 21 in all groups of cows without difference ($P > 0.05$). The administration of MFPA had no effect on serum lipid profile and ovarian activity in this study.

Keywords: ketosis; PPARs; blood biochemistry; milk production; transition cow

Production diseases in dairy cattle have a higher incidence during the transition period (Mulligan and Doherty, 2008). This period includes 3 weeks before and 3 weeks after calving. Cows have different endocrine and metabolic changes caused by calving and early high lactation (Grummer, 1995; Grummer et al., 2004). These cows are susceptible to metabolic disorders affecting health and production (Shibano and Kawamura, 2006).

The onset of lactation leads to increased metabolic rate in the animal body, in order to cover the needs of maintenance and production, otherwise the cows would be in a negative energy balance (NEB) (Villa-Godoy et al., 1988; Bell, 1995; Goff and Horst, 1997). When cows are in NEB, they use their body reserves, leading to lipomobilization of free fatty acids (FFA) and accumulation of triacylgycerols (TG) in liver tissue, affecting its

Supported by the National Autonomous University of Mexico, Schütze Segen, Mexico (Project PAPIIT 216409).

structure and function (Bobe et al., 2004; Shibano and Kawamura, 2006). An increase in lipid accumulation and decrease in glycogen in the liver are associated with higher incidence of hepatic lipidosis and ketosis (Drackley et al., 1992). NEB will make them susceptible to increased incidence of metabolic disorders (Jordan and Fourdraine, 1993). Therefore, nutrition, management, and preventive treatment of cows during the transition period will still be of great interest in the following years (Goff and Horst, 1997; Salgado et al., 2009).

Nowadays, the alternatives have been developed to reduce the presence of metabolic disorders during the transition period. These alternatives are designed to reduce body fat removal and the accumulation of TG in liver tissue to avoid affecting its structure, function, and prevent alterations in the energy metabolism (Grummer, 2008). The 2-methyl-2-phenoxy propionic acid (MFPA) is a substance that belongs to the family of fibrates that are used in the treatment of dyslipidemia (Kersten et al., 2000). These ligands are responsible for the peroxisome proliferator-activated receptors (PPARs). PPARs are classified into three isotypes – α, β, and γ. PPARs are involved in the regulation of lipid metabolism (Inoue et al., 2003; Kota et al., 2005; Ahmed et al., 2007; Bionaz et al., 2008). Little is known about the effect of PPARs on metabolism in obese dairy cows and their therapeutic application in prevention and treatment is still in development. The administration of MFPA during the periparturient period could reduce lipomobilization in fat cows. The objective of this study was to evaluate the effect of MFPA on serum lipid profile in transition period, and ovarian reactivity and milk production in dairy cows until day 60 postpartum.

MATERIAL AND METHODS

Animals and treatments

A total of 57 multiparous Holstein cows before calving were used. Animals belonged to a commercial farm (6800 cows) near the city of Torreon, Coahuila, Mexico, with an annual mean milk production 9455 kg/cow. Body condition score (BCS) was assessed (Ferguson et al., 1994) 21 days prepartum and the animals were randomly divided into 4 groups. Cows in group 1 (n = 14) and group 2 (n = 14) showed BCS greater than 4. Cows in group 3 (n = 15) and group 4 (n = 14) had BCS between 3.25 and 3.75. Cows were under the same conditions of feeding and management. Groups 1 and 3 were IM given 10 mg/kg of MFPA (Hepagen; Fatro, Bologna, Italy) 10–7 days before the expected date of calving and 6 h postpartum. Groups 2 and 4 were given 50 ml of NaCl 0.9% per cow as a placebo on the same days like the treated groups.

Sampling and analyses

Blood samples were taken from all the groups of cows by the tail vein puncture in 7 ml vacuum tubes without anticoagulant (Monoject®, Argtech, Inc., Manhattan, USA) to obtain serum 10–7 days prepartum before application of MFPA, 2 days after the first prepartum treatment, and 2, 10, and 21 days postpartum. The separation of clot from serum was performed within 1 h after sampling by centrifugation at 1200 *g* for 10 min. On days 21, 24, 27, 30, 33, and 36 postpartum blood samples with EDTA anticoagulant were taken to obtain plasma. Serum and plasma from each cow were preserved in plastic vials (Eppendorf, Hamburg, Germany) at –20°C until analysis in the laboratory.

