EFFECTS OF ELFAZEPAM ON THE PERFORMANCE OF GROWING LAMBS UNDER 35 C THERMAL STRESS

by

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TABLE OF CONTENTS

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LIST OF TABLES

LIST OF FIGURES

INTRODUCTION

Among environmental conditions that may impose stress on the general performance of an animal are temperature, humidity, and radiation. These conditions, if stressful, affect the animal's heat production system, and the energy available for production. It is common knowledge that the effects of heat on most animals are more devastating production-wise than those of cold, primarily because there are more effective physiological mechanisms for combating cold than for combating heat.

Since nutritional requirements of animals are affected by environmental temperature, a reduction or cessation of body growth often accompanies exposure to high temperatures apparently due to a combination of a reduction in voluntary food intake, increases in energy expended for heat dissipation, particularly through respiration enhancement; resulting in a reduction in the amount of nitrogen, fat, or water stored.

It is observed that animals that record a high intake of a balanced ration return high performance under disease-free conditions. The necessity to determine how an increased consumption of food by animals under stressful conditions can be achieved cannot, therefore, be overemphasized. The purpose of the present study were a) to determine the effects of Elfazepam on feed intake and growth rate of lambs under 35 C thermal stress, and b) to determine the effects of Elfazepam on plasma thyroxine (T_4) levels since this hormone is intimately associated with the growth rate of a young animal. Should Elfazepam support a sustained increase in feed intake and normal plasma thyroxine levels under 35 C thermal stress without reducing efficiency it might prove useful in the livestock industry in areas where a hot environment reduces performance.

LITERATURE REVIEW

The thermoneutral zone (TNZ) of shorn sheep has been consistently reported to be about 15 C. Temperatures above this are stressful to this animal as, under such conditions, heat loss must increase if normal metabolic rates, a constant internal body temperature, and physiological function are to be maintained.

It has been reported that the most rapid growth occured at around 21 and 16 C for 45- and 90 kg pigs respectively (1). At 30 C the growth rate was slower than at 10 C by virtue of the reduced feed intake that occured in spite of the systematic improvement in feed conversion with increasing ambient temperature (2). Feed intake falls with rising temperature to a point where the animal will not eat if the environment is so warm that they already experience hyperthermia (3), suggesting that animals eat to keep warm and stop eating to prevent excessive rise in body temperature. This proposes that feed intake is controlled as if it were an integral part of the system regulating body temperature: a concept now referred to as the thermostatic theory of food intake.(4).

Weight gains of about 5 gm have been reported to occur within 18 hours in rats kept between 22 C and 30 C; at 32 C no gain occured, while at still warmer temperatures a loss of weight was observed (5). Work with two-month old calves and yearling heifers have shown statistically significantly reduced feed consumption in both age groups as the environmental temperature increased from 1.5 C to 32 C (6). In other studies, it has been reported that the relationship between temperature and average daily weight gain in steers and lambs was quadratic during heat and linear during cold (7). The difference was explained by linear increases

in maintenance during cold in combination with maximum feed intake as compared to non-linear increases in maintenance during heat, with concurrent decreases in feed intake. Reduced feed intake and weight gain have been reported in rats exposed to 35 C heat, while exposure of pigs to an air temperature of 38 C has been observed to decrease feed intake from approximately 7 to less than 2 lb per day (8, 9). It has also been shown that Holstein yearling heifers gained only 0.5 kg per day when subjected to a very high environmental temperature (24 to 35 C) while those raised at 3.3 - 18.3 C gained 0.82 kg per day (10).

With the adverse effects of heat on animals and their feed consumption as well as performance so well documented by these and other workers (11, 12, 13, 14, 15) it becomes pertinent to explore avenues of increasing the intake of animals under such conditions. This might ensure an adequacy of protein and net energy available for metabolic purposes thereby improving growth raten efficiency, and health of the animal.

Different studies have been conducted in an effort to identify drugs that would stimulate feed consumption in animals under all kinds of stressful conditions. It has been reported that stressed (37 C) pigs showed a significantly lower performance which was improved by various drug treatments (16). The drugs included varying levels of protamone, hydroxyzine, and meprobamate. Other studies have consistently reported that one of the properties of members of the diazepine class of tranquilizers affects eating behavior in animals (17, 18, 19). Benzodiazepine derivatives are used mainly for the treatment of anxiety, among other conditions. This class of drugs possess the sedative properties encountered in major tranquilizers but there is behavioral tolerance to their sedative action,

and they exhibit their antianxiety action as tolerance is developed (19). The benzodiazepines have two opposing effects on behavior: a depressant action at high doses and a facilitating effect on behavior at lower doses (20); this latter distinguishes the minor tranquilizers from the major ones (19).

Diazepam has been shown to increase the eating caused by lateral hypothalamic stimulation (18), while pigs subjected to a progressive ratio schedule for food have been reported to show an increased breaking point after diazepam injection. This increase in breaking point was proposed to be a result of nonspecific response-releasing properties, or an increase in the pigs' motivation to work for food (21). Earlier work showed that chlordiazepoxide, in rats, increased drinking which was suppressed by learned taste aversion (22). Other studies have shown that methaminodiazepoxide hydrochloride significantly increased foor consumption in both rats and dogs (17), and that five different members of the benzodiazepine class have been observed to cause spontaneous eating in satiated rats (23).

