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FENPROSTALENE IN CATTLE: EVALUATION OF OXYTOCIC EFFECTS IN OVARIECTOMIZED COWS AND ABORTION POTENTIAL IN A 100-DAY PREGNANT COW

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ABSTRACT

Four ovariectomized cows were used to compare the uterotonic (oxytocic) properties of the prostaglandins F2α analogue fenprostalene to cloprostenol and PGF2α-tromethamine salt (dinoprost). Uterine activity was measured by electromyography with the duration and magnitude of activity quantified by microcomputer. The administration of 1 mg of fenprostalene to estradiol primed animals significantly increased uterine motility for approximately 19 h. This was significantly longer than the duration observed for either cloprostenol (500 µg, i.m., 8.9 h) or dinoprost (25 mg, i.m., 7.7 h). However, the level of activity was similar for the 3 compounds tested, with postinjection levels of oxytocic effect averaging 369 % for treated animals compared to 100 % for controls. Therefore, the difference in effects for the three prostaglandins may be due more to pharmacokinetic properties rather than to different potencies of the three compounds.

In addition, a pregnant cow (100 d gestation) was treated with fenprostalene (1 mg, s.c.). Fenprostalene treatment resulted in unchanged uterine activity for a 6-h period, followed by a four-fold increase in genital tract activity which lasted for 12 h. Thereafter, activity was inhibited for one day, followed by a sharp increase in uterine activity leading to abortion within 66 to 72 h after fenprostalene injection. The placenta was expelled 7 days after treatment.

Keywords: fenprostalene, prostaglandin F2α, uterine motility, cattle.

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INTRODUCTION

Prostaglandins of the F2 alpha type (PGF2α) are routinely used for reproductive management in dairy and beef cattle as estrus-control agents (1-3) for termination of unwanted pregnancies (4) and for the treatment of various reproductive diseases such as luteal cysts, pyometra and endometritis (5).

In field trials, Herschler et al. (6) reported that fenprostalene, a long-acting analogue of PGF2α, gave a higher rate of successful abortions than natural PGF2α, especially when given to cattle pregnant between 100 and 150 d. In a previous work on sheep (7), it was found that fenprostalene exerted far longer oxytocic effects than either dinoprost or cloprostenol. It was therefore suggested that both the luteolytic and long-acting oxytocic properties of fenprostalene could be responsible for its high efficacy in inducing abortion after 100 d of gestation in the bovine species. Our hypothesis, based upon observations made by others in the guinea-pig (8) and measurements of the PGF metabolite 15-keto-13,14 dihydro-PGFα in cattle (22), was that, in addition ot its luteolytic effect, fenprostalene induced sustained increases in uterine motility after 100 d of pregnancy and damaged the physical connections between the chorion and caruncles of the endometrium, which resulted in abortion through the release of endogenous prostaglandins. Nevertheless, definite data concerning the oxytocic properties of fenprostalene in cattle are lacking in the literature.

Uterine motility studies in the bovine have been conducted using a variety of techniques including the use of intraluminal rubber balloons (9,10) or electrodes clipped into the uterine wall through the cervix (11). These method were unsuitable to accurately evaluate spontaneous and/or drug-induced motility changes over a prolonged period of time.

Conversely, electromyographic techniques using electrodes chronically implanted into the myometrial wall (12-15) seemed relevant for use, especially when studying long-acting drugs. On the other hand, the oxytocic effects of drugs have been shown to be dependent on the stage of the estrous cycle: myometrial responsiveness being maximal at estrus (12,13). Preliminary studies in ovariectomized cows deprived of estradiol priming and/or bearing progestagen impregnated vaginal sponges showed that neither fenprostalene nor dinoprost were able to stimulate uterine motility under those hormonal conditions. Conversely, clear oxytocic responses were observed when either prostaglandins were injected into the same cows after estradiol priming.

Therefore, the purpose of this study was to electromyographically evaluate the relative oxytocic effects of the recommended therapeutic doses of fenprostalene, cloprostenol and dinoprost in ovariectomized cows primed with exogenous 17β-estradiol. In addition, the oxytocic and/or abortive capabilities of a single injection of fenprostalene was ascertained in a cow pregnant for 100 d.