The serum concentrations of the following analytes were determined: FFA, β-hydroxybutyrate (BHB), cholesterol, TG, albumin, total proteins (TP), enzyme activities of aspartate aminotransferase (AST), and creatine kinase (CK) (Randox Laboratories Ltd., Crumlin, UK) in a semi-automatic analyser (model Junior; Vital Scientific, Spankeren, the Netherlands). Analyses were performed in the laboratory of Clinical Pathology, Faculty of Veterinary Medicine of the National Autonomous University of Mexico. The plasma concentration progesterone (P4) was determined by means of radioimmunoassay with a commercial solid phase kit (Siemens, Los Angeles, USA). The minimum sensitivity of the assays was 0.03 ng/ml and intra and interassay variation coefficients were 4.6 and 8.7%, respectively, in order to identify postpartum ovarian reactivation.

Animals of the 4 groups underwent a daily clinical examination after the first milking (7:00–9:00 a.m.). The "fresh cow" program was applied, that was: to observe the animal daily, its appetite, behaviour, body temperature, make general physical examination and dark bowl test for diagnosis of mastitis. Transrectal examination was performed periodically for diagnosis of reproductive problems (retained placenta, endometritis, metritis). Milk production was registered daily in all animals until 60 days postpartum.

Statistical analysis

A two-factor repeated-measures analysis of variance was done to determine the difference in the levels of biochemical analytes between groups of animals. The model included the effect of treatment and time by treatment interaction, adjustments for multiple comparisons were performed by the Bonferroni method. The total milk production during 60 days postpartum was assessed by analysis of variance. A correlation test was used to observe the influence of FFA and BHB concentrations prepartum and postpartum on milk production. For the evaluation of ovarian reactivity, data