The experimental drug in this study, Elfazepam - 7-chloro-1-(2(ethyl sulfonyl)ethyl)-5-(2-fluoro-phenyl)-1, 3-dihydro-2H-1, 4-benzodiazepine-2-one, is relatively newer than the other members of the class. It has, however, been shown in various experiments to possess the property of increasing the food consumption of satiated animals. Elfazepam increased feed intake, weight gain, and feed efficiency of steer fed a basically roughage-based ration (24) in an experiment observed to be dose-independent. The drug increased total feed intake in sheep by increasing the amount eaten as meals and not by changing the amount eaten as nibbling (25). In other works the mean responses of cattle from 15 studies conducted at various sites in the U.S. indicated that while feed intake was significantly

increased on the average, the more dramatic responses were in gain and feed efficiency (25). One explanation for the improved efficiency could be the increased ration digestibility induced by Elfazepam (26) though such increases were observed to be generally greater on low quality, high forage diets. Other studies have also indicated that the overall digestibility of ration was not depressed by Elfazepam in spite of an increased intake (27). The latter workers reported both increased mean intake ($p < .06$) and increased mean weight gain ($p < .07$).

On the other hand it has been shown in one study that Elfazepam increased intake but decreased efficiency in steers (28); while others have shown that it had no effect on feed intake, weight gain, or feed efficiency during the growing phase in calves, but exerted a positive response in these three parameters during the finishing phase. It was proposed in the studies that the positive response during the finishing phase as compared to no effect during the growing phase might be related to differences in diet, feeding regimen, or environment (29). Various other studies have indicated that Elfazepam would increase feed intake in sheep under varying types of stressful conditions, including heat and debilitating diseases (30, 31). One of the few field studies of long duration conducted on the drug showed no positive response in finishing steers fed 6 mg per head daily or Elfazepam for 230 days; in fact it was reported that weight and efficiency of treated steers were lower than those of control animals (32).

The present studies would explore the effects of Elfazepam on the performance of ewe lambs under 35 C thermal stress. In previous studies wether lambs have been subjected to short-term (24 hours) heat (32 C) exposure, and one of the studies showed that treated lambs doubled water

intake in response to Elfazepam when feed was not available for the 60 minutes immediately following injection ($p < .01$); and 24-hour feed and water intake both increased ($p < .05$). Another report showed that the consumption of a protein deficient diet under 32 C heat stress increased on the first day of oral drenching of 16 mg Elfazepam, though the response on the following 3 days was less (30).

It is noteworthy that up till date the effects of Elfazepam under stressful heat have been tested only on short-term basis while the hormonal responses of tested animals have not been monitored as yet. It has been mentioned that some of the important physiologic acclimations to high environmental temperatures include reduced thyroid gland activity, with reduced metabolic rate (33). Studies on most species of animals have consistently reported lowered plasma thyroxine on exposure to stressful heat (10, 34). Daily thyroid secretion rate (TSR) observed in ewes in July has been reported to be significantly lower ($p < .01$) than the estimated secretion rates in any other month (35), just as a seasonal trend in thyroid secretion rates of young chicks has also been shown; the spring and summer rates being only about one-half the winter level (36). In cattle thyroxine secretion rates have been reported to be reduced three fold in the summer, an increasingly warm environment being suggested to be a greater stimulus to a reduction in thyrotropic hormone secretion than a gradually colder environment for increased thyrotropic activity (37). In the mare one study showed no significant difference in the plasma concentration means between late winter and summer (38), while work in the camel has shown that plasma thyroxine (T_4) levels were significantly higher ($p < .05$) in summer than in winter (39).

The initial responses of the thyroid gland in heat have, however

been observed to be only transient and are altered with prolonged heat exposure. In one related study it was reported that rams exposed to 32 C for up to 100 days showed a highly significant decrease ($p < .05$) in plasma thyroxine levels compared with pre-exposure values. Later on these values increased, and by day 100 were comparable to those found in the same animals exposed to 20 C. These increases were simultaneously accompanied by progressively increasing feed intake (40). Similarly, rats exposed to 34 C have been reported to show a depressed thyroid response during the first 40 days of exposure, which later increased to higher than control levels for the remainder of their lives (41). Findings similar to these have also been reported from studies with rats exposed to 34 C for 220 days (42).

Interest in thyroxine is often related to its role in the physiology of many life processes essential to animal productivity. Various experiments have been conducted to study the effects of added thyroactive substances in the ration of animals on growth, fertility, and lactation. While a few studies have indicated that feed intake increased considerably in rats treated with exogenous thyroxine (43), some have shown that neither feed intake nor water consumption was altered by thyroxine treatment in dairy cattle at both 18 C and 32 C (44). In swine it was reported that the rate of disappearance of ^{125}I thyroxine did not change whilst the ambient temperature reduced from 32 C to 8 C, unless the animal's feed intake was altered (45). On the practical side the association of low plasma thyroxine levels with high lactational performance reported in some studies has been attributed to (among other possibilities) a greater utilization of plasma thyroxine in higher producers (46).

Materials and Methods

Two environmental chambers of the Forma Scientific Walk-In Room type,[1] each measuring 11 m x 15 m x 8 m, and with a temperature sensitivity of ±0.5 C were used in these studies. Each chamber contained four pens of dimension 5.5m x 7.5m.

Sixteen ewe lambs of average age 10 weeks and average weight 31 kg were randomly selected into eight pairs, with four pairs each randomly assigned into experimental temperatures of 15 C and 35 C respectively. The lambs were all maintained in their respective chambers at 15 C (TNZ for shorn sheep) for a 10 day period of preconditioning. During these 10 days all lambs were supplied feed and water ad lib, the consumption by each pair being recorded (by difference) on daily basis. All lambs were sheared before they were placed in the chambers to provide a uniform initial exposure to chamber temperatures.