MATERIALS AND METHODS

Five healthy adult cows of the Francaise Frisonne Pie Noire breed, weighting 532 ± 40 kg, were used in our study. After 24 h fasting, the cows were tranquilized with xylazine hydrochloride,[a] injected intramuscularly (0.1 mg/kg) and given both epidural and local anesthesia with lidocaine hydrochloride.[b] Under aseptic surgical conditions, the cows were subjected to a flank laparotomy just anterior to the tensor fascia lata on either the right or the left side. Four of the cows, which were nonpregnant, were then bilaterally ovariectomized (OVX). The fifth, which was pregnant, was left intact. Electrodes similar to those described by Ruckebusch and Bayard (12) were positionned in groups of three at different sites on the greater curvature of at least one uterine horn. For the pregnant cow, two groups were implanted on the empty horn and four on the gravid horn.

After surgery, the cows were placed in individual stalls and fed a normal diet of hay and concentrates in two daily meals at 8:00 a.m. and 4:00 p.m. Water was available ad libitum.

Electrodes were connected to the recorder using an extension cable which allowed animal movements with minimum artifacts.

Uterine electromyograms (EMG) were obtained on a multichannel amplifier polygraph[c] that allowed direct recordings (time constant: 0.1 sec, paper speed: 3.6 cm/min) used discretionally as a control of the quality of EMG. In addition, EMG signals were continuously integrated as a monitoring procedure and displayed 24 h/d on a potentiometric recorder[d] (paper speed: 1mm/min). This integrated EMG was automatically quantified using an on-line microcomputer, and activity level was measured by 10-min epochs and expressed in arbitrary computer units (c.u.).

Design of study in OVX cows

The four ovariectomized cows were given at 2-3 day intervals a single i.m. injection of 17β-estradiol[e] (1 µg/kg), followed within 15 and 19 h later, by one of the prostaglandin treatments. Order of treatment was randomized and different across the four cows. The following analogues of PGF2α, referred to as test articles, were used: fenprostalene,[f] dinoprost tromethamol[g] and cloprostenol[h].

a Rompun, Bayer, Puteaux, France.
b Lucrocaine, Vetoquinol, Lure, France.
c Minihuit, Alvar, Montreuil, France.
d CR553, JJLLOYD Instruments, Southampton, United Kingdom.
e 17β-estradiol, Sigma Chem., St-Louis, Mo., in ethanol solution (1 mg/ml).
f Synchrocept B, Syntex Agribusiness, Louvain-la-Neuve, Belgium.
g Dinolytic, The Upjohn Co., Paris, France.
h Estrumate, ICI Pharma, Enghien, France.

Each prostaglandin treatment was administered at least three times to each of the four cows according to the recommended dose and route, i.e. fenprostalene (1 mg total dose) was injected s.c. (skin of the neck), dinoprost (25 mg total dose) and cloprostenol (500 µg total dose) were injected deep into the gluteus muscle. In addition, in two of the OVX cows, fenprostalene (1 mg total dose) was injected three times each by the i.m. route.

Evaluation of the oxytocic effects of the test articles was performed according to the following scoring method : a representative control period of four consecutive hours was selected by visual inspection of the charts from the 8 h preceding test-article injection. The mean ± SD control activity level (expressed in c.u.) was then calculated from these 24, 10-min periods and considered as 100 %.

A threshold value (referred to as a "key" value) corresponding to the control mean + 1 S.D., was then calculated. Significant oxytocic effects were determined, taking into account the post-injection periods during which activity levels were higher than, or equal to, this "key".

Statistical calculations were performed using one-way analysis of variance by ranks (Kruskal-Wallis) and Mann-Whitney test.

Design of study in pregnant cow

Only one cow, which was pregnant 67 d at the time of surgery, was used in this study. At 100 d of gestation, the cow was given fenprostalene as recommended (1 mg, s.c.). Uterine EMGs were continuously recorded and quantified. In addition, the luteolytic capability of fenprostalene was assessed by blood progesterone (16) and estrogens (17). Jugular vein blood samples were collected into chilled heparinized tubes at fenprostalene preinjection minutes 60, 45, 30 and 15 and at postinjection hours 1 to 12, 23, 24, 25, 28, 30, 48, 52, 56, 72, 80 and 120. Samples were rapidly centrifuged and stored at -20°C until assayed.

