The effect of phenothiazine upon thyroid function in dairy animals as shown by radioiodine

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Since phenothiazine is being used for the control of certain internal parasites in cattle, studies were made to determine the effect of prolonged administration upon thyroid function. At the dosage level administered, phenothiazine did not act as a goitrogenic agent. Editor.

Several investigators (4-6) demonstrated that the administration of the commercial form of phenothiazine (green) reduced the uptake of radioiodine by the thyroid in several species. Talmage et al. (6-8) reported that purified phenothiazine did not inhibit the uptake of radioiodine $I^{131}$. Since commercial phenothiazine (green) contains 0.3 to 0.4% organic iodine as an impurity, Nachimson et al. (4) compared the effects of phenothiazine and equal amounts of sodium iodide on thyroidal $I^{131}$ uptake and concluded that the effect of phenothiazine could not be explained entirely by its iodine content. Wasserman et al. (10) also concluded that in addition to the iodide ion another factor, much less potent than iodine, was also responsible for a slight but definite depression of thyroid uptake of radioiodine.

Since phenothiazine is currently being recommended for the control of certain internal parasites by continuous feeding at the rate of 1-2 g. per day to cattle, studies were undertaken to determine the effect of prolonged administration on thyroid function at the 2-g. level.

EXPERIMENTAL PROCEDURE

Two Jersey heifers and one Guernsey ranging in weight from 600 to 1,000 lb. were allowed access for several months to iodized salt blocks containing 0.01% potassium iodide. Phenothiazine (green) at the rate of 2 g. per day was administered by capsule for 10 days. At the end of this time carrier-free radioiodine (Na$^{131}$) was injected intravenously. Phenothiazine was continued at the same rate throughout the experiment.

Daily measurements of thyroidal $I^{131}$ were started 24 hours after injection and continued for 18 days by means of a scintillation counting system and head

Received for publication May 21, 1956.

1 Contribution from the Mo. Agricultural Experiment Station. Journal Series No. 1622. Approved by the Director.
2 Aided-in-part by a grant from the U. S. Atomic Energy Commission [Contract No. AT (11-1)-301].
holder described by Pipes et al. (5). After several weeks the same three animals were again injected with I\textsuperscript{131}, and similar studies were made of the accumulation and release of I\textsuperscript{131} by the thyroid in the absence of phenothiazine. The data obtained in these experiments were calculated and expressed according to the methods and terminology of Brownell (3) as adapted to the dairy cow by Blincoe and Brody (2).

Since the thyroid is secreting I\textsuperscript{131}-tagged hormone during the uptake phase and since the theoretical uptake (U) is determined by a series of measurements and subsequent extrapolation to zero time, it is a more satisfactory parameter of thyroid function than the maximum observed uptake. The k\textsubscript{4} value represents the rate constant for release of thyroid hormone from the gland.

EXPERIMENTAL OBSERVATIONS

Feeding phenothiazine to three dairy heifers at the rate of 2 g. per day reduced the theoretical uptake (U) of I\textsuperscript{131} to 13.2%, compared to the uptake of 35.6% during the control period of these animals. Thus, the uptake of I\textsuperscript{131} during the experimental period of phenothiazine feeding was reduced to 37% of that found during the control period. Measurement of the thyroidal-I\textsuperscript{131} release rate calculated as the k\textsubscript{4} value showed 0.0041 for the controls and 0.0033 for the phenothiazine-treated animals (Figure 1). However, the k\textsubscript{4} value (the net rate of release of thyroidal I\textsuperscript{131} uncorrected for reutilization of metabolized

![Graph](image_url)

Fig. 1. Reduced rates of uptake of I\textsuperscript{131} and negligible changes in the rate of secretion of thyroid hormone in dairy animals under phenothiazine administration are shown.
I\textsuperscript{131}-tagged hormone) remained unchanged, indicating that the $k_4$ value was altered because of dilution of metabolized hormonal I\textsuperscript{131} with iodine from administered phenothiazine.

It has been shown in this laboratory by Pipes \textit{et al.} (5) that goitrogenic agents (thiouracil and 6-methyl thiouracil) increase the rate of release twofold or more. During phenothiazine administration, however, the $k_4$ value was slightly reduced and the $k_4'$ value was unchanged.

\textbf{DISCUSSION}

As inorganic stable I\textsuperscript{127} or organically bound iodine that can be metabolized to yield inorganic iodine is increased, the per cent uptake of a tracer dose of I\textsuperscript{131} is reduced owing to simple dilution. The present observations indicate that a similar situation exists in animals fed phenothiazine with a high iodine content.

Goitrogenic agents inhibit the synthesis of thyroid hormone and prevent the formation of organically bound iodine. However, Taurog \textit{et al.} (9) have demonstrated that goitrogenic substances do not inhibit the uptake of iodine by the thyroid but prevent the retention of iodine. A rapid uptake of iodine was observed in these investigations, followed by an exceedingly rapid rate of release. Since the rate of release of thyroid hormone is not increased by phenothiazine, this compound evidently does not act as a goitrogen at the levels administered. These findings are in accord with those of Nachimson \textit{et al.} (4), who found that prolonged administration of phenothiazine did not produce a goitrogenic effect, as shown by the lack of change in thyroid size. Further evidence indicating that commercial phenothiazine is not goitrogenic has been presented by Allcroft and Salt (1), who found that protein-bound iodine levels were not depressed in sheep.

This study is believed to indicate that the iodine content of commercial phenothiazine reduces the uptake of I\textsuperscript{131} owing to simple dilution of the tracer dose. It does not exclude the possibility that other causative agents may be present (4, 10). It was shown by the technique employed that phenothiazine at the level of 2 g. per day did not behave similarly to goitrogenic agents, such as thiouracil, which increase the apparent rate of release of the thyroid hormone.

\textbf{SUMMARY}

Commercial phenothiazine, when administered at the rate of 2 g. per day to dairy heifers, reduced the uptake of I\textsuperscript{131} but did not induce hypothyroidism, as shown by the release rates of thyroid hormone from the gland. Thus at the dosage administered phenothiazine does not act as a goitrogenic agent.

\textbf{REFERENCES}