Jugular vein blood samples were obtained three days a week commencing each day at 4 p.m. These samples were allowed to stand for some 5 minutes and then transferred into iced water contained in a basin. They were finally kept in the refrigerator and centrifuged the following day; the serum being stored in glass vials in the freezer until assayed.

After the initial 10-day preconditioning period (interval 1), one group of lambs were exposed to 35 C for 12 weeks while the other group remained at 15 C. These 12 weeks consisted of a 4-week predrug/acclimation period (interval 2), a 6-week drug trial period (interval 3) followed by a 2-week post-drug period (interval 4). Feed and water continued to be available ad lib, with water consumption measured daily and feed intake

[1] Forma Scientific, Inc. Marietta, Ohio

measured weekly. Rectal temperature of each sheep was measured daily commencing at 4 p.m., simultaneously with blood collection on those days the two coincided. There was an initial pre-experiment weighing, after which the lambs were weighed once a week throughout the course of the experiment.

At the end of the 4-week acclimation interval Elfazepam[1] was administered to two randomly selected pairs of each group by oral drenching. The drug was carried in a propylene glycol vehicle and was administered in syringes such that each treated lamb received 4 mg at each drenching (i.e 2ml of a 2mg/ml solution). Oral drenching was done twice daily at 8 a.m and 4:30 p.m, so a total of 8mg of Elfazepam was administered per head per day for 6 weeks. The remaining 2 pairs of each group individually received a total of 4ml of the propylene glycol carrier in two equally divided doses at the same time of day as the other lambs received the drug. Treatment with Elfazepam and vehicle was stopped at the end of six weeks of administration.

Frozen serum samples were later thawed to room temperature and thyroxine (T_4) determinations were carried out by the radioimmunoassay (RIA) technique using specific antibodies to thyroxine obtained from rabbits.[2]

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[1] Elfazepam (a Smith-Kline product) was supplied by Dr. C. A. Baile of University of Pennsylvania.

[2] Radioactive thyroxine was obtained from Beckman Instruments, Inc. Fulleron, CA 92634.

The data were analysed employing the two-way analysis of variance, general linear model, Duncan's multiple range test, and the Student's t-test for paired samples.

Results and Discussion

None of the variables measured was significantly affected by temperature - treatment combination.

Temperature had a significant elevating effect on rectal temperature ($p < .01$), and water consumed per kilogram metabolic body weight ($W\ kg^{.75}$) when viewed on a 14-week basis. The drug did not show any significant effect on any parameter on a 14-week basis.

During the four weeks of acclimation (interval 2) when the two groups of lambs were at 15 C and 35 C respectively, ambient temperature had a significant depressing effect ($p < .05$) on plasma thyroxine (T_4) levels (Table 1, Fig. 2) and feed consumed per unit metabolic body weight (Table 3, Fig. 4); while it had a significant elevating effect ($p < .05$) on water consumed per unit metabolic body weight (Table 4, Fig. 3), and rectal temperature ($p < .01$), Table 2, Fig. 1).

During the treatment interval Elfazepam exerted an effect on average daily weight gain ($p < .05$) independent of ambient temperature (Table 9) but not on other variables. On partitioning the treatment effect Elfazepam showed a significant effect ($p < .05$) on average daily weight gain and feed consumed per unit weight gained (Table 10) in the lambs maintained at 35 C. Comparison of results during the experimental with the pre-experimental interval in animals kept under 35 C showed that feed consumption was depressed during Elfazepam treatment (Table 11) although the average consumption of all four pairs over the entire 14 week period

RATION COMPOSITION

Ingredients	%
Soybean meal (5-04-600)	5.0
Ground sorghum grain (4-04-444)	39.4
Molasses (4-00-668)	5.0
Dehy. alfalfa (1-00-023)	50.0
Proximate analysis	
Dry matter	87.17
Protein	13.50
Ether extract	2.35
Crude fiber	15.37
Ash	6.41
Energy	4057
N mg/g	21.59

TABLE 1*

COMBINED EFFECTS OF TREATMENT AND TEMPERATURE ON PLASMA THYROXINE (T_4) LEVELS (ng/ml)

Interval of Experiment	Temp. C	Animal Group: Control	SE	Experimental	SE	Temp. C	Animal Group: Control	SE	Experimental	SE
1	15	$128^{a,b,c,d}$	8.0	$122^{a,b,c,d}$	8.0	15	$121^{a,b,c,d}$	8.0	$135^{a,b,c,d}$	8.0
2	35	104^{d}	4.5	101^{d}	4.5	15	$109^{c,d}$	4.5	$128^{a,b,c,d}$	4.5
3	35	$127^{a,b,c,d}$	3.6	$127^{a,b,c,d}$	3.6	15	$119^{b,c,d}$	3.6	$138^{a,b,c}$	3.6
4	35	151^{b}	8.0	$147^{a,b,c}$	8.0	15	$125^{a,b,c,d}$	8.0	158^{a}	8.0

*Each mean consists of 8 observations for intervals 1 and 4, 16 for interval 2, and 24 for interval 3.

