

Investigations on Spontaneous and Glucocorticoid Induced Glucosuria in the Bovine Animal*

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Introduction

The pathologic excretion of glucose in urine is encountered in a number of diseases in which either the glucose concentration in primary urine, due to an elevated blood glucose level, exceeds the reabsorption capacity of the kidney (e.g. diabetes mellitus and in other conditions where the so-called anit-insular hormones predominate), or the renal threshold is pathologically lowered (e.g. mercury and chromate intoxication) - so-called renal glucosuria. Some of these cases have already been described in the ruminant (5, 7, 8, 17). Central nervous disorders (e.g. rabies) can also lead to glucosuria - presumably due to stimulation of the cerebral glucose regulatory center (10, 15, 19). Transient glucosurias were observed following therapeutic glucose infusions, glucocorticoid therapy (2, 3, 8, 9, 22), and after transport (1, 12, 23, 24).

In 1977, during routine examination of bovine patients upon admission to the II. Medizinische Tierklinik at the University of Munich Veterinary School, it was discovered, using quick-test-sticks (Combur-8-Test, BOEHRINGERM, HRING), that 9% of the animals had glucosuria. Similar observations were made by MEHLS (16) in the Klinik fur Rinderkrankheiten at the Veterinary College Hannover. In both clinics it was observed that tests for glucosuria had become negative after two days.

Since the test sticks were originally intended for monitoring human diabetics, they have a lower limit of detection of around 50 mg/dl (2.78 mmol/l) urine glucose, as higher concentrations are considered pathologic in humans (18). These observations led the present investigation to ask whether a physiologic glucosuria can be expected in adult bovines, and whether application of trade name glucocorticoids in recommended dosages can lead to significant loss of glucose via the kidneys.

Materials and Methods

Seven 4 to 5½ year old cows from the German Simmental,

Brown Swiss and Holstein Friesian breeds were used in the experiments (VI - V7). The cows weighed between 425 and 730 kg, were clinically healthy, non-pregnant and non-lactating. The animals were fed a mixed ration consisting of 10 kg hay and 3 kg concentrates, and they had free access to water. Blood samples were taken from the jugular vein. Urine was collected quantitatively using a balloon urinary catheter which was connected via an extension tube to a container.

Blood and urine glucose concentrations were determined using the hexokinase method according to the directions of BOEHRINGER Mannheim (4). Direct absolute eosinophil counts were carried out in all blood samples using DUNGER's solution and a FUCHS-ROENDAHL counting chamber (21).

In order to eliminate the effect of possible diurnal variations in the parameters to be investigated, the first blood and urine samples were always drawn at 10 a.m. The urinary catheter was inserted at this time. Blood and urine samples were collected every 3 hours during the day, whereas nocturnal intervals were 6 to 8 hours. A double determination was carried out on each sample.

The individual experiments extended over a period of several days (usually about a week) and were concluded when blood and urine glucose levels reached the initial values. Each experiment was preceded by a 24-hour pre-trial period in order to insure that variations encountered later while under glucocorticoid treatment were not caused by other factors such as manipulation stress. After this 24-hour period the hormone under investigation was injected intramuscularly.

Each animal was allowed a rest period of at least two weeks between subsequent experiments.

Each of the following four preparations were investigated in a series of five experiments:

1. Dexamethasone-21-(3, 6, 9-trioxaundecanoate in alcohol solution (DEVAN-Hoechst), later referred to as preparation A. Dosage: 5mg/100 kg body weight.
2. Dexamethasone-21-isonicotinate in suspension (VOREN-Boehringer), later referred to as preparation B.

