EFFECT OF INTRAVENOUS INFUSION OF GLUCOSE AND/OR FRUCTOSE ON THE COMPOSITION OF BLOOD PLASMA AND THE CLINICAL RESPONSE OF THE CALF

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Résumé

EFFET D’UNE PERFUSION INTRAVEINEUSE DE GLUCOSE ET/OU DE FRUCTOSE SUR LA COMPOSITION DU PLASMA SANGUIN ET LA REPONSE CLINIQUE DU VEAU. — Des perfusions intraveineuses de glucose (0,4 g/kg) ou de glucose (0,4 g/kg) + fructose (en général 1 g/kg) à des veaux ont été suivies de manifestations cliniques différentes selon les animaux, allant de l’absence de réaction jusqu’à la mort dans certains cas.

Fructosémie. La perfusion du mélange fructose + glucose entraîne une fructosémie maximale inférieure à celle observée après perfusion de glucose seul, sauf chez les veaux qui sont morts après la perfusion et chez les nouveau-nés (âgés de moins de 36 h) dont la fructosémie initiale n’était pas nulle.

Glycémie. En aucun cas, le fructose associé au glucose n’a éliminé le rebond hypoglycémique que l’on rencontre habituellement après une perfusion de glucose seul. Les animaux qui sont morts ont montré une hypoglycémie particulièrement prononcée (0,4 g/l).

Introduction

In therapeutics, the parenteral administration of sugars has two main objectives:

1° to cover the energy needs of a body in a state of partial starvation, and
2° by covering the energy needs, to save the break down of protein.

When stress occurs, glucose metabolism is disturbed and gluconeogenesis from amino acids is increased. These disturbances cannot be corrected by increasing the supply of glucose as the use of glucose decreases in relationship with the increase in supply to the body (Heller, 1974).

Other substrates have been proposed, such as fructose, xylitol and sorbitol. One of the advantages of these substances is that their conversion to glucose does not occur instantaneously and hence the regulatory mechanisms of glucose concentration are less perturbed.

Calves with diarrhoea are often in a state of hypoglycaemia (Tennant et al., 1968) and in a condition comparable to that of hypovolemic shock. One might well wonder, under these conditions, if the substitution of other carbohydrates than glucose may not be better adapted for treatment.

The purpose of this experiment was thus to compare the effects of administering high levels of glucose, fructose and glucose and fructose together on the behaviour and the blood glucose level of healthy and diarrheic calves.
Materials and methods

Animals
Six diarrheic calves and twenty one (21) healthy calves of both sexes received one or two intravenous infusions of glucose and/or fructose. The calves used and the treatment they received are summarised in table 1.

Feeding
1° Calves with diarrhoea were suckled by their dams (experiment carried out in the field in a suckler herd). All calves had received colostrum at birth.

2° New-born calves received colostrum from their dams after the infusion.

3° The calves aged between 1 and 3 weeks received reconstituted milk starting with a concentration of 120 gms of milk powder mixed with 880 gms of water. Some calves were fed approximately 2 1/2 hours before the perfusion. Others were perfused 15 hours after their last feed. All calves had received colostrum at birth.

The calves in the last two groups were of varying breeds, mostly milk breeds. The experiments were carried out at the laboratory.

Composition of the infusions
The composants of analytical quality were dissolved in distilled water. The solutions were prepared immediately before use. The dose administered, expressed in gms/kilo live weight, is shown in table 1.

When the solutions contained only one of the two sugars their osmotic pressure was brought to isotonicity by the addition of NaCl. Each infusion consisted of 1 litre. The infusions were carried out in a jugular vein using a regular flow rate so that the time of administration was about an hour. The liquid was heated to 40 °C by passing it through a coil held in a water bath at this temperature.

Blood samples
Blood samples were taken by means of a catheter fixed in the other jugular vein. Before each sample was taken the catheter was rinsed with heparinized physiological saline. As a rule, 15 to 18 blood samples were taken from each calf during the 24 hours following the perfusion. The first five samples were taken during the two hours following the end of the perfusion. The blood was collected in heparinized tubes and centrifuged at 9 600 g for 15 minutes. The plasma thus separated was then stored at 18 °C until analysis.

Analysis
Blood sugar analysis was carried out using an automatic «Technicon» as developed by Michel (1971).

Glucose was measured using the glucose-oxidase enzymic method.