^{a,b,c,d}Values with the same superscript are not significantly different, ($p < .05$)

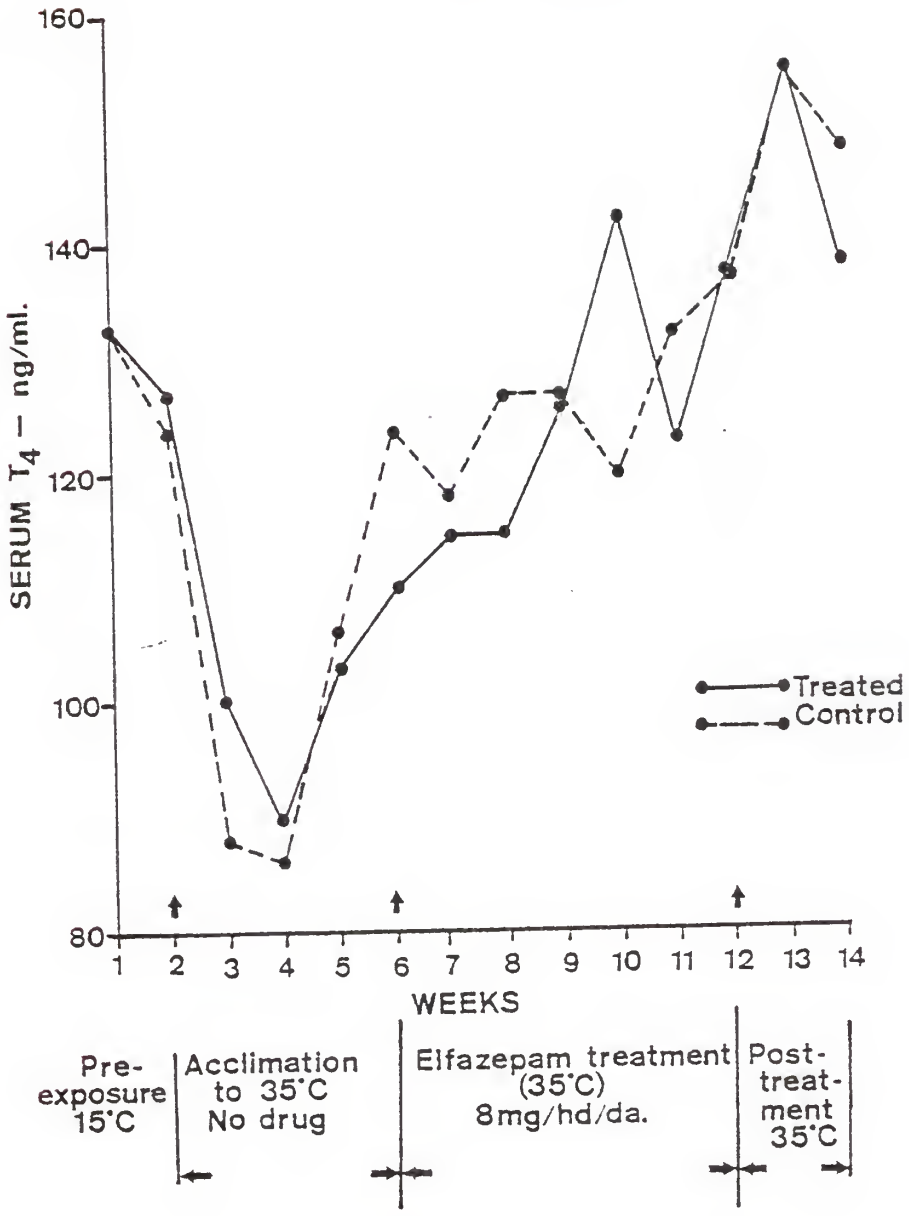

Figure 1. Effects of temperature and treatment on plasma thyroxine (T_4) level. Each point represents the mean of 8 observations on 4 lambs that received identical treatment.

TABLE 2*

Effect of Treatment and Temperature on Rectal Temperature (C)

Interval of Experiment	Temp. C	Animal Group Control	SE	Experimental	SE	Temp. C	Animal Group Control	SE	Experimental	SE
1	15	39.4^{b}	.07	39.2^{b}	.07	15	39.4^{b}	.07	39.2^{b}	.07
2	35	40.3^{a}	.09	40.3^{a}	.09	15	39.0^{b}	.09	39.0^{b}	.09
3	35	40.4^{a}	.14	40.4^{a}	.14	15	39.0^{b}	.14	39.3^{b}	.09
4	35	40.1^{a}	.07	40.2^{a}	.07	15	39.1^{b}	.07	39.3^{b}	.07

*Means consist of 8 observations for intervals 1 and 4, 16 for interval 2, and 24 for interval 3.

^{a,b}Values with the same superscript are not significantly different, ($p < .05$).