Table 1. Lipid profile and selected biochemical values in dairy cows

	Group	Prepartum cows		Postpartum cows			Reference values
		10 days	7 days	2 days	10 days	21 days	
FFA (mmol/l)	1	0.49 ± 0.28	0.73 ± 0.64	1.06 ± 0.59	1.17 ± 0.72	1.14 ± 0.55	≤ 0.4
	2	0.53 ± 0.27	0.54 ± 0.36	1.14 ± 0.80	1.06 ± 0.57	1.05 ± 0.71	
	3	0.47 ± 0.23	0.63 ± 0.37	0.83 ± 0.36	1.08 ± 0.39	1.00 ± 0.27	
	4	0.59 ± 0.44	0.37 ± 0.29	1.03 ± 0.49	1.04 ± 0.57	1.05 ± 0.56	
BHB (mmol/l)	1	0.56 ± 0.23	0.61 ± 0.49	0.88 ± 0.48	1.43 ± 1.17*	0.75 ± 0.57	≤ 1.2
	2	0.39 ± 0.09	0.40 ± 0.12	0.67 ± 0.27	0.85 ± 0.50	1.07 ± 0.95	
	3	0.51 ± 0.13	0.55 ± 0.10	0.63 ± 0.15	0.89 ± 0.31	0.60 ± 0.35	
	4	0.52 ± 0.12	0.46 ± 0.10	0.83 ± 0.40	0.84 ± 0.51	0.72 ± 0.69	
TG (mmol/l)	1	0.31 ± 0.08	0.28 ± 0.09	0.13 ± 0.06	0.13 ± 0.07	0.14 ± 0.08	0–0.24
	2	0.28 ± 0.06	0.33 ± 0.08	0.10 ± 0.04	0.10 ± 0.02	0.16 ± 0.08	
	3	0.30 ± 0.10	0.26 ± 0.11	0.11 ± 0.03	0.14 ± 0.05	0.14 ± 0.02	
	4	0.30 ± 0.11	0.26 ± 0.12	0.15 ± 0.14	0.15 ± 0.10	0.13 ± 0.06	
Cholesterol (mmol/l)	1	2.69 ± 0.51	2.55 ± 0.47	2.35 ± 0.48	2.73 ± 0.88	3.57 ± 1.18	2.6–6.0
	2	2.67 ± 0.58	2.78 ± 0.50	2.30 ± 0.49	3.37 ± 1.06	4.53 ± 1.42	
	3	2.40 ± 0.65	2.34 ± 0.62	2.44 ± 0.49	3.07 ± 0.73	4.00 ± 1.23	
	4	2.77 ± 0.76	2.74 ± 0.76	2.78 ± 0.77	2.97 ± 0.89	4.52 ± 1.07	
TP (g/l)	1	71.32 ± 11.76	66.21 ± 4.45	64.07 ± 9.14	72.00 ± 6.49	75.04 ± 6.48	59–80
	2	71.27 ± 5.67	72.78 ± 4.67	70.62 ± 6.13	75.71 ± 7.18	81.64 ± 8.19	
	3	64.32 ± 3.47	65.04 ± 4.99	66.61 ± 4.98	76.40 ± 6.62	81.06 ± 6.46	
	4	66.85 ± 4.25	65.18 ± 4.62	67.15 ± 5.04	70.47 ± 5.65	76.17 ± 3.91	
Albumin (g/l)	1	35.94 ± 2.17	35.64 ± 1.64	35.21 ± 2.75	34.92 ± 2.86	33.77 ± 3.87	30–36
	2	35.34 ± 2.64	35.78 ± 2.48	35.67 ± 4.18	35.35 ± 2.59	35.92 ± 2.58	
	3	35.24 ± 2.18	35.10 ± 2.38	35.94 ± 2.65	35.00 ± 3.60	35.66 ± 3.77	
	4	35.64 ± 2.76	35.49 ± 2.95	36.40 ± 2.21	34.01 ± 2.69	36.62 ± 2.68	
CK (μkat/l)	1	1.38 ± 0.76	2.28 ± 1.17	5.29 ± 3.55	3.61 ± 2.49	2.20 ± 1.66	< 4.99
	2	1.54 ± 1.00	1.09 ± 0.29	2.39 ± 2.12	1.88 ± 0.58	2.55 ± 1.33	
	3	1.37 ± 0.43	1.75 ± 0.70	4.52 ± 3.15	1.98 ± 0.61	1.93 ± 0.76	
	4	1.91 ± 0.97	2.13 ± 1.22	3.15 ± 2.32	3.42 ± 2.68	2.71 ± 1.28	
AST (μkat/l)	1	0.85 ± 0.18	0.88 ± 0.27	1.46 ± 0.74	1.70 ± 1.03	1.20 ± 0.54	0.5–2.0
	2	0.75 ± 0.22	0.69 ± 0.10	1.03 ± 0.33	1.05 ± 0.21	1.05 ± 0.14	
	3	0.79 ± 0.13	0.82 ± 0.13	1.49 ± 0.76	1.11 ± 0.24	1.06 ± 0.24	
	4	0.95 ± 0.31	0.94 ± 0.33	1.23 ± 0.29	1.45 ± 0.73	1.16 ± 0.28	

FFA = free fatty acids, BHB = hydroxybutyrate, TG = triacylglycerols, TP = total proteins, AST = aspartate aminotransferase, CK = creatine kinase

*statistically significant difference in values between groups ($P < 0.05$)

group 1 (fat cows; $n = 14$) and group 3 (normal BCS; $n = 15$) were administered MFPA IM at a dose of 10 mg/kg 10–7 days before the expected calving date and 6 h after calving; control: group 2 (fat cows; $n = 14$), group 4 (normal BCS; $n = 14$)

were analyzed by an independent contrasts test at a significance level of 0.05, using Fisher's exact value. The results were analyzed using SPSS software for MS Windows 2010.

RESULTS

During the study, different diseases were observed in 21 sick cows (36%) of all the cows studied (n = 57). The following diseases were diagnosed: subclinical mastitis (2 cases in group 1, 2 in group 2, and 2 in group 3); subclinical ketosis (2 cases in group 1 and 1 in group 2); parturient paresis (1 case in group 1 and 1 in group 2); displaced abomasum (2 cases in group 1); subclinical laminitis (1 case in each group); bronchopneumonia and endometritis (2 cases in group 3 and 2 in group 4).