RESULTS

Study in ovariectomized cows

Controls motility patterns. Spontaneous motility was absent in the uterus of cows deprived of estradiol. In contrast, motility was promoted when animals were given estradiol. The dosage regimen used throughout these experiments (1 µg/kg, i.m.) allowed the onset of motility events after an average delay of 7 h, mainly in the form of discrete episodes of 6 to 8 min duration, occurring at approximately hourly intervals and called regular activity. Between two such episodes, activity was often present in the form of randomly-occurring spiking activity called irregular activity.

Effects of prostaglandins treatments: qualitative aspects. Fenprostalene, as well as dinoprost and cloprostenol, led to a dramatic increase in the frequency of occurrence of regular activity episodes and/or to the enhancement of irregular activity. Speeding up of regular activity was more likely the response to the s.c. injection of fenprostalene. In contrast, almost continuous activity was generally observed after i.m. injections of either fenprostalene, cloprostenol or dinoprost (Figure 1).

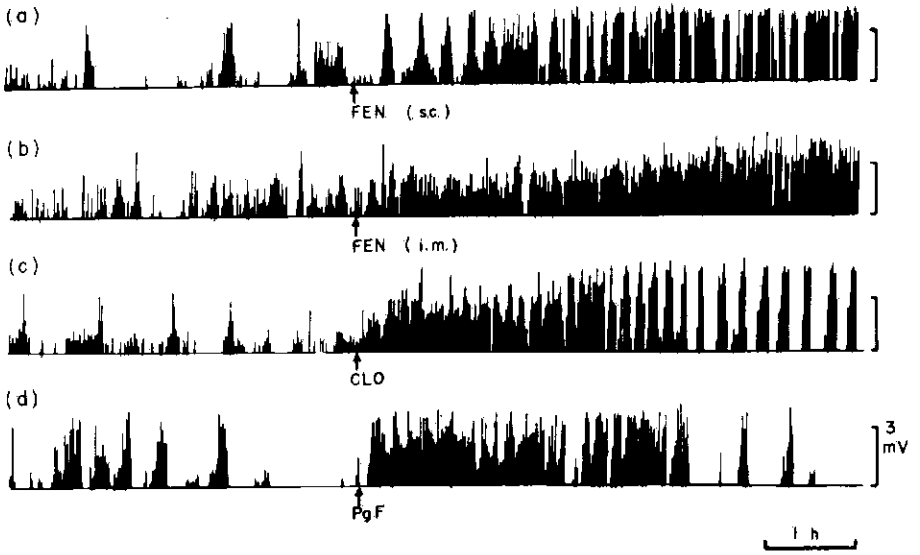

Figure 1. Enhancement of uterine motility after single injections of test articles: fenprostalene (fen: (a) s.c. and (b) i.m.), (c) cloprostenol (clo, i.m.) and (d) dinoprost (pgf, i.m.). A slightly delayed discrete response pattern was often observed after s.c. injection of fenprostalene ; an almost continuous activity pattern was the immediate response to i.m. injections.

Effects of prostaglandin treatments: quantitative aspects.

1) Oxytocic effects were expressed in terms of duration and magnitude of drug action. A standardized scoring method was employed using the activity values given by the microcomputer at each 10-min period. For each injection of test article included in the full study, eight variables (V1 to V8) were calculated to characterize the parameters of the oxytocic response: a) five time-parameters: V1 = delay of onset of the oxytocic

response ; V2 = total duration of oxytocic response, calculated from the sum of the following 3 phases ; V3 = early discrete response (neglected in final results) ; V4 = duration of continuous response ; V5 = duration of late discrete response: b) three magnitude-parameters: V6 = magnitude of continuous response ; V7 = magnitude of discrete resonse ; V8 = total oxytocic effect ; V8 = (V4 x V6) + (V5 x V7).

The meaning of each variable is presented with a graphic example (Figure 2). The relative oxytocic effects of fenprostalene (s.c. and i.m.), cloprostenol and dinoprost are also shown (Tables 1 and 2).