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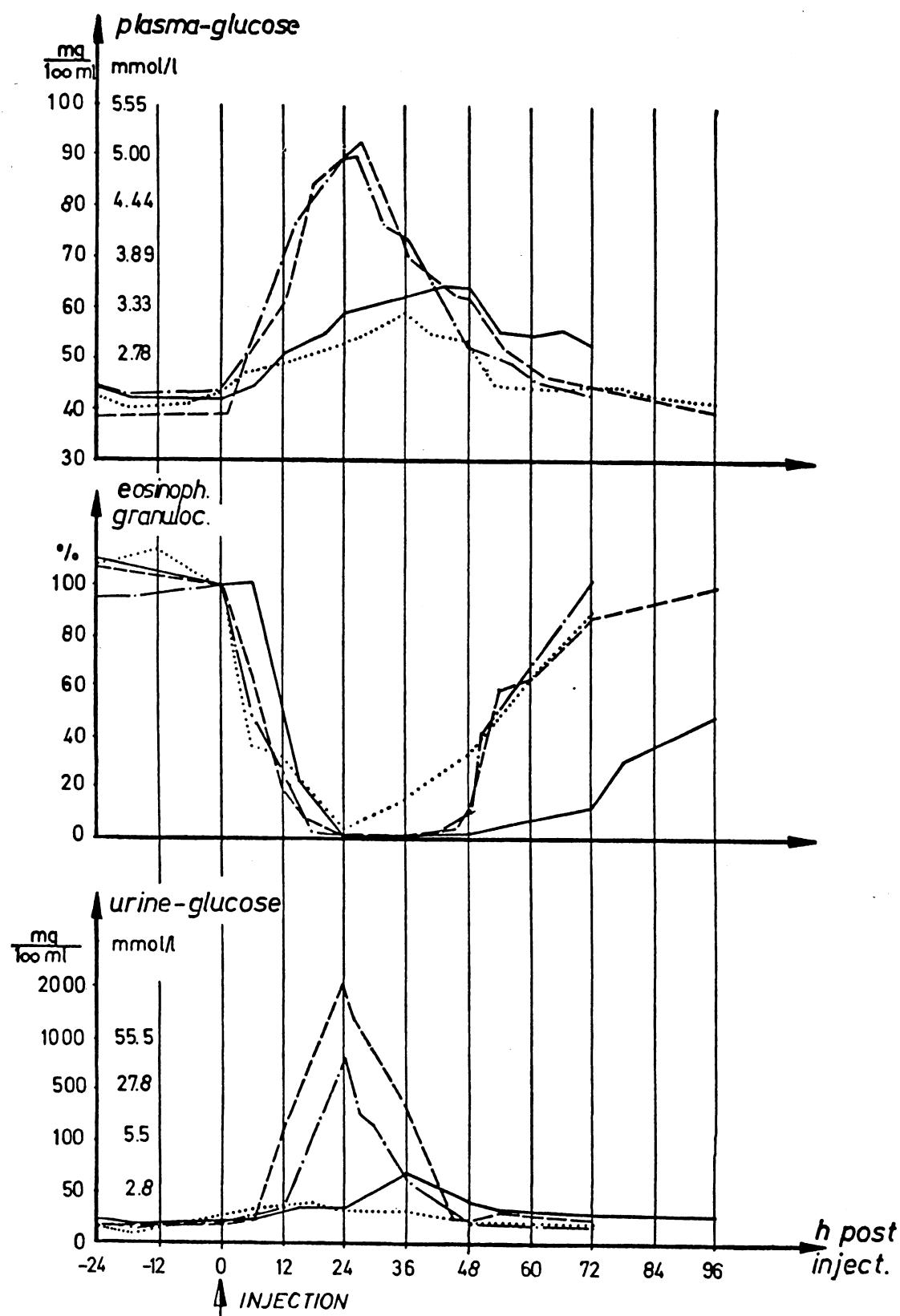


Figure 1: Average values of blood and urine glucose concentrations (mg/dl, mmol/l) and of eosinophil counts (% of initial values) following glucocorticoid treatment in four test groups.

Dosage: 15 mg/animal.

3. Dexamethasone-21-o-phosphate in solution (FORTECORTIN-Merck), later referred to as preparation C. Dosage: 20 mg/animal.
4. Prednisolone acetate (1-dehydro-hydrocortisone-acetate) in suspension (HOSTACORTIN-Hoechst), later referred to as preparation D. Dosage: 200 mg/animal.

Results

Average values from each of the four test groups are presented in Figure 1 and Table 1. Individual date can be found in SCHILLINGER's Dissertation (20). Absolute amounts of glucose excreted by individual animals are shown in Figures 2 through 5.

In the 24 hours prior to glucocorticoid application, measurable urine glucose concentrations were detected in all cases, ranging from 5.6 mg/dl (0.31 mmol/l) to 34.4 mg/dl (1.91 mmol/l). The corresponding absolute amount of glucose in the collected urine ranged from 0.6 to 2.7 g.