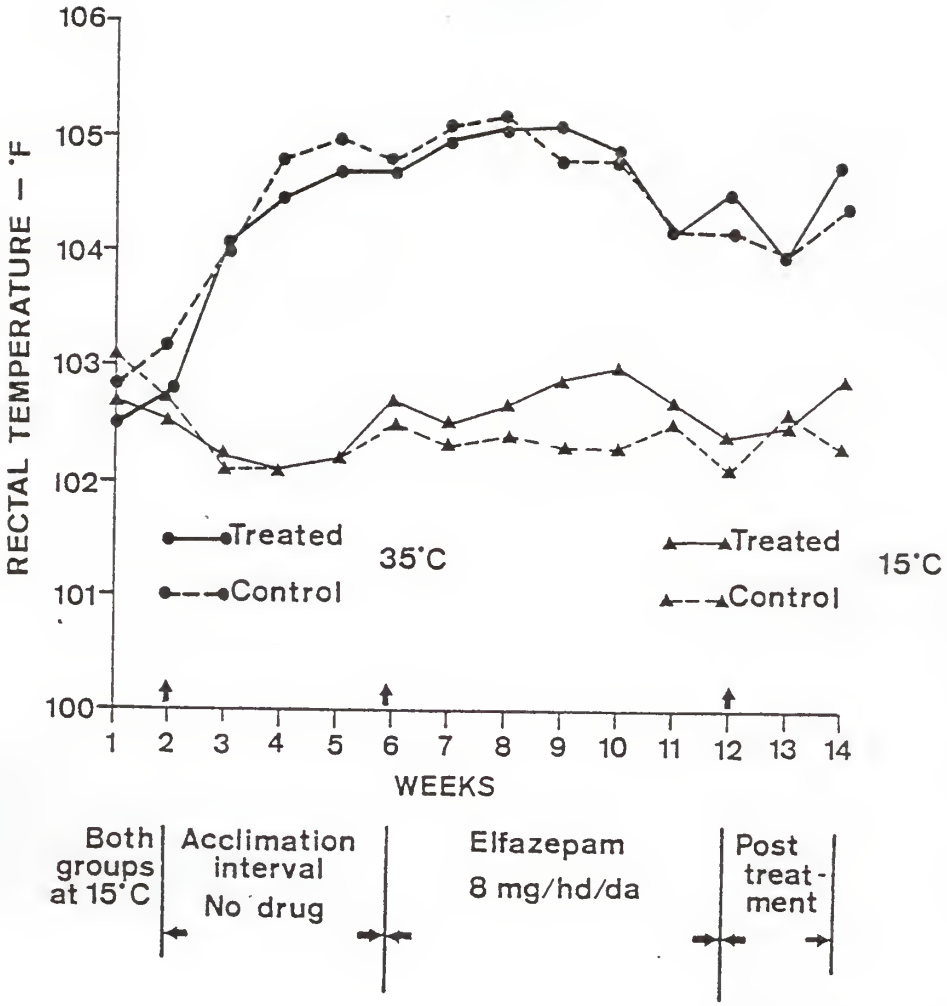

Figure 2. Effects of temperature and treatment on rectal temperature. Each point represents the mean of 28 observations on 4 lambs that received identical treatment at each experimental ambient temperature.

TABLE 3*

Effects of Temperature and Treatment on Feed Intake ($gm/kg^{.75}/da$)

Interval of Experiment	Temp. C	Animal Group				Temp. C	Animal Group			
		Control	SE	Experimental	SE		Control	SE	Experimental	SE
1	15	89^{a}	1.5	89^{a}	1.6	15	90^{a}	1.6	91^{a}	1.5
2	35	$68^{b,c}$	1.4	76^{a}	1.4	15	83^{a}	1.4	81^{a}	1.4
3	35	$65^{b,c}$	1.3	$63^{b,c}$	1.3	15	72^{a}	1.3	76^{a}	1.3
4	35	$61^{b,c}$	1.5	$59^{b,c}$	1.6	15	79^{a}	1.6	77^{a}	1.5

* Means consist of 4 observations for intervals 1 & 4, 8 for interval 2, and 12 for interval 3.

^{a,b,c} Values with the same superscript are not significantly different ($p < .05$)

TABLE 4*

Effects of Temperature and Treatment on Water Intake (ml/kg$^{.75}$/da)

Interval of Experiment	Temp. C	Animal Group Control	SE	Experimental	SE	Temp. C	Animal Group Control	SE	Experimental	SE
1	15	$171^{c,d}$	9	$163^{c,d}$	9	15	$163^{c,d}$	9	$117^{c,d}$	9
2	35	313^{a}	5	339^{a}	5	15	174^{c}	5	$184^{c,d}$	5
3	35	252^{b}	2	$302^{a,b}$	2	15	140^{d}	2	148^{d}	2
4	35	$235^{b,c}$	9	$302^{a,b}$	9	15	137^{d}	5	144^{d}	9

* Means consist of 4 observations for intervals 1 and 4, 8for interval 2, and 12 for interval 3

a,b,c,d Values with the same superscripts are not significantly different ($p < .05$).