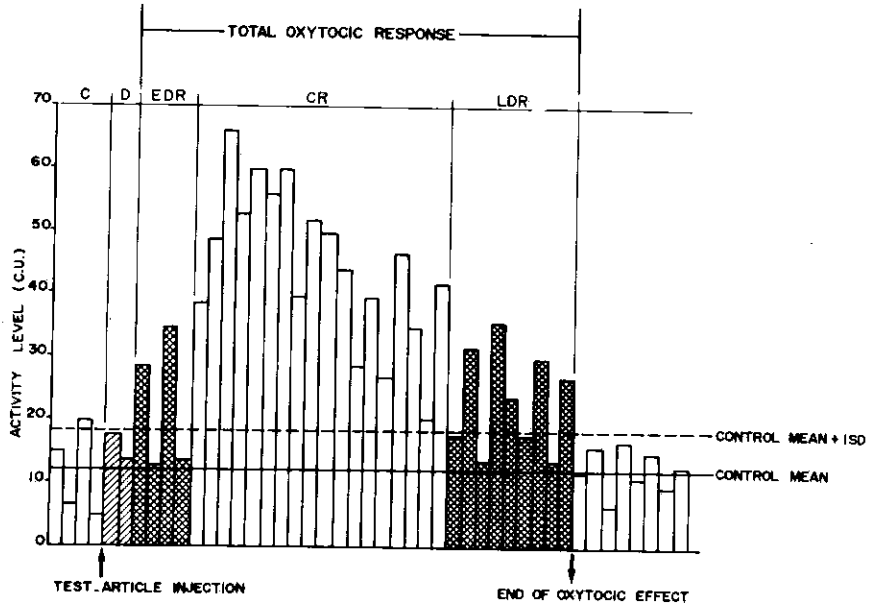

Figure 2. Graphic example of the scoring procedure. Oxytocic response parameters were characterized using the activity values given periodically by the microcomputer (c.u.: computer units). Values higher than control mean + 1 S.D. ("key" value) were considered as significant oxytocic responses. Duration and magnitude of the different phases of the oxytocic response were calculated: C = control, D = delay, EDR = early discrete response, CR = continuous response, LDR = late discrete response.

Table 1. Characteristics of oxytocic effect parameters (mean ± SD values) for the four treatments. Parameters of time are in hours; parameters of magnitude are in % (control level = 100 % ; see text and Figure 2 for definitions and Table 3 for statistics).

	Oxytocic Response					
	Delay of onset (h)	Early discrete (h)	Continuous (h)	Continuous (%)	Late discrete (h)	Late discrete (%)
	V1	V3	V4	V6	V5	V7
Fenprostalene (s.c., n = 15)	0.22 ± 0.18	0.49 ± 0.73	11.97 ± 2.83	364.0 ± 128.82	6.99 ± 4.68	184.20 ± 46.90
Fenprostalene (i.m., n = 6)	0.19 ± 0.20	0	10.30 ± 4.98	374.33 ± 121.77	4.53 ± 1.98	192.83 ± 39.74
Cloprostenol (n = 12)	0.06 ± 0.08	0	6.96 ± 1.92	386.50 ± 145.29	1.97 ± 1.19	191.58 ± 94.88
Dinoprost (n = 14)	0.04 ± 0.07	0	5.12 ± 1.72	349.71 ± 99.16	2.60 ± 2.20	158.07 ± 41.03

Table 2. Relative oxytocic effects of recommended therapeutic doses of fenprostalene (s.c. and i.m.), cloprostenol and dinoprost (mean ± SD) in OV cows under estradiol priming. Effects of the latter test article have been taken as reference to calculate the ratios (see text and Figure 2 for definitions and Table 3 for statistics).

	Total oxytocic response		
	Duration (h)	Duration x Magnitude[a]	Ratio
	V2	V8	
Fenprostalene (s.c., n = 15)	18.91 ± 5.73	5767.84 ± 2516.27	2.624
Fenprostalene (i.m., n = 6)	14.84 ± 4.73	5092.30 ± 2889.70	2.316
Cloprostenol (n = 12)	8.91 ± 1.89	3198.50 ± 1754.88	1.455
Dinoprost (n = 14)	7.72 ± 3.13	2198.50 ± 831.43	1.000

[a] arbitrary unit.

2) Comparisons among treatments were performed using appropriate statistical tests.

The delay of action (V1) was not different for fenprostalene s.c. and fenprostalene i.m. ($P = 0.05$), whereas the effects of dinoprost and cloprostenol were significantly more rapid ($P < 0.01$).