After application of preparation A, blood glucose levels increased on the average 150%, and urine glucose levels rose drastically to an average maximum of 2155 mg/dl (119.7 mmol/l). The values ranged from 48 mg/dl (2.67 mmol/l) to 5404 mg/dl (300.2 mmol/l). A similar marked blood glucose elevation was obtained with a 20 mg/animal dosage of preparation C. Average values from the five experiments showed that maximum blood glucose levels of 102% above starting values were induced. The corresponding urine glucose concentrations ranged from 524 mg/dl (29.1 mmol/l) to 2147 mg/dl (119.3 mmol/l).

In contrast to the previously mentioned experimental groups, preparation B did not create such a dramatic increase in blood glucose levels, resulting in a moderate glucosuria. On the average, a maximum blood glucose elevation of 54% over base values was observed. In all five experiments a weekly positive urine glucose reaction was detected using the test sticks.

The average blood glucose concentration of the five cows receiving preparation D was elevated to a maximum of 42% above initial values, and in only one case was the urine glucose concentration elevated above the lower limit of detection of the test sticks. Using the MANN-WHITNEY-WILCOXON test, blood glucose concentrations at 24 h and 48 h post inj. proved to be significantly higher than initial values for all groups ($p < 0.05$), except for group D (only values at 24 h significantly higher).

Absolute eosinophil counts dropped to practically zero for the period between 15 and 48 hours following application of the test glucocorticoids in all groups except the prednisolone group (preparation D) in which a much shorter and less pronounced reduction of circulating eosinophils was observed (Figure 1).

Discussion

Since the diagnostic application of enzyme tests has come into use in human medicine, it has been possible to demonstrate a permanent physiologic glucosuria (11, 18),

which on the basis of the present study was also found to occur in the bovine. The studies also show that application of glucocorticoids according to the manufacturers' recommendations can lead to an increased excretion of glucose in the urine. The results indicate that the level and length of glucosuria varied greatly between test groups and between individual animals. Although several cases were encountered in which values for glucose excretion remained within the normal limits outlined above, other cases were

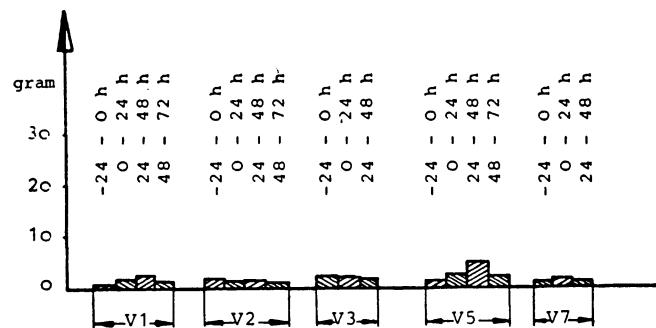


Figure 2: Absolute glucose losses (g) of five cows following administration of preparation A.

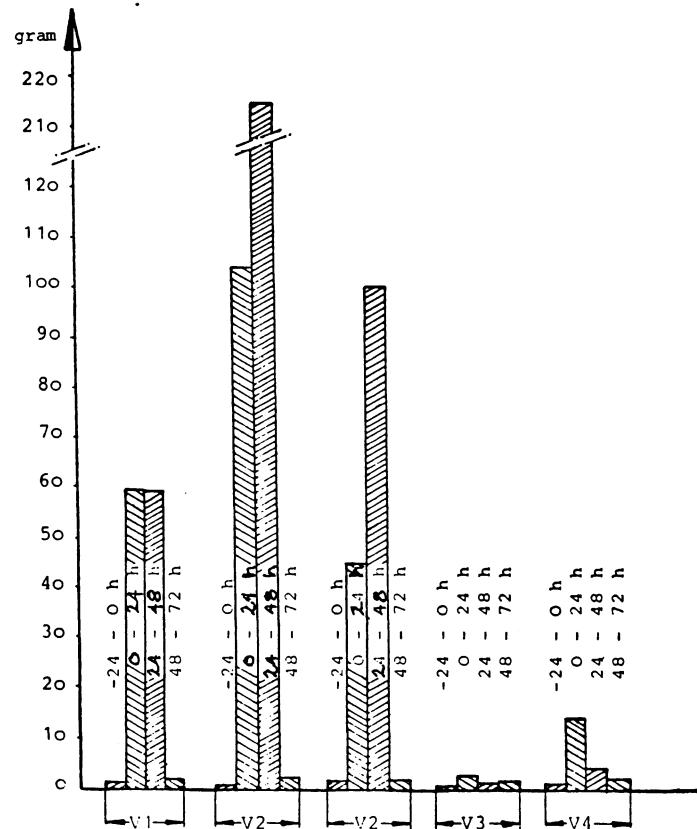


Figure 3: Absolute glucose losses (g) of five cows following administration of preparation B.

