TOXICITY OF PHENOTHIAZINE DERIVATIVES EXCRETED IN THE MILK OF DAIRY COWS TREATED WITH MASSIVE DOSES OF THE DRUG*

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The effectiveness of phenothiazine as an anthelmintic has resulted in its widespread and, in some cases, indiscriminate administration to animals. In recent years the recognition of the toxic reactions of this drug has led to increased caution in its dosage. Stewart (8), in a review of the subject, indicated that man and the bovine are the most susceptible species to phenothiazine poisoning, and that the young are less resistant than the adults. Hence, it would appear that the infant might be highly sensitive to this drug.

Portions of phenothiazine derivatives are excreted in the milk of lactating ewes (9) and goats (6) following medication. Though milk contaminated with these derivatives usually is diverted from food channels, occasionally it is offered inadvertently for human consumption (1), thus constituting a potential health hazard.

Adult cattle ordinarily are not heavily infested with internal parasites, but the unthrifty condition of a cow in areas where parasitic infestation is common may lead to phenothiazine therapy. The possibility that milk from a cow treated with this drug might be fed to infants presented a problem warranting investigation. In this study single massive doses of phenothiazine were given to individual lactating cows for the purpose of ascertaining: the clinical effects on the cows, the period of elimination of the phenothiazine derivatives in the milk, and the toxic effects of the contaminated milk on young rats.

EXPERIMENTAL

Effects of massive doses of phenothiazine on lactating dairy cows. A representative of each of three breeds, Guernsey, Holstein, and Jersey, were used in this investigation. Pertinent data on the experimental subjects are presented in table 1.

The cows were in an excellent state of health. They were subjected to standard managerial and feeding practices; the rations, consisting of a

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TABLE 1

<table>
<thead>
<tr>
<th>Breed</th>
<th>Age</th>
<th>Body weight</th>
<th>Stage of gestation</th>
<th>Stage of lactation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guernsey</td>
<td>7</td>
<td>1055</td>
<td>78</td>
<td>210</td>
</tr>
<tr>
<td>Holstein</td>
<td>5</td>
<td>1065</td>
<td>154</td>
<td>182</td>
</tr>
<tr>
<td>Jersey</td>
<td>8</td>
<td>990</td>
<td>51</td>
<td>174</td>
</tr>
</tbody>
</table>

Experimental cows that received massive doses of phenothiazine

Concentrate mixture, beet pulp and either hay or silage, were fed twice daily, at the milking periods.

Each cow was dosed with 125 grams of commercial phenothiazine, which amount was approximately twice the maximum recommended for adult cattle. Observations during the four days following medication revealed no changes except a precipitous drop in the milk production of two of the cows and a slight decrease in that of the third. The milk yields persisted at the lowered level for two to three days but subsequently returned to the pre-treatment level for the Holstein and the Jersey cows, the higher producers, but remained low for the Guernsey.

Abnormal red coloration was observed on the udders of the cows the day following the administration of the drug. This, presumably, was the result of oxidation of the phenothiazine conjugates (5, 9) in the urine that had come in contact with the surface of the udder.

Period of excretion of phenothiazine derivatives in the milk. In accordance with common practices the cows were milked at 12-hour intervals. Samples of milk from the individual animals were collected at each milking for a period of 72 hours following administration of the drug.

Determinations of the presence of phenothiazine derivatives were made by qualitative methods described by Collier (5). Acidification of the milk samples with strong hydrochloric acid, producing a mauve color, was the most satisfactory test used. Exposure of the samples to air and light for several hours resulted in the development of a pink color in the serum phase of the milk. This color was difficult to detect in samples having a high carotenoid content; the yellow seemed to mask the pink. In addition to the procedures indicated by Collier (5), it was found that mixing "Aerosol",

TABLE 2

<table>
<thead>
<tr>
<th>Breed</th>
<th>Hours after dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>12</td>
</tr>
<tr>
<td>Guernsey</td>
<td>+++</td>
</tr>
<tr>
<td>Holstein</td>
<td>+++</td>
</tr>
<tr>
<td>Jersey</td>
<td>+++</td>
</tr>
</tbody>
</table>
EXCRETION OF PHENOTHIAZINE DERIVATIVES

a surface-tension-reducing reagent, with milk containing the conjugates of phenothiazine produced a transitory pink color, which was adequate for detection but unsatisfactory for estimating the degree of concentration.

As shown in table 2, the phenothiazine products were in the milk for periods of 36 to 60 hours after dosing. The highest concentrations apparently were in the first milking following administration.

