Oxytocin Update for Practicing Veterinarians

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Oxytocin is a small octapeptide hormone released from the posterior pituitary via a neuroendocrine reflex initiated by mechanical stimulation of the teats. Oxytocin release causes marked contraction of smooth muscle, in particular the uterus and the myoepithelial cells surrounding the milk secreting alveolus of the mammary gland. Functionally, oxytocin has a role in parturition and milk ejection. Oxytocin will cause similar physiologic responses across many species.

Petersen and Ely at the University of Minnesota in 1941 were the first to demonstrate oxytocin's specific role in milk ejection. Numerous studies were conducted throughout the 1940's and early 1950's on the physiologic effects of oxytocin. Most studies did demonstrate an increase in milk production when oxytocin was administered for consecutive milkings over a short period of time (5–10 days).[10,13,14]

Donker et al.[3] demonstrated large increases in milk and butterfat production in a three lactation study of one set of identical twins. Comparisons in milk and fat production was made by injecting one cow with oxytocin (3 IU) at each milking for an entire lactation while the other cow served as control.

Injection of exogenous oxytocin may not always result in increased milk production. The injection of relatively large doses of oxytocin inhibited milk production in laboratory rats.[11] Hansel and Wagner found that injecting high doses of oxytocin (100–400 IU) in dairy cattle also reduced milk yield during oxytocin treatment period.[7] However, this data was not sufficiently strong to be very conclusive.

Recently, Galton and Norstrand reported 10–12% increases in lactational milk production when cows were injected with 20 IU's of oxytocin just prior to each milking for an entire lactation.[5] Response to the oxytocin injection was not apparent until after 60 days in milk. The mechanism of this increased production was not explained by the Cornell research. However, there are two theories speculating the reason that continuous use of exogenous oxytocin increases milk production. The most substantiated theory is that injection of oxytocin at each milking causes greater evacuation of milk at milking time thus reducing the amount of residual milk. This would be similar to the mechanism given for increased milk yield due to 3X milking. Removal of milk both from the udder and each individual alveolar cell results in maintaining higher rates of secretory activity in alveolar cells for longer periods of time. The other theory involves a speculated indirect interaction of oxytocin on other hormones such as prolactin, somatotropin, etc., resulting in higher secretory activity of the alveolus. This proposed mechanism has no proven scientific support at this time.

Publicity of the recent Cornell findings has created considerable interest on the part of both veterinarians and farmers. Some have felt compelled to use oxytocin as a production aid. Yet, there are many unanswered questions about long term continuous use of oxytocin.

Donker et al. found that cows continuously treated with 20 IU of oxytocin at each milking became dependent on exogenous oxytocin to achieve milk letdown.[4] This dependence was transitory with normal milk letdown returning a few days after the oxytocin injections were stopped. Hansel and Wagner made a similar observation in cows being injected with large doses (100–400 IU) of oxytocin.[7]

During the late 1950's and early 1960's, researchers became interested in the potential of oxytocin use in regulation of the estrous cycle. Armstrong and Hansel found that injection of 100 IU's oxytocin subcutaneously in dairy heifers early in the estrous cycle inhibited corpus luteum development and shortened the estrous cycle to an average of 11 days.[1] Other studies with oxytocin doses ranging from 50–200 IU administered either IV or SubQ in both lactating cows and heifers showed similar results with estrous cycle lengths as short as 8–12 days.[2,7,8,15] However, the use of oxytocin or oxytocin in combination with progesterone did not prove to be a practical method of estrous synchronization in cattle. It is interesting to note that the leuteolytic effect of oxytocin required the presence of the uterus. Hysterectomized heifers did not

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respond to the oxytocin treatment. One could speculate that this may implicate an oxytocin-prostaglandin link.

The oxytocin dose levels in these experiments was clearly in excess of that necessary to provoke maximum milk letdown response. Gorewitt and Sage, for example, demonstrated maximum milk letdown response was achieved at 2–3 IU oxytocin IV.[6] Studies of the long termed effects at "moderate" oxytocin dosage levels (20–40 IU) on reproductive performance have not been conducted.

The Bottom Line: It's Illegal

The bottom line on this issue is that oxytocin is not labeled for continuous use as a production aid. To use it in this manner is illegal. The FDA approved labeled indicates very clearly that oxytocin is a therapeutic prescription drug (Figure 1.)

In order for oxytocin to be approved for injection at each milking as a production enhancing drug will require extensive research similar to any other drug intended to be used in this manner.