The total duration of oxytocic effects (V2) of fenprostalene after s.c. administration was significantly longer than the duration of effects of either cloprostenol or dinoprost ($P < 0.01$). In contrast, the duration of oxytocic effect after i.m. injection of fenprostalene was shorter than after s.c. injection but not significantly ($P > 0.05$).

Total oxytocic activity (V8) was significantly different among the four treatments (Kruskal-Wallis test; $P < 0.001$). Fenprostalene s.c. led to the highest value and dinoprost to the lowest. If dinoprost, which is closer to the natural hormone, was taken as a unit, a therapeutic dose of fenprostalene (s.c.) was 2.6 times more oxytocic, while cloprostenol was only 1.5 times more oxytocic than dinoprost (Table 2).

For the other variables, similar comparisons were performed among treatments. No significant differences existed for fenprostalene according to the route of administration. In contrast, effects of fenprostalene (s.c.) differed from the effects of both other prostaglandins, except for magnitude of effects (Table 3).

Table 3. Significance level of the statistical test (Mann-Whitney) used to compare the effects of fenprostalene (s.c.) with the other test articles, i.e. fenprostalene (i.m.), cloprostenol and dinoprost. Definition of variables V1 to V8 is available in text.

Parameters		Fenprostalene (i.m.)	Cloprostenol	Dinoprost
Time	V1	ns	$P < 0.01$	$P < 0.01$
	V2	ns	$P < 0.01$	$P < 0.001$
	V3	-	-	-
	V4	ns	$P < 0.001$	$P < 0.001$
	V5	ns	$P < 0.001$	$P < 0.01$
Magnitude	V6	ns	ns	ns
	V7	ns	ns	ns
Total	V8	ns	$P < 0.01$	$P < 0.001$

ns = not significant ($P > 0.05$).

Study in the pregnant cow

Uterine contractility before fenprostalene injection. Electromyographic records started at Day 84 of gestation, 16 d after electrodes implantation. From that time until Day 90, an almost flat record was obtained, suggesting absence of contractions in the bovine pregnant uterus. Nevertheless, between Days 91 and 94, a few strong nonsimultaneous, random, episodes of activity were recorded on the pregnant horn, at some electrode

sites (two to six episodes/24 h). Between Days 95 and 100, the frequency of occurrence of such episodes progressively increased, with an average of 9/24 h and their periodicity was more regular throughout the nycthemere (2.35 ± 1.08 h). These episodes resembled those recorded in the estrogen primed OVX cows and were therefore called regular activity episodes. Between two such episodes random activity occurred and was labeled irregular activity (Figure 3).

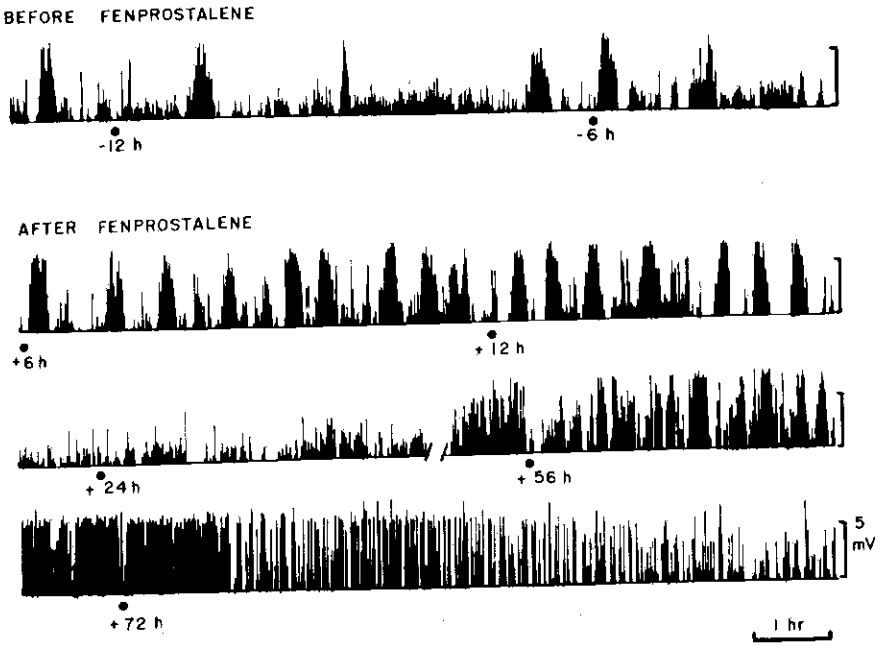

Figure 3. Activity pattern recorded on the pregnant uterine horn of a 100-d pregnant cow, before and after fenprostalene injection (time 0 not shown). The frequency of occurrence of regular activity episodes was markedly increased from the 6th to the 18th hour postinjection as compared to preinjection controls. Abortion occurred around 72 hrs after fenprostalene during a phase of intense activity, immediately followed by a sharp drop in motility.

