Technique for In-vitro Evaluation of Release of Antibiotics into Milk from Carrier Vehicle

I. A. SCHIPPER,2 R. N. REOPELLE3 and L. J. SCHERMEISTER3

Department of Veterinary Medicine and College of Pharmacy, North Dakota State University, Fargo, North Dakota 58105

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ABSTRACT

An apparatus to determine the rate of release of chemotherapeutics from vehicles was developed. It consists of a semi-permeable chamber within a larger glass chamber. The semi-permeable chamber has direct contact with milk within the glass chamber. Preliminary evaluation for rapidity of release of chemotherapeutics by vehicles, in decreasing amount of antibiotic released, showed them to be water, sesame oil, sweet cream butter, peanut oil with aluminum monostearate, lanolin and petrolatum.

The efficaciousness of bovine intramammary mastitis therapy depends on the rapidity and completeness of release of the chemotherapeutic agent from the vehicle (2,6,9,15,19,29). Factors such as chemotherapeutic dosage and frequency of administration, route of administration, stage of lactation, degree of inflammation, frequency of milking or nursing and type of vehicle or carrier used may all contribute to the degree of dispersion and longevity of chemotherapeutic materials in the mammary secretions (3,5,7,8,10,11,13-18,21-30, 32,33,35,37-39). Intramammary administration of chemotherapeutic materials is one of the primary sources of chemotherapeutic residues in milk. The degree of alveolar tissue penetration is also dependent upon the vehicular binding of chemotherapeutic agent (7,8,15,34, 35). Methods of evaluation of chemotherapeutic release from vehicles have been reported (9). Use of animal sacrifice and mammary gland analysis have been demonstrated. Though very applicable, this method is also costly (31,36).

This investigation was initiated primarily to attempt to establish a practical applicable technique for preliminary determination of release of chemotherapeutics from vehicles used in intramammary medicants and to use several basic vehicular materials as test compounds.

MATERIALS AND METHODS

Testing apparatus

An in-vitro method of using a semi-permeable (6000-8000 MWCO cellulose) membrane within a glass tube was employed for determining chemotherapeutic agent release (Fig. 1). Vehicles to be tested were placed in the dialysing chamber which had previously been placed within a sealed glass tube. The dialysing chamber was then filled with 50 ml of sterile whole milk and sealed on both ends with glass plugs.

Release of oxytetracycline from all the vehicles studies was determined by an in-vitro method and is represented by Fig. 1. The method employed a cellulose membrane that simulated the cell membranes through which the medication after release from the vehicle must diffuse to penetrate intra- and interalveolar areas of mammary glands.
The aqueous vehicle released oxytetracycline in increasing amounts, reaching a maximum at 4 h (Fig. 2). Thereafter, 37 to 43 μg/ml were present in the milk. This amount of oxytetracycline was four times the concentration generally lethal for mastitic organisms (19). The amount of free diffusable antibiotic did not increase after a 4-h period.

In addition to the three standard carriers, butter and white petrolatum were tested as possible vehicles. Butter was chosen because it is a naturally occurring fraction of milk and white petrolatum because it is anhydrous. Commercial butter rapidly released the antibiotic within a 1-h period and thereafter the release rate was comparable to that of the sesame oil vehicle. Under the conditions of the experiment, white petrolatum did not release the antibiotic.

**DISCUSSION**

Based on this investigation, it would appear that the apparatus described provides an inexpensive means of making preliminary evaluations of the rapidity of chemotherapeutic agent release from vehicles.

Evaluation of the common vehicles demonstrated that if rapidity of chemotherapeutic agent release is desired, that the aqueous vehicle would be the one of choice. Previous investigations have demonstrated that the aqueous vehicle provides a more rapid and complete distribution of chemotherapeutic agents under in-vivo evaluation (37). Butter offered the advantage of a comparatively rapid release. It also is a natural lacteal secretion and less likely to be toxic to the mammary tissue. Both lanolin and peanut oil with aluminum monostearate provided nearly comparable rates of release. The investigation indicates that petrolatum would not be an acceptable vehicle for intramammary mastitis chemotherapy agents, based on antibiotic release.

![Figure 2. The rate of release of tetracycline hydrochloride from various vehicles over a seven-hour period as determined by the glass tube - semipermeable membrane apparatus.](image)

REFERENCES