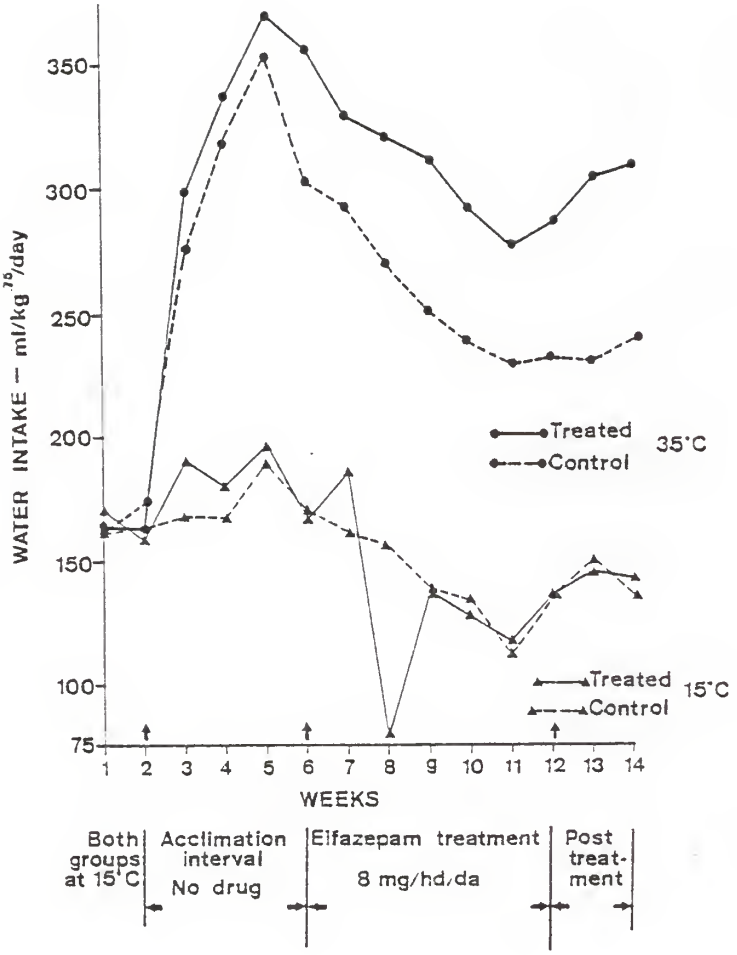

Figure 3. Effects of temperature and treatment on water consumed per kilogram metabolic body weight. Each point represents the mean of 2 observations on 4 lambs that received identical treatment.

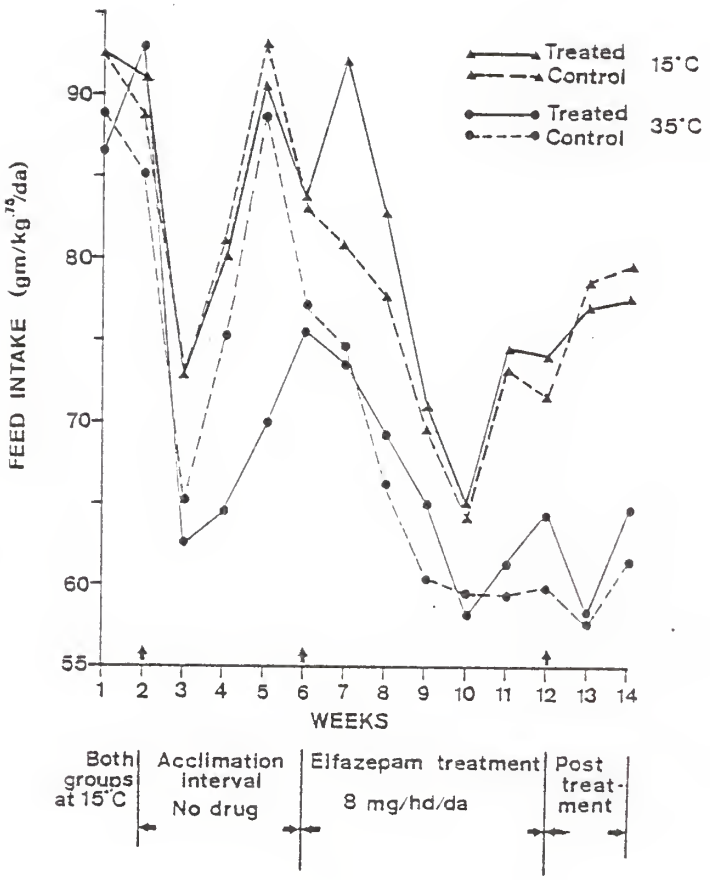

Figure 4. Effects of temperature and treatment on feed intake per kilogram metabolic body weight. Each point represents the mean of 2 observations on 4 lambs that received identical treatment.

TABLE 5*

Effect of Treatment and Temperature on Feed per unit Weight Gain (kg/kg)

Interval of Experiment	Temp. C	Animal Group				Temp. C	Animal Group			
		Control	SE	Experimental	SE		Control	SE	Experimental	SE
1	15	10.2^{b}	.72	11.6^{b}	.72	15	10.5^{b}	.72	11.2^{b}	.72
2	35	8.6^{c}	.67	8.2^{c}	.67	15	5.9^{d}	.67	6.3^{c}	.67
3	35	26.3^{a}	1.55	11.3^{b}	1.55	15	$9.2^{b,c}$	1.55	$9.7^{b,c}$	1.55
4	35	4.9^{d}	.72	5.7^{d}	.72	15	5.2^{d}	.72	7.9^{c}	.72

* Means consist of 4 observations for intervals 1 and 4, 8 for interval 2, and 12 for interval 3.

^{a,b,c,d} Values with the same superscript are not significantly different, ($p < .05$).

was apparently equal for treated and control groups. A corresponding significant depression of water consumed per metabolic body weight was also recorded.

The main effect of temperature on the variables under discussion generally conformed with reports on similar experiments in the literature; thus the lambs on exposure to 35 C showed a significant depression ($p < .05$) in plasma thyroxine (T_4) level in the first two weeks of exposure. From the third week the level returned to around pre-exposure values, unaffected by Elfazepam treatment. This is in conformation with the results of a previous study which reported a depression of thyroxine response in rats during the first 40 days of exposure to 34 C, but later an increase to higher than control values for the remainder of their lives (41). Similar results have also been reported by other workers (44, 40).

The elevated rectal temperature is in agreement with the results of other studies and may be explained by the suggestion that body temperature is inversely related to ambient temperature from 7 C through 32 C and that at ambient 35 C heat loss mechnisms are not as effective as they were at 32 C, and thus the consequent hyperthermia (8).