Activity patterns after fenprostalene administration. Primary oxytocic effect: fenprostalene given at Day 100 of gestation markedly enhanced the number of activity episodes (Figure 3). Oxytocic effects started after a delay of 6 h and lasted for 11.50 h, during which 19 episodes were recorded at the most electromyographically active electrode site, a 4.2-time increase when compared with 9 episodes/24 h recorded the day before fenprostalene.

Secondary inhibition phase : a prolonged phase of relatively lower activity followed this early oxytocic effect. Throughout this phase, which lasted about one day (25.17 h), episodes of activity were not recorded. Only a low level irregular activity was still present and tended to increase progressively during the second half of this period.

Activity at the time of abortion : activity levels were raised dramatically during the following 30 h, and both regular and irregular activities were present. Computer values obtained between 66 and 72 h postinjection showed a 5-fold increase compared with preinjection controls (143 ± 25 vs 29 ± 12 c.u./h). At this time some uterine contents were expelled and subsequently activity levels dropped dramatically but only for 8 to 12 h. Indeed, a new dramatic increase (up to 6 times preinjection values) occurred within 12 to 18 h after abortion. This high-level activity persisted for 3 days. On the fourth day, 7 d after fenprostalene, the placenta was expelled and then activity rapidly disappeared. The uterus remained quiescent until the first estrus, 14 d after abortion.

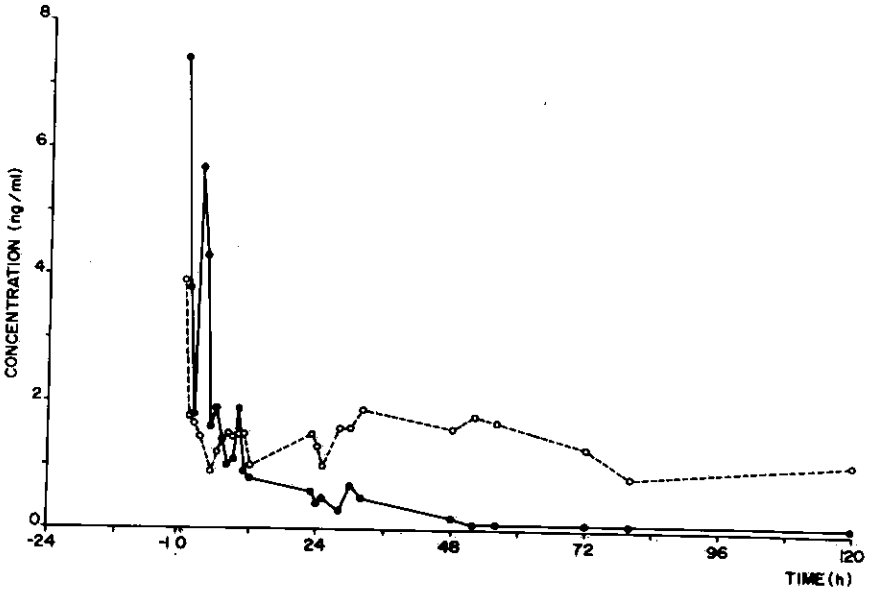

Figure 4. Plasma levels of progesterone (●——●) and total estrogens (o----o) after a single injection of fenprostalene (1 mg, s.c.) to a 100-d pregnant cow. A sharp drop in progesterone levels was achieved within 5 h postinjection.

Luteolytic effects of fenprostalene. Plasma levels of progesterone and total estrogens before and after fenprostalene are shown (Figure 4). A sharp drop in progesterone levels was observed within 5 h after fenprostalene, indicating the rapid onset of luteolysis. In contrast, evident changes in total estrogens were not observed.