Serum concentrations of FFA 10 days prepartum were mildly increased (between 0.47 and 0.59 mmol/l) in the four groups of cows (Table 1). In the second sampling only group 4 showed a decline (0.37 mmol/l). In the postpartum period, the groups showed a mild increase in serum FFA, with no statistically significant difference (P > 0.05) between all the groups (Table 1). BHB serum concentrations significantly increased at day 10 postpartum in group 1; these fat cows were treated with MFPA showing subclinical ketosis (BHB = 1.43 mmol/l, P < 0.05). The values of BHB slightly increased postpartum in groups 2, 3, and 4 (P > 0.05), it did not indicate the presence of subclinical ketosis (BHB < 1.2 mmol/l). Mean serum values of TG, cholesterol, TP, albumin, AST, and CK were within the range of reference values during the time of the study and there was no statistical difference among groups (P > 0.05) indicating that the liver integrity and function are not affected (Table 1).

No significant difference was found for milk production between the four groups (P > 0.05) during the first 60 days postpartum (Table 2). The correlation between serum concentrations of FFA, BHB, with total milk production at 60 days postpartum is presented in Table 3.

Progesterone concentrations were greater than 1 ng/ml indicating postpartum ovarian reactivation in the four groups. There was no significant difference (P > 0.05) between groups at days 21 and 36 postpartum (Table 4).

Table 2. Milk production (kg) in cows during the first 60 days in lactation

Group of cows	n	Mean	Standard deviation
1	14	1637.48	751.20
2	14	1965.98	518.76
3	15	2136.16	566.13
4	14	1859.18	659.63

group 1 (fat cows) and group 3 (normal BCS) were administered MFPA IM at a dose of 10 mg/kg 10–7 days before the expected calving date and 6 h after calving; control: group 2 (fat cows), group 4 (normal BCS)
no significant difference between means (P > 0.05)

Table 3. Correlation between serum concentrations of free fatty acids and β-hydroxybutyrate and total milk production at day 60 of lactation

Analyte		Cows (n = 57)	P
FFA	10 days prepartum	–0.058	0.33
FFA	7 days prepartum	–0.239	0.04*
FFA	2 days postpartum	–0.254	0.03*
FFA	10 days postpartum	–0.044	0.37
FFA	21 days postpartum	0.183	0.09
BHB	10 days prepartum	–0.106	0.22
BHB	7 days prepartum	–0.266	0.02*
BHB	2 days postpartum	–0.190	0.08
BHB	10 days postpartum	–0.059	0.33
BHB	21 days postpartum	–0.086	0.26

FFA = free fatty acid, BHB = hydroxybutyrate
*negative trend observed in the correlation between BHB and FFA with total milk production

Table 4. Ratio of cows with ovarian activity at days 21 and 36 postpartum (n = 57)

Cows	21 days postpartum	36 days postpartum
Group 1	3/14	10/14
Group 2	6/14	11/14
Group 3	8/15	14/15
Group 4	5/14	12/14

group 1 (fat cows) and group 3 (normal BCS) were administered MFPA IM at a dose of 10 mg/kg 10–7 days before the expected calving date and 6 h after calving; control: group 2 (fat cows), group 4 (normal BCS)
cases with plasma concentrations of progesterone > 1 ng/ml
no significant difference between groups (P > 0.05)

DISCUSSION

An extensive review on prevention of hepatic lipidosis and ketosis in the transition period in dairy cows is described by Grummer (2008). The use of fibrates for the treatment of dyslipidemia has been documented in several previous studies in rats and humans (Inoue et al., 2003; Kota et al., 2005; Ahmed et al., 2007; Bionaz et al., 2008; Litherland et al., 2010). PPARs are key transcription factors that catalyse and coordinate different biochemical processes in order to achieve energy homeostasis in the body (Yamamoto et al., 1996; Inoue et al., 2003; Kota et al., 2005). Several natural and synthetic compounds can act as agonists of PPARs and increase the capacity of hepatocytes to carry out the oxidation of long chain FFA by inducing mitochondrial and peroxisomal oxidation (Litherland et al., 2010). These activate the PPARα, leading to a decrease in TG levels by increasing the expression of lipoprotein lipase and inhibition of apolipoprotein CIII (apoC III) in the liver (Kota et al., 2005). A reduction in hepatic production of apoC-III serves as an inhibitor of lipolytic processing and clearance of very low density lipoproteins, recovering the liver function and maintaining energy production (Kersten et al., 2000).