Toxicity of phenothiazine derivatives excreted in the milk of the cows. Samples of milk collected from the individual cows at the 12-hour and the 24-hour periods were fed to young rats to ascertain whether any toxic reactions would be evinced. Immediately after the collections, half of each sample was stored in the raw state at 35°F., but the other half was boiled for three to five minutes (recommended treatment of milk for infant feeding) before storing.

Thirteen month-old rats, grouped as indicated in table 3, were restricted to diets of the various milk samples for 72 hours. During a preliminary

<table>
<thead>
<tr>
<th>Period of collection</th>
<th>Treatment</th>
<th>No. of rats</th>
<th>Av. wt. of rats</th>
<th>Daily consumption per 100 grams of body wt.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>grams</td>
<td>Average</td>
</tr>
<tr>
<td>12-hour</td>
<td>None</td>
<td>3</td>
<td>55</td>
<td>70</td>
</tr>
<tr>
<td></td>
<td>Boiled</td>
<td>3</td>
<td>55</td>
<td>74</td>
</tr>
<tr>
<td>24-hour</td>
<td>None</td>
<td>3</td>
<td>52</td>
<td>74</td>
</tr>
<tr>
<td></td>
<td>Boiled</td>
<td>3</td>
<td>55</td>
<td>71</td>
</tr>
<tr>
<td>Daily (herd)</td>
<td>Pasteurized</td>
<td>1</td>
<td>57</td>
<td>77</td>
</tr>
</tbody>
</table>

adjustment period of 60 hours, the individual rats were fed pasteurized whole milk ad lib. The pasteurized milk diet was replaced by the experimental samples, a fresh supply being provided twice daily.

The rate of consumption of the milk samples, as shown in table 3, reveals a marked individual variation but no significant group differences. Evidently the presence of the phenothiazine conjugates in the milk did not change its palatability. Clinical examinations of the rats during and after the milk feeding period revealed no discernible toxic effects.

DISCUSSION

In accord with the report of Britton (4), the phenothiazine derivatives eliminated in the milk seemed to have a preservative value. The milk samples containing the conjugates were in excellent condition after storage for 31 days at 35°F. Furthermore, as noted by Swales and Collier (9), samples exposed to light and air in a warm room for several days showed no
evidence of decomposition. These properties, either bacteriostatic or bactericidal, have been ascribed to the oxidation product, thionol (4). The microbiological phase of the subject merits further investigation.

Boiling the milk for several minutes apparently modified neither its physiological effects on rats nor its qualitative reactions to various agents. The effects of extensive boiling, producing a concentration of the products, were not investigated. This type of treatment, however, is beyond the limits of practical measures used in the home preparation of milk for direct consumption.

Although phenothiazine derivatives are eliminated in the milk of cows treated with the drug, the concentration of these conjugates from recommended therapeutic doses probably is too small to cause serious toxic reactions in the consumer. No ill effects have been demonstrated in pigs (2), kids (6) and lambs (9) that have consumed milk from their respective dams treated with the commonly prescribed doses of phenothiazine. In recovery trials with sheep Swales and Collier (9) observed that between 80 and 85 per cent of a therapeutic dose of phenothiazine was eliminated in the feces and urine; thus only a small percentage could be excreted in the milk.

Though it is hazardous to attempt to translate experimental findings, particularly in toxicity studies, from young rats to infants, the results of this investigation suggest that milk from cows given a therapeutic dose of phenothiazine is not likely to be toxic to the normal human subject. The cows in this experiment were given twice the recommended amount, which should have produced a concentration of derivatives in the milk at least as great as the maximum from the standard doses given to any other adult cattle. Furthermore, the rats, though more resistant than the human being (8), consumed quantities of milk per unit of weight from five to six times greater than normally would be fed to babies (7).

The element of human variation in susceptibility to phenothiazine, as indicated in results reported by Bercovitz et al. (3), warrants adherence to the general recommendation that milk from cows treated with the drug either be discarded or be used for purposes other than human consumption during the period that the derivatives are excreted. This introduces the problem of determining whether or not the conjugates are in the milk. Since the pink color that develops upon exposure to air frequently is difficult to detect in milk having highly pigmented fats, this procedure, though practical, cannot be regarded as an infallible indicator of the absence of the derivatives. Therefore, as a precautionary measure, it probably is well to divert the milk from food channels for a period of two to three days following medication.

**SUMMARY**

1. Oral administration of 125 grams of commercial phenothiazine, over twice the maximum recommended therapeutic dose, to healthy adult lactat-
ing cows produced no detectable deleterious effects other than a temporary repression of milk production.

2. Derivatives of phenothiazine were detected in the milk for periods of 36 to 60 hours following administration of the drug.

3. Young rats restricted to diets of the milk collected at the 12-hour and the 24-hour periods after dosage manifested no discernible symptoms of toxicity.

REFERENCES