The reduced absolute feed consumption and increased water intake in response to elevated ambient temperature are also in agreement with previously reported data (3,4,8) just as the reduction in absolute feed intake, reflected in comsumption per unit metabolic body size is in agreement with the results of a study which reported a 35% decrease in feed intake in sheep during the first 10 days of exposure to 32 C (36). But the return to levels equal to or just lower than pre-exposure values reported by these workers was not observed in this experiment. This may be explained by a reduction in the effectiveness of heat loss mechanisms at

35 C compared to 32 C. A return to pre-exposure consumption at this temperature (35C) could possibly have greatly enhanced the hyperthermia experienced by these animals.

The main effect of temperature on average daily weight gain was more pronounced than anticipated. The lambs exposed to 35 C did not only slow down on weight gain but invariably lost weight; the control group losing more consistently than the treated group. This was in agreement with gains in body weight at temperatures from 22 C to 30 C, no gain at 32 C and loss of weight at 35 C observed in rats (4). In fact an overnight loss of 34 gm has been reported in rats exposed to 35 C.

Elfazepam did not in any way alter the effects of temperature on the variables reported above as analysis of the data did not show any significant interaction between treatment and temperature. As mentioned earlier, no significant effects were observed on plasma thyroxine levels rectal temperature, feed consumption, and water intake by Elfazepam. During the experimental interval a significant depression of both feed intake and water consumption was observed. These observations are variously in agreement with the findings elsewhere that not only did the drug have no significant effect on feed intake in finishing steers but that weight gain of treated steers was lower than those of control animals in an experiment that lasted 230 days (32). In other similar studies it has been reported that Elfazepam had no effect on feed intake, gain, or feed efficiency during the growing phase in calves (29). But the results conflict with the report that Elfazepam increased feed intake in sheep under heat stress in the only published study that has been conducted under this condition with the drug; though it should be mentioned here that the latter

TABLE 6*

Main Effect of Ambient Temperature on Plasma Thyroxine (T_4) Levels During Pretreatment Period

Week of Experiment	Temperature C	Thyroxine (T_4) ng/ml	SE	Temperature C	Thyroxine (T_4) ng/ml	SE
1	15	122.5^{a}	7.8	15	121.5^{a}	7.8
2	15	118.0^{a}	7.8	15	123.5^{a}	7.8
3	35	$94.7^{a,b}$	6.0	15	117.9^{a}	6.0
4	35	88.5^{b}	6.0	15	109.0^{a}	6.0
5	35	110.0^{a}	6.0	15	122.7^{a}	6.0
6	35	116.7^{a}	6.0	15	114.2^{a}	6.0

* Each mean consists of 8 observations.

^{a,b} Values with same superscript are not significantly different, ($p < .05$).

TABLE 7*

Main Effect of Ambient Temperature on Rectal Temperature During Pretreatment Period

Week of Experiment	Ambient Temperature C	Rectal Temperature C	SE	Ambient Temperature C	Rectal Temperature C	SE
1	15	$39.2^{c,d}$	.06	15	$39.4^{b,c,d}$	.06
2	15	$39.4^{b,c,d}$	.06	15	$39.2^{c,d}$	.06
3	35	40.0^{a}	.04	15	39.0^{d}	.04
4	35	40.3^{a}	.04	15	38.9^{d}	.04
5	35	40.5^{a}	.04	15	39.0^{d}	.04
6	35	40.4^{a}	.04	15	$39.1^{c,d}$	.04

* Each mean cosists of 8 observations.

^{a,b,c,d} Values with the same superscript are not significantly different, ($p < .05$).

TABLE 8*

Main Effect of Ambient Temperature on Water Intake (ml/kg$^{.75}$/da)

Week of Experiment	Ambient Temperature C	Water Intake	SE	Ambient Temperature C	Water Intake	SE
1	15	116^{c}	7.5	15	116^{c}	7.5
2	15	118^{c}	7.5	15	164^{c}	7.5
3	35	286^{a,b}	10	15	179^{b,c}	10
4	35	327^{a}	10	15	174^{c}	10
5	35	361^{a}	10	15	193^{b,c}	10
6	35	328^{a}	10	15	169^{c}	10

* Means consist of 4 observations, each.

^{a,b,c} Values with the same superscript are not significantly different ($p < .05$)

work was conducted on short-term effects (hours) in contrast to the chronic effects (weeks) investigated in the present studies.

The only variables Elfazepam significantly affected positively were average daily weight gain and feed per unit gain. As outlined in Table 8 the drug significantly ($p < .05$) increased the daily weight gain of treated lambs. A concurrent increase in feed efficiency was recorded that might explain why, in spite of the significant negative effect on feed consumption there was a significant positive effect on body weight gain. These findings may find explanation in the report that Elfazepam increased digestibility of feed in treated animals, with resultant increase in body weight gain during treatment (26). A possible explanation for the increased digestibility is that rumen liquor resident time is increased (30) while rumen motility, abomasal contratility, electromyographical activity, and secretory function are decreased (47, 48). These contribute to a reduced passage rate, allowing increasing fermentation time for microbial digestion. The findings are also in agreement with the findings in previous studies that while feed intake was increased significantly the more remarkable responses were in weight gain and feed efficiency. It is possible that the reduced activity of the animals (from a possible tranquilizing effect of the drug) might have augmented net energy available for gain, with resultant improved body weight gain as well as efficiency of gain. It must be stressed that with the paucity of pharmacological information on Elfazepam the tranquilizing dose is not available in the literature.