This study showed that the concentration of serum FFA in prepartum cows was slightly higher than 0.4 mmol/l. This analyte prepartum (> 0.4 mmol/l) is used as a predictor of lipomobilization and possible hepatic lipidosis, especially in cows with a BCS above 3.75 (LeBlanc, 2002; Nuñez and Bouda, 2007; Padilla et al., 2007). The serum concentrations of FFA in our study are consistent with those reported by Litherland et al. (2010). Applying a PPARα agonist prepartum and short time after calving had no significant effect on serum FFA. However, Smith et al. (2007, 2009) reported that the prepartum application of 4-thiazolidinedione (TZD), a PPARγ activator, reduced FFA concentrations prepartum but not postpartum. Yamamoto et al. (1996) in a study using rats fed with fenofibrate found that it alters the metabolism of exogenous FFA by oxidation and TG secretion by the liver of treated rats compared with controls. They attribute the drug effect on the intracellular metabolism. The cows of group 1 with higher BCS than 4 and treated with MFPA showed an increase in serum BHB at day 10 postpartum corresponding to subclinical ketosis associated with a greater number of postpartum diseases (8 cases). LeBlanc et al. (2005) and Quiroz-Rocha et al. (2009) reported that BHB monitors NEB and retained placenta. Our data are consistent with those reported by Smith et al. (2009) and Litherland et al. (2010) finding no effect on serum concentrations of BHB by the application of an agonist for PPARγ and PPARα, respectively.

The concentrations of TG, cholesterol, albumin, TP, activity of enzymes AST and CK after the administration of MFPA were not significantly different among all the groups of cows. These results are similar to those in cows treated with agonists by other authors (Smith et al., 2007, 2009; Litherland et al., 2010).

In our study, milk production was not affected by treatment of MFPA ($P > 0.05$). Smith et al. (2007) monitored milk quality in the first 8 days postpartum and milk amount up to 30 days and found no significant differences by treatment. In a second study by Smith et al. (2009), milk production up to 63 days of lactation tends to be lower and the percentage of milk fat is reduced in cows treated with 4 mg/kg TZD in the prepartum.

In our study, a negative trend was found between serum FFA and milk production at day 60 of lactation. Meikle et al. (2004) described a negative correlation ($r = -0.24$) between serum FFA and milk production and also between serum concentrations of BHB and milk production. The negative relationship between NEB and milk production could be explained by the risk of disease at a higher concentration of FFA and BHB, and when the animal is sick, milk production is diminished.

The severity of NEB in early lactation is associated with impaired ovarian function and delayed return to oestrus (Jolly et al., 1995). The increase in serum concentrations of ketone bodies is negatively associated with the resumption of postpartum ovarian activity, causing greater number of days open, and, therefore, affects the reproductive cycle of the cow (Reist et al., 2000). In our study, we found serum concentrations of P4 greater than 1 ng/ml at day 21 in the four groups of cows. Higher ovarian activity occurred in group 3 cows and lower activity in cows of group 1. This indicates that cows with the severe subclinical ketosis can be affected on their ovarian activity. After application of a ligand for PPARγ to cows, Smith et al. (2009) found serum concentrations of progesterone >1 ng/ml at day 21 postpartum, with no significant differences ($P > 0.10$); this is similar to that found in our work.

CONCLUSION

The determination of key blood analytes such as FFA and BHB is useful to prevent postpartum problems, however, in this study, IM application of MFPA prepartum and in the early hours postpartum to fat cows (BCS > 4) and to cows with normal BCS (3.25–3.75) had no significant effect on serum lipid analytes. Furthermore, in this study both milk production and postpartum ovarian activity exhibited no apparent changes after the application of MFPA in transition period due to the short duration and rapid adaptation to NEB showed by the cows.

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Received: 2012–03–16
Accepted after corrections: 2012–06–27

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