DISCUSSION

At the recommended therapeutic doses, the three prostaglandins developed clear-cut uterotonic (oxytocic) effects in ovariectomized cattle under estradiol priming. The longest oxytocic action was obtained with fenprostalene given s.c., whereas activity levels attained within the duration of oxytocic effects were similar for the three prostaglandins. Consequently, it is likely that the difference in the overall oxytocic effects were related more to pharmacokinetic properties rather than to different potencies of the three compounds.

In this respect, available pharmacokinetic data indicate an elimination half-life of 3 h for cloprostenol after i.m. injection of 500 µg to cattle (18). Similarly, a plasma half-life of 2.5 h was calculated for PGF2α-Tham after i.m. injection of 25 mg to cattle (19). Both doses were identical to those used in this study. The half-life value calculated for fenprostalene in polyethylene glycol 400 vehicle after s.c. administration of 1 mg to cattle was about 24 h (6). Such kinetic values tentatively explained the longer-acting effect of fenprostalene.

The oxytocic effects of therapeutic doses of the three prostaglandins were more than twice as long in cattle than reported in ovariectomized estrogen treated ewes (18.95 vs 8.52 h; 7). Nevertheless, their relative ranking was respected, i.e. fenprostalene > cloprostenol > dinoprost.

When given to a cow pregnant for 100 d, fenprostalene possessed both oxytocic and abortive capabilities. According to available data from pregnant ewes (20,21) which showed that the pregnant uterus is quiescent during about the first third of gestation, it can be supposed that the appearence of activity episodes within Days 90 to 100 corresponded to the actual time of physiologic onset of motility in the bovine pregnant uterine horn. Indeed, this stage of gestation corresponded to onset of massive local releases of estrogens by the uteroplacental unit and the strengthening of the connections between the chorion and the caruncles of the endometrium (23,24). Presence of local amounts of estrogens in the myometrium allowed uterine responsiveness to oxytocic drugs such as prostaglandins of the F2α type.

The direct uterine contractile effect of fenprostalene lasted for approximately 12 h in our study on one pregnant cow. This oxytocic effect appeared to start after a latency of 6 h. In fact, this lag-time corresponded to the decay of plasma progesterone levels from the normal values recorded during pregnancy (about 8 ng/ml) to values lower than 2 ng/ml. It can be supposed that high circulating progesterone levels prevented the onset of fenprostalene-induced oxytocic effects, which corresponds to the results of our preliminary experiments. The fact that fenprostalene was a long-acting oxytocic PGF2α analogue (about 19 h), according to the results of our study in estrogen-primed OVX cows, allowed the re-emergence of an oxytocic stimulus once progesterone decline was achieved and the enhancement of uterine activity from the 6th to the 18th postinjection. It is probable that a prostaglandin analogue with a shorter duration of action would be less effective in inducing myometrial contractions, at least when administered as a single injection, and would probably necessitate repeated injections to produce an oxytocic effect similar to that observed in our study after a single injection of fenprostalene.

In this respect, it can be emphasized that shorter acting prostaglandins analogues like cloprostenol have been shown to be highly effective in inducing luteolysis and subsequently abortion when given before pregnancy Days 150 to 160 (22). Our hypothesis, which needs further investigation, was that long-lasting stimulation of myometrial contractions, like those induced by fenprostalene, could be decisive in efficiently promoting abortion and uterine emptying during later stages of pregnancy.

Indeed, according to Lindell et al. (22), who measured 15-keto-13,14 dihydro PGF2α in pregnant cattle that were given cloprostenol, it can be suggested that the long-lasting oxytocic effects of fenprostalene may have caused enough damage to the uteroplacental connections to provoke the release of massive amounts of endogenous prostaglandins: the higher the contractions, the higher the release of oxytocic prostaglandins and vice-versa. Finally, in our study, abortion occurred within 66 to 72 h during a phase of intense activity, probably under the oxytocic influence of great amounts of endogenous prostaglandins.

In conclusion, due to its long-acting oxytocic properties, fenprostalene appeared to be suitable for increasing uterine motility in cattle under different endocrine conditions such as pregnancy beyond the 100 to 150th d of gestation (presence of both estrogens and progesterone) or estrus (estrogen domination). Therefore, fenprostalene would probably be of interest in bovine veterinary practice when evacuation of uterine contents is required.

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