$^{F_{1}}g_{*}$ 1 : MTU levels in plasma (O), urine (\odot) and milk (\bigtriangleup) at various times after oral administration of 4 g MTU to a cow.



Use the second s

Dastic bottle which the aid of an inox catheter. A homogeneous sample (10.20 m1) was transferred in a plastic bottle and immediately frozen at -18°C. Inaughter, before slaughter, urine and blood was sampled. Immediately after from the thyroid was dissected and weighed. Samples were then taken the thyroid and M. diaphragma, packed in plastic bags and chilled at -18°C Mu destination.

Number and periods (8-78 days). My (usually 5 g) was suspended in 100 ml water and sucked into a plestic strings. A plastic tube was fitted on the syrings and the suspension ejected at the back of the cows' mouth. Blood was sampled at regular intervals from immediately cooled in ice-water and centrifuged (1500 g) within 2 h period. My (usually to be a string of the deep-freeze (-18°C) until analysis. For thyroxine termination in serum, blood was similarly collected in venoject tubes (lice. Containing no heparin). The blood was kept at room temperature during 6 h since in the serum was then immediately frozen (-18°C) and analyzed for Myroxine within 3 weeks after sampling. Urine was collected from cows in a

Materials and Methods Junct of the second second second successful and the second secon

In contrast with laboratory animals. In contrast with laboratory animals, where the metabolism of thyreostatics was in comparing studied (8), data on the excretion and distribution of thiouracils in comparing the second state of the second second second second state of the second se

Regulations in the EEC prohibit the use of thyraostatics for cattle fattening. These drugs inhibit the thyraid function : the decreased production of thyraid hormone educes basal metabolism, lowersgastro-intestinal motility and favo-a Considerable increase in live weight gain, although this results mainly from increased filling of the gastro intestinal tract and augmented water reten-tion in the slaughter animals.

Introduction

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The results of a representative experiment, obtained after administration of a single oral MTU does to a cow, are shown in Fig. 1. Maximum MU levels were found 4.8 h after ingestion in urine, plasma or m1k. Concentration of MTU in urine was 50-100 times that of plasma and 250-500 times that of m1k. The MTU levels in these fluids show a very rapid and parallel decline in function of time in the first 80 h after treatment. Analysis of plasma or urine, obtained 3-17 days after administration of the drug, show evidence for a second phase during which the elimination of MTU is 15 times slower than observed in the first 80 hours after MTU treatment (Table 1). At slaughter, the MTU concentration in the thyroid was always higher than in plasma or which are days after administration of the drug, the residue con-centration of MTU in the thyroid was 50-200 times that of M. diaphragma or plasma. The MTU-level in the thyroid decreased in function of fine withdrawal period with an apparent half-life of 3 days (r= -0.99, $p \le 0.001$; n = 8 days after the MTU concentration in the thyroid was solve the tort of the drug of the solve of the sol

In the second experiment different animals were treated with a daily dose of 5 g MIU during periods of 2, 3 or 4 weeks. After 40-14 days of MIU treatment the appetite decreased and the reactions of the animals become apathetic. Approximately 5-6 days after stopping the MIU-treatment, there was a temporally increased diversis, the appetite returned and the reactions of the animals become





After a 2, 3 or 4 week MTU-treatment the MTU levels in urine and plasma are 2-3 times higher than the maximum concentration observed after ingestion of a single dose. After withdrawal of the drug, the data show that there are at least 2 phases in the disappearance of MTU from plasma or urine (Fig. 2). In the first 4-5 days after stopping MTU-treatment, the MTU-levels in plasma and urine declined rapidly. Then the elimination rate decreased by a factor 20 so that, after a withdrawal period of more then 80 days, still distinct levels of MTU (> 10 ppb MTU) were found in urine or plasma. During that period the residue levels in urine were ano significant differences in the climination cows during either 2, 3 or 4 weeks. The MTU concentrations in the thyroid were studied over a withdrawal period of 5-80 days (Fig. 3). During this period the apparent half-life of



Fig. 3 : Concentration of MTU in the thyroid (▲) and M. diaphragma (△) of cows at various withdrawal periods after daily ingestion of 5 g MTU during 2-4 weeks.

MTU in this organ was at least three times less than that observed in plasma or urine over the same period. In cows, treated with MTU for at least 3 weeks, the MTU concentration in M. diaphragma showed a parallel decrease with that of the thyroid. The MTU residue levels in the thyroid were 3 times higher than that of M. diaphragma over the withdrawal period studied.

 $8:4_{\underline{\text{Highlows levels in cows after oral ingestion of methylthiouracil}}$

The serum levels of thyroxine (T₄) were studied in 6 cows during a 3 or 4 week MTU treatment. Normal T₄-values ranged between 9-20 µg T₄/ 100 ml serum. After 10-14 days of MTU treatment the T₄-values decreased to a minimum 16-22 days after starting the MTU-treatment ; the minimum values ranged between 3,2-7.6 µg T₄/ 100 ml serum. Similar observations were made by Pohlschmidt & Forschner (12) after feeding MTU to 7 bulls over a period of 26 days; however, their minimal T₄-values were lower and ranged between 1-2 µg T₄/ 100 ml serum. The time-course of the T₄-values during the experiments were similar if the T₄-content was expressed as a percentage of its initial value (Fig. 4).: minimal T-values were 37 ± 3% of its initial values. Three days after withdrawal of the drug, the T₄ content of serum increased and reached a maximum 5-6 days after stopping the MTU treatment. Then the T₄-content declined to 70% of its original value after which the T₄-values started oscillating.



