REVERSIBLE SUPPRESSION OF LACTATION BY COLCHICINE

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1. Introduction

The plant alkaloid, colchicine [1], is known to suppress secretion of very low density lipoproteins by the liver [2,3] and of insulin by beta cells of the pancreas [4]. In the present study the effects of the compound on lactation in the goat was examined. Intramammary infusions of colchicine (1–5 mg) were observed to inhibit both the synthesis and secretion of milk. There did not appear to be selective inhibition of either the synthesis or secretion of any particular milk component. Rather this drug exhibited the capacity to 'turn off' lactating cells. Vinicristine, another plant alkaloid, behaved similarly. The effect is reversible provided milking is continued and treatment with these drugs is not intense and prolonged.

2. Materials and methods

The goat affords a valuable in vivo system for assaying the effects of drugs and metabolic regulators on the mammary epithelial cell. By infusing the substance to be evaluated into one half of the udder via the teat canal it is possible to study effects of the agent in terms of the product (milk) synthesized and secreted by the cells on that side of the udder. Since there is no direct circulatory connection between halves of the udder, agents infused into one side must ordinarily enter the general circulation to reach the other side. Thus changes seen in milk from the infused side are usually delayed and diminished, if detectable at all, in milk of the non-infused side.

Goats yielding approximately 2–4 litre of milk per day were infused in one side of their udders with colchicine (Sigma Chemical Co., St. Louis, Missouri, U.S.A.). Five-ml quantities of aqueous solutions containing varied amounts of the compound were delivered by inserting a canula (1.5 mm ID) connected to a 5 ml syringe through the opening into the teat canal. Following injection the solution was massaged (upward) into the secretory tissue. Milkings obtained every 12 hr from the two sides of the udder were measured for volume. In an effort to reveal the disposition of infused colchicine in the milk subsequently recovered, a ^{14}C-labeled preparation of the compound (Ring C methoxy [^{14}C] New England Nuclear, Boston, Massachussets, U.S.A.) was added to the solution to be infused. Analysis of the preparation by thin-layer chromatography indicated that greater than 90% of the activity applied to the plate moved with the mass of an authentic reference colchicine. Radioactivities of milk samples were determined by liquid scintillation spectrometry (Packard Tricarb Model 3330) of 1 ml samples in 15 ml of Aquasol (New England Nuclear, Boston, Massachussets, U.S.A.). Two 4-mg infusions of colchicine were prepared to contain 500 000 cpm of the ^{14}C isotope. Each of two goats was treated with the infusion and radioactivities in the milks collected at 12-hr intervals from both sides of the udder were assayed.

Vincristine, like colchicine, is known to cause disassembly of microtubules within cells [4,5]. To determine whether this alkaloid is also capable of suppressing lactation, it (vincristine sulfate, Eli Lilly and Co., Indianapolis, Indiana, U.S.A.) was tested in limited trials by the methods employed for colchicine.

3. Results and discussion

The effects of infusing colchicine into the udder of a goat on the yields of milk is shown in fig. 1. With an initial infusion of 1 mg of colchicine into the left side of the udder the amount of milk from that side was depressed to 67% of the normal at 36 hr post injection after which the milk flow returned to normal in 36 to 48 hr. Following several days (days 4–7, fig. 1) of normal milk yields from both sides of the udder the previously untreated side was infused with 5 mg of colchicine. This depressed milk yield in that side to 33% of normal in 36 hr after which the flow returned to normal in approximately 48 hr. Similar effects were obtained with a second goat using 3 mg of colchicine and a third goat infused with 2 and 4 mg respectively into the two sides of the udder. A plot of the data for the three animals relating the amount of colchicine infused to the yield of milk is presented in fig. 2.

Milk flow in one side of an udder was completely inhibited for a 12-hr period in an animal that had been infused with 2 mg of the drug and then, 5 days later after full recovery of milk flow, was treated with 4 mg more in the same side. This suggests a 'memory' of earlier treatment that amplifies the effects of a subsequent dose.