Fom the results outlined above, the effects of Elfazepam were expressed only in weight gain and feed efficiency. But as Table 8 shows, these effects are short-lasting and the treated animals showed no advantage

TABLE 9*

Main Effect of Elfazepam on Average Daily Weight Gain (gm)

Week of Experiment	Elfazepam Administered (mg/hd/da)			
	0	SE	8	SE
7	156[b]	30	286	30
8	169[b]	30	185	30
9	120[b]	30	178	30
10	138[b]	30	138	30
11	107[b,c]	30	125	30
12	103[b,c]	30	89	30

* Pooled temperature effect

[a,b,c] Values with the same superscript are not significantly different, ($p < .05$).

TABLE 10*

Main Effect of Elfazepam on Feed per Unit Weight Gain (kg/kg)

Week of Experiment	Elfazepam Administered (mg/hd/da)			
	0	SE	8	SE
7	$8.1^{b,c}$	.75	4.8^{d}	.75
8	6.8^{c}	.75	11.2^{b}	.75
9	18.2^{a}	.75	13.4^{b}	.75
10	$8.0^{b,c}$	.75	9.7^{b}	.75
11	19.8^{a}	.75	9.7^{b}	.75
12	17.6^{a}	.75	21.8^{a}	.75

* Each mean consists of 4 observations.

^{a,b,c,d} Values with the same superscript are not significantly different, ($p < .05$).

over control animals by the third week of treatment. Table 9 also shows that while Elfazepam increased feed efficiency on the first week of treatment the effects had reduced considerably by the third week, and ceased completely by the 4th week. Further, a comparison of weight gains during the pre- and experimental interval revealed that the difference was not statistically significant (Table 11). It is particularly noteworthy that Elfazepam did not show any significant effects on the feed consumption or weight gain of the group treated at 15 C as shown in Fig. 4. This is most contrary to expectation since it was anticipated that the effects of the drug on feed consumption and growth should be most evident at this temperature.

It is not certain if the effect of Elfazepam is dose-related. Observation has shown, however, that the major distinction between the sedative-hypnotics and minor tranquilizers is a very much flatter dose-response slope with the minor tranquilizers (24, 49) to which group Elfazepam belongs. It is noteworthy that the drug did not exhibit effects expected of a feed intake stimulant under the conditions of the present experiment. It is possible that the experimental temperature of this experiment (35 C) could have erased whatever effects the drug could have at 32 C, for example. But from the results of this work the role of Elfazepam (as a feed additive or any other form of application) especially under stressful environmental heat conditions is highly doubtful.

TABLE 11

Effects of Elfazepam on Lambs Maintained at 35 C

Item	Pre-experimental Interval n	Mean	SE	Experimental Interval n	Mean	SE
Rectal Temperature, C	16	40.3	.08	24	40.4	.06
Avg. Daily Wt. Gain, g	16	95	4.8	24	153[a]	4.2
Plasma Thyroxine (T_4), ng/ml	16	101.1	5.3	24	127.1[a]	4.3
Avg. Daily Feed Intake, g/kg$^{.75}$	8	72	.52	12	64[b]	.48
Avg. Daily Water Intake, ml/kg$^{.75}$	8	339	1.1	12	302[b]	1.2

[a] Means differ significantly from pre-experimental interval ($p < .01$)

[b] Means differ significantly from pre-experimental interval ($p < .05$)

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EFFECTS OF ELFAZEPAM ON THE PERFORMANCE OF GROWING LAMBS UNDER 35 C THERMAL STRESS

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The effects of Elfazepam on performance and plasma thyroxine (T_4)responses were studied in growing ewe lambs during a 12 week exposure to 35 C thermal stress. 16 lambs were involved in the experiment which was designed to consist of four intervals: a 2-week preconditioning interval during which all lambs were maintained at 15 C and introduced to experimental ration and bleeding procedure; a 4-week acclimation interval during which one group of lambs was exposed to 35 C and the other group remained at 15 C; a 6-week interval of Elfazepam administration; and a 2-week post-experiment interval. Two lambs each were housed in the pens of a controlled (± .5 C) walk-in type environmental chamber. Food and water were available ad lib The water intake of each pair was measured and recorded daily while feed consumption was measured and recorded weekly, both by difference. All lambs were sheared and weighed before initial introduction to the chambers and weighed once weekly thereafter. Jugular vein blood was collected from each lamb thrice weekly commencing 4 p.m, and rectal temperature was measured daily commencing at the same time. During the experimental interval Elfazepam was dissolved in propylene glycol (2 mg/ml) and administered orally twice daily to four lambs of each group at 8 mg/hd/da. The remaining 8 lambs received 4ml. of propylene glycol in two equal divided doses daily, each. Elfazepam treatment did not significantly affect feed and water intake of treated lambs, neither did it affect rectal temperature and plasma thyroxine (T_4) level. The drug significantly increased average daily weight gain of treated animals during the first week of treatment, but the effect was only short-lived and it disappeared by the third week of treatment. Concurrently, it increased feed efficiency of treated lambs,

but this effect was also transient and was not detectable after the second week of treatment. Similar effects were observed among lambs maintained at 15 C and 35 C. Exposure to 35 C significantly depressed plasma thyroxine level but after the initial depression the values returned to equal or higher than pre-exposure levels by the end of the twelfth week of exposure. A significant elevation of rectal temperature beyond pre-exposure values was also recorded at 35 C, along with a non-significant depression of feed intake and a significant elevation of water intake. The data from these studies suggest that Elfazepam may not be of much assistance in improving the feed intake and performance of animals exposed to stressful heat of long duration.