Fructose was measured by the optical density method as follows. The plasma containing fructose was heated in the presence of phosphoric acid, the dehydrated product hydroxymethyl-5-furfural being formed. This derivative then was combined with thiobarbituric acid to form a yellow substance whose optical density at 420 nm was then measured. A comparison of the average values obtained was carried out using the t test. The slope of the curves of the dispersion for the sugars injected were compared by an analysis of the covariance (Snedecor and Cochran, 1971). The average values are expressed with their standard deviation.

Results
A. The animals' reactions
1° The diarrheic calves showed no sign of pain during the perfusion. One of them died 5 days after the experiment. Another was slaughtered after developing respiratory complications.

2° The new-born calves showed no appreciable clinical reactions.

3° In the group of young animals, 7 died after the glucose or glucose + fructose perfusions. In one of the cases the time laps between the perfusion and death was 5 days. Thus death could have been due to several causes. However in two other cases, it would be seem that death could be directly attributed to the perfusion, the animals dying within 45 hours of the perfusion. The four other calves died two or three days after the perfusion. All animals which died were male. For all of them it was their first perfusion and there was always glucose in the solution.

B. Evolution of the blood fructose concentration
In calves 33 hours old and older there was no blood fructose before the infusion.
TABLE 1
Characteristics of the experimental animals and of the treatments.

<table>
<thead>
<tr>
<th>Groups of animals</th>
<th>Treatment g/kg body weight</th>
<th>Breed (*)</th>
<th>Sex</th>
<th>Age (d)</th>
<th>Weight (kg)</th>
<th>Notes (**)</th>
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<td>9</td>
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</table>

*: Au = Aubrac, BA = Brune des Alpes, Ch = Charolais, J = Jersiais, Lm = Limousine,
PN = Black Pied, PR = Red Pied, SI = Salers.
**: 1 = 1st perfusion; 2 = 2nd perfusion; + = dead calf; T = Twin.
1. After fructose alone.

In 4 fed calves the infusion with fructose alone gave a maximum blood fructose concentration of $1.84 \pm 0.03 \text{ g/l}$. The half-life of the fructose was between 16 and 39 minutes (fig. 1A, group 3.4).

2. After fructose + glucose.

2.1. In the three surviving fed calves, the infusion of fructose + glucose caused a blood fructose concentration of $1.26 \pm 0.10 \text{ g/l}$ with a half-life between 16 and 30 minutes (fig. 1A, group 3.2).

The fructose concentration is significantly less than in the previous group but the half-life of fructose is not changed.

2.2. In 4 fasting calves the blood fructose concentration at $1.09 \pm 0.15 \text{ g/l}$ and the half-life $20.6 \pm 4.2$ minutes were similar to those of the fed calves (compare fig. 1B, group 4.2 ; fig. 1A, group 3.2).

It would seem that glucose increases the space of diffusion of the fructose without altering the clearance rate. Fasting of calves had no noticeable influence on this phenomena.

2.3. In the three fed calves (fig. 1C) which died after the infusion of fructose + glucose, the blood fructose concentration went up to $1.86 \pm 0.13 \text{ g/l}$, a level which is significantly higher than in the surviving calves and is similar to the level in the group which had received fructose alone. The half life of fructose varied from 27 to 54 minutes, but is not significantly different from the other groups.

In these calves it seems that glucose did not increase the space of diffusion of fructose as was the case in the surviving group of calves.

2.4. In 3 fasting newborn calves, after an infusion of fructose + glucose, the blood fructose concentration went up to $1.86 \pm 0.13 \text{ g/l}$, a level which is significantly higher than in the surviving calves and is similar to the level in the group which had received fructose alone. The half life of fructose varied from 27 to 54 minutes, but is not significantly different from the other groups.

In these calves it seems that glucose did not increase the space of diffusion of fructose as was the case in the surviving group of calves.

2.5. In 6 diarrheic calves (group 1.0) after a perfusion of fructose + glucose the blood fructose level reached $0.82 \pm 0.18 \text{ g/l}$ with a half-life for fructose varying between 11 and 48 minutes. Seeing that the quantity of fructose administered was only $0.75 \text{ g/kg body weight}$ it is to be expected that the maximum blood fructose level was approximately 25% less than in groups 3.2 (fig. 1E) and 4.2 (fig. 1F).

C. Evolution of the glycaemia

1° After infusion of fructose alone (fig. 2A, group 3.4).