Fig. 4 : Time-course of T₄-serum levels during and after treatment of 3 cows (\blacksquare , \Box , \bigcirc) with a daily dose of 5 g MTU (T₄-values are expressed as percentages of its respective control values).

Discussion

Data on the excretion and distribution of thiouracils in cows are rather scarce and limited to studies over short withdrawal periods (2, 3, 9). Early studies in ruminants suggested an efficient absorption of the thyreostatic drugs : maximum blood levels were observed 4-5 h after a single oral dose of thiouracil. Elimination was rapid since 24 h later the plasma thiouracil concentration dropped below the 1 ppm level (9).

Our measurements, obtained after single oral administration of MTU to cows, confirm the initial rapid disappearance of MTU from plasma, urine or milk [Fig. 1]. However, 80-100 h after MTU administration, elimination slows down so that 17 days after MTU treatment still appreciable levels of MTU are found in urine and plasma. As shown in earlier experiments (2, 3), the thyroid shows a specific and efficient accumulation of MTU over that of other muscular tissues. After a single oral administration of MTU to cows, the residue ratio of thyroid/M. diaphragma is not constant but drops from 150-200 at 3 days to a value of 1-3 at 17 days after MTU administration.

Table 1 : Half-life of MTU in plasma, urine, muscle and thyroid tissue after oral administration of the drug to cows.

Dose	Fluid or tissue	Half-life of MTU first phase second phase	דמ2
single dose	24.50		
1 x (2 or 4 g)	urine, milk (2)	6 ± 0.5 h	
1 x 5 g	plasma (8)	6 ± 0.5 h 3.6 days	16 day
1 x 5 g	thyroid (8)	2.9 days	29 day
multiple dose	plasma urine (8)	15 + 3 h 24 ± 1.7 days	65 day
14, 21 or	thuroid (13)	9.7 days ¹	77 day
28 x 5 g	M.diaphragma(10)	9.7 days ¹	66 day

) : number of cows (

: estimated from analysis of samples obtained at sloughter after withdrawal times of at least 3 days.

²: withdrawal period (days) during which the concentration of MTU residues in the biological matrix exceeds 0.01 ppm.

After feeding cows with MTU for longer periods (14-28 days) the initial elimination of MTU from plasma, urine or tissues is 2.5-3.3 times slower than observed after a single oral administration of MTU (Table 1). The increased half-life of MTU in urine, plasma or thyroid and the similar half-life of MTU in thyroid and M. diaphragma probably reflects that cow tissues reached steady state levels after feeding MTU for at least 14 days. In comparison with earlier experiments (3, 12), the specific and sensitive detection method employed here allowed detection of significant MTU-lovals⁹ the thyroid, muscular tissue, plasme or urine over a tenfold extended with drawal period.

8:5

Prolonged administration of goitrogenic substances to cattle results in symptoms of hypothyroidism : histological hypertrophy of the thyroid glad often used in regulatory control as evidence for illegal treatment with thyreostatics. The time course of the thyroxine levels shows that MTU treatment of cows during one month will not result in a sufficiently long period of hypothyroidism to provoke detectable lesions of the thyroid. This and the of correlation observed between the results obtained from histological even ination and chemical analysis of thyroids taken from regulatory control (equation).

From this study it is evident that after MTU-treatment of cows during 4 weight followed by a withdrawal period of one month still appreciable residue level (co 0.1 ppm MTU) may be found in muscular tissue. MTU treatment thus real in higher residue concentrations in muscular tissue. MTU treatment funger approach that was expected from earlier experiments (2, 9, 12). For register tary control on the living animal, urine sampling is the obvious choice. During inspection in the slaughterhouse, thyroid should be selected as the target tissue for optimal detection of the illegal use of thyreostatice.

Conclusions

Treatment of cows with MTU results in a rapid appearance of the drug in plasma. urine and milk whereas MTU selectively accumulates in the thyroid. MTU levels in plasma or urine show a biphasic elimination : after an initia trapid decline, observed in the first 4 days after treatment. the MTU excre tion slows down by a factor 15-30 depending on the treatment. Feeding to cows over prolonged periods results in a slower MTU elimination so that after a withdrawal period of one month, appreciable residue levels of the drug were found in the thyroid, muscular tissue, urine or plasma.

The time-course of serum thyroxine levels during MTU treatment of cows suggests that histological or macroscopical examination of the thyroid for cannot be used as a reliable screening parameter for the illegal use of the reostatics in cattle fattening. For regulatory control, MTU residues enough be monitored in the thyroid, urine or muscular tissue using a sensitive of specific chemical method.

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