observed in which the upper limit of detection of the urine test sticks was exceeded. Furthermore the duration of glucosuria was directly proportional to the level and duration of blood glucose increase. The following factors must be considered as possible causes for the marked differences in urine glucose concentrations:

1. Varying effects of different glucocorticoids on the blood glucose level (e.g. because of the different galenic preparation - solution vs. suspension).
2. Individual characteristics of the animals, and
3. Daily variations in urine quantity (influenced by fluid intake).

The individual differences in maximum urine glucose concentrations are reflected also in the absolute amount of glucose excreted and the duration of detectable glucosuria (which is natural, as the absolute amount is a function of the other two parameters) (Figures 2 to 5). These figures clearly show the marked influence of individual factors on glucocorticoid action. As can be seen from the application of preparation A to experimental animal V2 (Figure 3), the action of a particular glucocorticoid can vary even though the same dosage was applied to the same animal in two consecutive experiments.

The quantitative determination of glucose loss in collected urine revealed that experiments with preparation A led to the largest total amounts of glucose excreted (Figure 3). Almost equally high losses were observed during treatment with preparation C (Figure 5). On the other hand, preparations B and D (Figures 2 and 4) never resulted in a high enough glucose loss to significantly influence the energy balance. The largest quantity of glucose excreted in a 48 hour period was 320 g (V2, preparation A). This example shows that under glucocorticoid therapy (in therapeutic doses) glucose losses can occur, which must be taken into consideration. The significance of these losses becomes clearer when one compares them to the total daily glucose turnover, which ranges from 1500 to 2000 g in a fresh cow. This amount of glucose lost in the urine has to be synthesized via gluconeogenesis, and thus creates an unnecessary metabolic strain. It should also be pointed out that 200 g of glucose is normally infused in the treatment of acetonemia, which corresponds roughly to the amount of glucose that can be lost in the urine, as illustrated in these experiments. The extent to which similar results can be expected in high producing lactating cows remains to be investigated.

It can be concluded from the results that repeated hormone injections for the treatment of acetonemia is useless as long as diagnostic test sticks show the urine to be positive for glucose. A second glucocorticoid injection within 48 hours of the first treatment is not indicated since most of the hormones used in the treatment of acetonemia are long-acting preparations. A glucocorticoid overdose should also be avoided because the resulting hyperglycemia may have detrimental effects. KURZWEG *et al.* (14) and KRONFELD (13) observed that plasma glucose levels

above 85 mg/dl (4.72 mmol/l) could cause reduced rumen motility eventually leading to ruminal stasis in two to three days. Dirksen (6) also suspects that hyperglycemia negatively influences abomasal motility.

As to the finding of transient glucosuria in hospitalized bovine patients, no correlation to certain diseases could be established. This is in accordance with the results of MEHLS (16). However, anamnestic investigation revealed previous administration of glucocorticoids or glucose by the practitioner in a number of cases. For the rest of the cases a transport induced hyperglycemia is assumed to be responsible - the transport by motor vehicle acting as stressor (in the sense of the general adaptation syndrome of SELYE). Further investigations in this direction are being conducted.

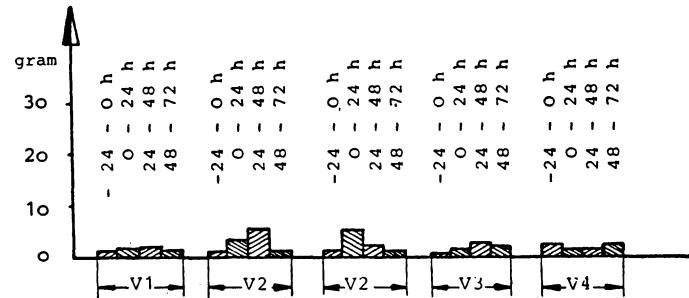


Figure 4: Absolute glucose losses (g) of five cows following administration of preparation C.