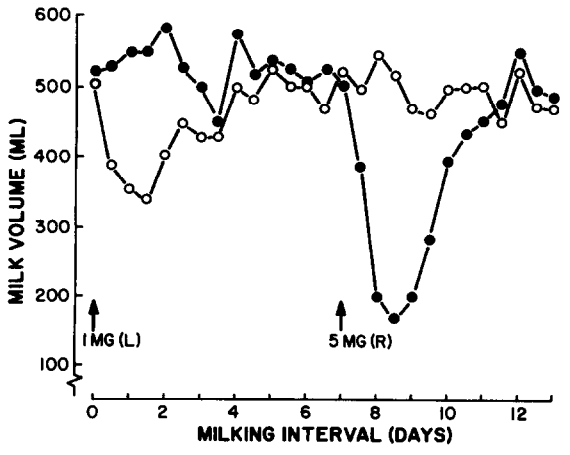

Fig. 1. The effects of intramammary infusions of colchicine on the volume of milk obtained at 12 hr intervals from the left (o–o–o) and right (•–•–•) halves of a goat's udder. The first infusion was 1 mg of the alkaloid in 5 ml of water into the left half of the udder following the complete milking on day zero. The second infusion was 5 mg in 5 ml of water into the right half following the complete milking on day seven.

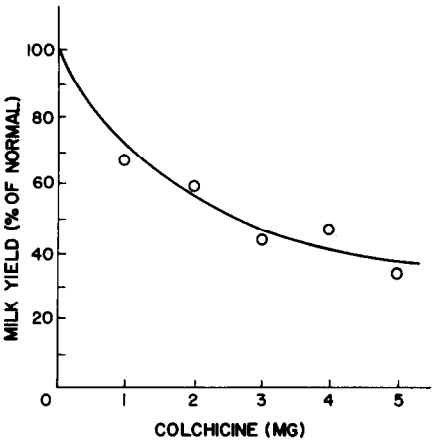

Fig. 2. The relationship between the amount of colchicine infused into one half of a goat's udder on the milk yield. Data are maximum depressions in yields from 12-hr milkings.

In the experiments involving [^{14}C]colchicine, radioactivity in the first 12-hr milkings from the infused sides was 1 to 2% of that infused. Activity in two subsequent milkings from the infused sides and the three milkings from the uninfused sides were essentially nil. These findings indicate that colchicine infused into the udder tends to be retained in the animal rather than to be shed in the milk.

Milk obtained at times when lactation was substantially depressed by colchicine appeared to be normal regarding odor, flavor, appearance, fat and protein content, gel-electrophoretic pattern of proteins and fatty acid composition of fat. This suggests that cells which continued to function were producing typical milk. There are two principal secretory mechanisms of the lactating cell, one in which fat globules are enveloped in plasma membrane and expelled from the cell and the other involving the emptying of Golgi vesicles containing the skim milk constituents (casein micelles, whey proteins, lactose, salts, water, etc.) through the plasma membrane of the cell [6]. The selective suppression of either mechanism, or of the biosynthetic pathways generating secretory products, should produce a significant distortion in the milk composition. Such variation was not observed. Colchicine could have blocked milk synthesis and/

or milk secretion. At the points of maximum suppression of milk yield a comparative slackness in the infused side of the udder was evident consistently. It is reasoned that blockage of synthesis would cause such a slackness, but that blockage of only secretion might cause a back up of fluid in cells and tissue resulting in distention of the udder.

Trials in which vincristine was tested revealed the compound to suppress lactation in a manner very similar to colchicine but at about one-tenth the dose for the latter. For example infusing 0.1 mg of vincristine depressed milk yield to 69% of normal and 0.2 mg depressed to 53% of normal. These depressions were maximal at 48 hr and fully reversed by 96 hr.

In other studies, cellular effects of colchicine and vincristine have been attributed to interactions with microtubules [4,5] or with plasma membrane [7,8]. Their mode of action in suppressing lactation will require further research. In addition to the lactating cell, functioning of the capillary endothelium, through which milk precursors are supplied, may need to be considered. The value of the two drugs in mastitis therapy will also bear investigation. A reversible means of resting mammary tissue from lactation while it combats mastitic infection should have merit.

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