At present, there is no human safety data on oxytocin used as a production aid. Since oxytocin will illicit similar physiologic responses across many specifies, including man, this becomes a very important question. When cows are treated at each milking, how much oxytocin can be found in the milk? If oxytocin is in milk, how stable is it? Is oxytocin in milk broken down quickly by the enzyme oxytocinase as it is in the cow's own bloodstream? Are there any side effects on the cow relative to health and productivity?

These are just a few of the kind of questions that must be answered before approved usage of oxytocin as a production aid is given.

Will Oxytocin be Approved as a Production Aid

There are presently 10 companies that have an FDA approved oxytocin label. Only five are currently marketing a product. What is the likelihood that any one of these companies will attempt to do the necessary research to get FDA approval? In the author's opinion, there appears to be little economic incentive for any single company to make such an investment. Therefore, it is doubtful that there will ever be any attempt to seek FDA approval for oxytocin used as a production aid.

Conclusion

From the limited amount of research conducted to date, it appears that injection of moderate doses of oxy tocin at each milking will increase milk production. However, there are many unanswered questions about the use of oxytocin in this manner. Perhaps the most important issue is the question of human safety of dairy products potentially containing oxytocin. Until more information on oxytocin is generated and FDA approval for oxytocin use as a production aid is given, it should only be prescribed and used according to its therapeutic intent.

FIGURE 1.

NADA 046-822

Product name	Vetocin Injection
Sponsor	Forbes Labs
Active ingredients	Oxytocin
Classification	Oxytocics
Formulation	20 USP units of oxytocin/ml
Product type	Therapeutic drug R_X Route injectable IM, IV, SQ
Approved species	Dairy cattle, beef cattle, horses, cats, dogs, sheep, and swine
Withdrawal time	Cattle, swine, sheep, and horses: None Milk discard: None
Indications	Use as a uterine contractor to precipitate and accelerate normal parturition and postpartum evacuation of uterine debris. In surgery, it may be used postoperatively following cesarean section to facilitate involution and resistance to the large inflow of blood. It will contract smooth muscle cells of the mammary gland for milk letdown if the udder is in the proper physiological state.
Directions	When using for obstetrical purposes, administer the following doses: *Ewes: 1.5 ml to 2.5 ml *Sows: 1.5 ml to 2.5 ml *Cows: 5.0 ml When using for milk letdown, administer the following doses by IU injection: *Sows: 0.25 ml to 1.0 ml *Cows: 0.5 ml to 1.0 ml
Further information	Do not use in cases of dystocia due to abnormal presentation of the fetus until correction is accomplished. For prepartum usage, full relaxation of the cervix should be accomplished either naturally or by administration of estrogen prior to oxytocin therapy. Treatment may be repeated as conditions require.

References 21 CFR 522, 1680; Fed. Reg. 06/10/74 (20370)

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Abstracts

Comparison of the efficacy of dermal formulations of ivermectin and levamisole for the treatment and prevention of *Dictyocaulus viviparus* infection in cattle

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Four groups of six parasite-naive calves were infected at seven day intervals with three doses of infective larvae of *Dictyocaulus viviparus.* Twenty-one days after the first dose three of the groups were treated either with an injectable formulation of ivermectin at a dose rate of 200 ug/kg bodyweight, or with pour-on preparations of levamisole at 10 mg/kg of ivermectin at 500 ug/kg. On day 28 two calves from each group were slaughtered and their burdens of lungworms counted. On day 35 the remaining calves were reinfected with *D viviparus* infective larvae at a rate of 80 L3/kg. The levamisole preparation was 94-6 per cent effective and both ivermectin preparations were 100 per cent effective against the initial infections. The ivermectin-treated calves were protected from the reinfection which subsequently became patent in the levamisole-treated and control calves.

Estimation of the developmental age of the bovine fetus and newborn calf

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Jersey cows from several herds provided 97 fetuses and 34 calves at fixed gestional intervals between 80 and 290 days after conception. The fetuses and calves were killed, weighed and measured and after dissection, the sizes and weights of a range of skeletal and soft tissues were recorded. Six morphological measurements emerged as most suitable for the determination of developmental age in the normal fetus. By plotting their mean values and 95 percent tolerance limits, the rates of growth and the variability of each measurement were defined. Long bone length was the most useful single measurement for predicting the developmntal age of the fetus. Brain weight, bodyweight, crown-anus length and long bone length showed curvilinear growth patterns; age prediction equations derived from these measurements are complicated to use and additional simplified formulae have been derived. The number of appendicular ossification centres also had predictive value, but it could not be used to determine fetal developmental age between 100 and 160 days gestation.