The infusion of fructose was immediately followed by a hypoglycaemia. The lowest blood glucose level was found 5 hours after the end of the perfusion at $0.64 \pm 0.13 \text{ g/l}$.

2° After infusion of glucose alone.

In all cases the infusion of glucose was followed by a hyperglycaemia. In 3 new-born calves (fig. 2B, group 2.2), the blood glucose level at the start was $0.82 \pm 0.08 \text{ g/l}$ and reached $1.40 \pm 0.24 \text{ g/l}$ which rapidly dropped, the minimum level being reached at $0.55 \text{ g/l}$, 2 hours after the end of the infusion. During this period the half-life of plasma glucose varied from 0.97 hours to 3.13 hours. From that moment on the blood glucose level increased during the following 18 hours.

2.2. The 4 fasting calves (fig. 2A ; group 4.1) experienced the same changes in the blood glucose level. The calf which died 5 days of the experiment was not different from the others and is thus included in this group. The initial blood glucose level was $0.94 \pm 0.05 \text{ g/l}$. At the end of the infusion, the blood glucose level had reached its maximum at $1.63 \pm 0.25 \text{ g/l}$ which then fell 3 hours later to a level inferior to the initial level ($0.68 \pm 0.08 \text{ g/l}$) and stayed at this level until next fed.

2.3. The group of 3 fed calves (group 3.3) was too uneven (1 living, 2 dead) to draw any conclusions.

3° After infusion of glucose + fructose

3.1. New born calves (fig. 2B, group 2.1).

In these three calves, the hyperglycaemia observed was comparable to that seen in group 2.2 (new-born, glucose alone) but the resulting hypoglycaemia was a lot more pronounced, the minimum level being found 5 hours after the perfusion at $0.29 \text{ g/l}$. The half-life varied between 1.27 and 2.14 hours.

The presence of fructose is again shown to favourise the hypoglycaemia.

3.2. Fasting calves (fig. 2C, group 4.2).

It is in this group that the hypoglycaemia was found to be particularly marked as
Fig. 1: Changes in blood fructose level after an intravenous infusion of fructose or fructose + glucose, in calves.

A: comparison between fructose (3.4) and fructose + glucose (3.2) [fed calves].
B: comparison between fructose (3.4) [fed calves] and fructose + glucose (4.2) [starving calves].
C: comparison of fructose + glucose between dead (3.1) and surviving (3.2) [fed calves].
D: comparison of fructose + glucose between newly-born (2.1) and older (4.2) [starving calves].
E: comparison of fructose + glucose between healthy (3.2) and diarrhoeic (1.0) [fed calves].
F: comparison of fructose + glucose between healthy starving calves (4.2) and diarrhoeic fed calves (1.0).

i: Infusion.
Fig. 2: Changes in blood glucose level in calves, after an intravenous infusion of fructose and/or glucose. For the meaning of groups (gr.) see table 1, or the legend of fig. 1.

M: meal.
I: infusion.
3 hours after the end of the infusion the plasma concentration of glucose was only 0.38 ± 0.12 g/l.

After a meal however these calves regained a blood glucose level comparable to that of the other groups.

3.3. Fed calves surviving (fig. 2C, group 3.2).

The graph of the blood glucose level against time in this group is no different from the others except for the fact that the hypoglycaemia lasted for less time in the fed calves than in the fasting calves (P < 0.05).

3.4. Fed calves which died (fig. 2D, group 3.1).

This group showed a very marked hypoglycaemia, comparable to that in the fasting calves. However there was a difference between them in so far as the blood glucose level after a meal returned to a level inferior to the normal as was the initial blood glucose concentration. A complete collapse of blood glucose then followed in a few hours leading to the death of the animal.

3.5. Diarrheic calves (fig. 2D, group 1.0).

Before the infusions the average blood glucose level was 0.81 ± 0.12 g/l. The lowest blood glucose levels were found in the clinically sickest calves.

At the end of the infusion the averaged blood glucose level had increased to 1.72 ± 0.23 g/l but two hours later the blood glucose level had fallen to its initial concentration although a slight increase occurred during the following 7 hours.

In the sick calves the dip in the curve for the blood glucose concentration was not as pronounced as in the other calves.