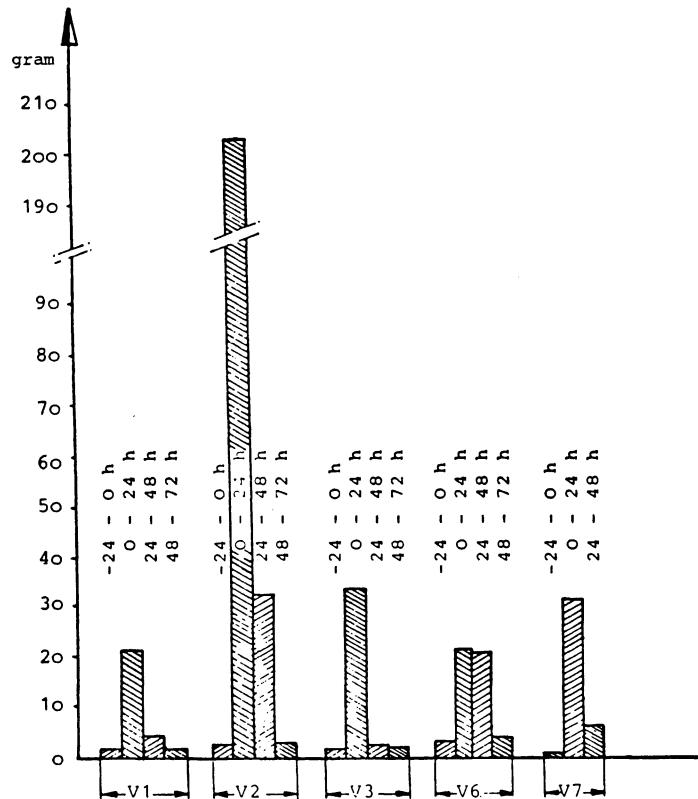


Figure 5: absolute glucose losses (g) of five cows following administration of preparation D.

TABLE I. PARAMETERS OF GLUCOSE EXCRETION

Preparation	Dosage	Average maximum of blood-glucose (% of initial values)	Average maximum of urine-glucose (mg/dl, + s)	Absolute glucose excretion (g/48 h, + s)
A (solution)	5 mg/100 kg	150.6 + 45.8	2156 + 2353	121.2 + 126.8
B (suspens.)	15 mg/animal	53.7 + 17.7	97.6 + 51.6	5.3 + 2.4
C (solution)	20 mg/animal	102.6 + 29.6	989 + 656	74.5 + 89.4
D (suspens.)	200 mg/animal	41.6 + 23.2	48.0 + 10.6	4.5 + 2.1

SUMMARY

A physiologic glucosuria of 5.6 mg/100 ml (0.31 mmol/l) up to 34.4 mg/100 ml (1.91 mmol/l) can be demonstrated by enzymatic methods in cows. Thus commercial sticks for urinalysis are also suitable for the detection of pathologic glucose excretion in cattle, as their lower limit of detection is around 50 mg/100 ml (2.78 mmol/l).

Following intramuscular application of dexamethasone-21-(3, 6, 9-trioxaundecanoate) (DEVAN-Hoechst, solution; 5 mg/100 kg body weight), dexamethasone-21-isonicotinate (VOREN-Boehringer, suspension; 15 mg/animal), and dexamethasone-21-O-phosphate (FORTECORTIN-Merck, solution; 20 mg/animal) to cows increased glucosuria occurred in all of 5 experiments per preparation. Glucosuria could not be observed after application of prednisolone acetate (HOSTACORTIN-Hoechst, suspension; 200 mg/animal). The level and duration of glucocorticoid induced glucosuria varied greatly between animals and preparations. The amount of glucose excreted seems to depend mainly upon the level and duration of the induced hyperglycemia.

Total glucose losses after application of glucocorticoids varied between the physiologic basal excretion of 0.6 to 2.7 g and 215.5 g in 24 hours, depending upon individual characteristics of the test animals and gradually different effects of the individual drugs on blood glucose level (e.g. due to different galenic preparation.).

Glucosuria could be detected by the means of urinalysis sticks in 9% of all bovine patients (calves, heifers, cows, and bulls) admitted to the II. Medizinische Tierklinik of the University of Munich in 1977. In all cases detectable glucose excretion had ended after two or three days. In part of the patients the transient glucosuria was of iatrogenic origin (previous administration of glucocorticoids or glucose by the practitioner).

For the rest of the cases a transport induced hyperglycemia is assumed to be responsible.

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