It is not possible to calculate the average half-life for glucose during the period of rapid dispersion as the variability between the animals would not permit it. However, one can say roughly speaking, that it is in the order of 2 hours no matter what the age of the calf. In the diarrheic calves there was a tendency, non-significant, for the half-life to be somewhat shorter (from 0.49 hours to 2.05 hours).

**Discussion**

The group of new-born calves stands out from the others on two points. Firstly the blood fructose concentration was greater and secondly by the slowness by which the fructose disappeared from the plasma (fig. 1D). Why there should be an increase in the metabolic activity towards fructose, with age, in the calf is not clear. However Ballard and Oliver (1965) have shown that fructose is metabolized more quickly by the liver of lambs a few days old than by the liver of new-born lambs, and that strangely enough, that the necessary enzymes for the metabolism of fructose only appear when there is no more fructose in the blood.

It should also be noted that the calves which received fructose alone had a blood fructose concentration higher than that seen in the group of calves which received a mixture of glucose + fructose.

Glucose probably increases the diffusion space of fructose by its property of stimulating the secretion of insulin. It is well known that insulin favours cellular penetration of sugars (Levine and Goldstein, 1955).

The fact that the calves which died (glucose + fructose) reached a high blood fructose concentration (fig. 1C) comparable to that seen in the calves which had received only fructose, could signify that these calves were « immature » and incapable of responding to the perfusion of glucose by the release of insulin. But in that case why had they a lower blood glucose concentration after feeding? (fig. 2D) [table 2].

One might give the following explication: a hypoglycaemia is produced 2 to 3 hours after an oral administration of glucose which results in a hypersecretion of insulin (Veverbrants et al., 1969). This is the same time lapse which occurred between the meal and the initial blood glucose concentration reading in these calves.

Consequently one might envisage that the pancreas, being partly « worn out », was incapable of producing sufficient insulin. Insulin being the factor which determines the diffusion space of fructose. This hypotheses is even more persuasive knowing that the level of plasmatic insulin is much less after an intravenous administration of glucose than after oral ingestion of glucose (Elrick et al., 1964).

However, on the other hand, the following meal seems to have started a fatal hypoglycaemia. The fact that no deaths occurred in the group of new-born calves in which very low blood glucose levels were recorded (fig. 2B) may be explained by the fact that during the first few hours following birth the calf is very resistant to a hypoglycaemia (absence of clinical signs). This phenomena
is transitory and depends on the secretion of adrenaline by the adrenal medulla associated with the high concentration of lactate (Comline and Edwards, 1968).

Fructose, alone or associated with glucose, caused within three hours of the end of the perfusion such a drop in the blood glucose level that the levels recorded at this time were less than the initial levels, apart from the diarrhoeic calves which regained the initial levels. These results confirm those obtained by Edwards and Powers (1967) and Sasaki et al. (1971) in new-born calves. According to Edwards and Powers, the hypoglycaemia found in this case is not due to insulin for they found no increase in the level of insulin in jugular blood taken during the course of the infusion. However, Edwards (1970) has shown in some later experiments that the concentration of insulin in the portal vein can increase quite significantly. Finally, it has been shown in man that the insulin secretory action of fructose is in direct correlation with the blood glucose concentration before the perfusion (Dunnigan and Ford, 1975).

**Conclusion**

At the doses used, fructose associated with glucose did not considerably modify the shape of the curve for the variations of the blood glucose concentration. In any case fructose did not eliminate the rebound of hypoglycaemia following a perfusion of glucose.

The deaths which were found in the fed calves associated with a hypoglycaemia could be attributed to a physiological derangement characterised by a hypersecretion of insulin. Further studies, with particular reference to the dosage of insulin are necessary to better understand this phenomenon. Moreover, glucose tolerance tests might well be carried out in order to find out the frequency of such anomalies in the calf.

(Accepted for publication, March 1977.)
Summary

Intravenous infusions of glucose (0.4 g/kg) or glucose (0.4 g/kg) + fructose (usually 1 g/kg) to calves were followed by various clinical reactions from absence of reaction up to death of a few calves.

Fructosemia.

After fructose + glucose infusion, the blood fructose concentration reached a level inferior to the highest value observed after only glucose infusion, except in the calves dead after the perfusion and in the newly-born calves (the initial fructose concentration was not nil).

Glycaemia.

In any case, fructose associated with glucose, did not eliminate the rebound of hypoglycaemia following usually a perfusion of glucose. In calves where the death occurred, the hypoglycaemia was specially marked.

Références


