HEPATIC BIOTRANSFORMATION RATE IN CALVES FED FOOD RATIONS WITH PROTEIN OR CARBOHYDRATE SUPPLEMENTS

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Abstract

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The purpose of the study was to evaluate (on the basis of pharmacokinetics of antipyrine) the hepatic biotransformation rate in calves in neonatal period. The calves received supplementary casein or glucose in their food ration. It was found that an increased protein content in the diet significantly increased the hepatic biotransformation rate as indirectly indicated by the monooxygenase activity linked to cytochrome P-450. Increased carbohydrate content in the diet produced an opposite effect upon the activity of the system. From these results it can also be concluded that a high-protein diet would increase whereas a high-carbohydrate diet would decrease the metabolism of other of drugs in calves, provided they would undergo the same biotransformation process as antipyrine does.

Antipyrine, neonatal period, casein, glucose, liver, MFO system

The liver is responsible for the greater part of the metabolism of a number of drugs and endogenous substrates via the cytochrome P-450 dependent hepatic microsomal monooxygenase (MFO) system (Danhof and Teunissen 1984; Poulsen and Loft 1988; Viktorov and Rybak 1990; Hartleb 1991). Antipyrine is widely used as a model substrate for cytochrome P-450 dependent metabolism (Poulsen and Loft 1988; Loft 1990). Antipyrine is eliminated primarily via hepatic metabolism, has a low intrinsic clearance and is negligibly bound to tissue and plasma proteins (Danhof and Teunissen 1984; Loft 1990; Janus et al. 1991). The compound is almost completely metabolized in the liver by at least three oxidative reactions with rapid renal elimination of these metabolites (Viktorov and Rybak al. 1990; Hartleb 1991). Estimates of half-life and metabolic clearance of antipyrine have therefore been used to assess the drug metabolizing activity of the liver in man and animals and its modification by genetic and multiple environmental factors (Penno and Vesell 1983; Danhof and Teunissen 1984; Vesell 1984; Kalow 1987; Poulsen and Loft 1988; Loft 1990).

The effects of changes in dietary macronutrient composition on the hepatic microsomal enzymes have been studied extensively in man and laboratory animals (Campbell and Hayes 1976; Campbell 1977; Anderson et al. 1979; Krishnaswamy et al. 1984; Alvares et al. 1986; Bidlack et al. 1986; Young and Yoo 1988; Pantuck et al. 1989; Butler and Dautermann 1990; Pantuck et al. 1991). These studies show that protein and carbohydrate content in diet influence the activities of these enzymes.

The aim of this study was to determine hepatic biotransformation rate in neonatal calves that received supplementary casein or glucose in their food ration. On the basis of antipyrine test an attempt is made to explain whether, and if so, to what extent the increase of protein or carbohydrate content in the diet influenced the activity of hepatic microsomal monooxygenases in young calves.

Materials and Methods

The experiment was carried out on 30 clinically healthy calves of lowland black and white breed, aged 5-19 days. During the experiments the animals were kept in standard rearing conditions. The calves were divided (by "randomization method") into three groups: "control", "experimental I", and "experimental II" with 10 individuals in each.

Throughout the experiment, the calves were fed the following food rations:

a) standard diet (control group): 1 kg of whole milk powder dissolved in 8 l of water (protein 280 g, carbohydrates 400 g, fat 260 g). The energy content 21200 kJ.
b) "casein" diet ("experiment I" group): standard diet + 70 g (25% of the total protein content) of casein (BDH Chemicals Ltd.), (protein 350 g, carbohydrates 400 g, fat 260 g). The energy content 22400 kJ.
c) "glucose" diet ("experiment II" group): standard diet + 100g (25% of the total carbohydrate content) of glucose (POCH Gliwice), (protein 280 g, carbohydrates 500 g, fat 260 g). The energy content 22900 kJ.

Calves in the control group were fed the standard diet throughout the experiment. Calves in the "experiment I" group received additional casein in their food ration for the first 7 days of the experiment, and for the next 7 days they were switched to the standard diet. Calves in the "experiment II" group received additional glucose in their food ration for the first 7 days of the experiment, and for the next 7 days they were switched to the standard diet. Antipyrine test was carried out on the 5th, 12th and 19th days of life. In calves in the experimental groups, the test was performed before feeding the experimental diet (day 5 of life), then immediately after the end of feeding the experimental diets (day 12), and one week later (day 19).

Before the blood collections began, a polyethylene cannula was inserted into the vena jugularis externa. During the experiment, the animals did not obtain any drugs that could interfere pharmacokinetically with antipyrine. Antipyrine (Phenazone - Sigma Chem. Co.) was administered intravenously at a dose of 15 mg/kg body maass in a sterile solution. Blood samples were collected at time "0" and 1,2,3,4,5,6,8,12,18 and 24 hours after antipyrine administration. Blood samples were collected into test tubes with heparin (250 I.U. Heparinum - Polfa). Plasma was separated at stored at -20 °C until analysed.

Antipyrine concentration in plasma was determined using spectrophotometric method according to B r o d i e et al. (1949). The pharmacokinetics of antipyrine was calculated according to one-compartment open model (D a n h o f and T e u n i s s e n 1984; L o f t 1990; H a r t l e b 1991). Elimination coefficient (k) and antipyrine initial concentration (C_0) were calculated by least squares regression analysis from the plasma concentration (C) versus time (t) curves. Other parameters of antipyrine pharmacokinetics (V_d - volume of distribution, -Δ-coefficient of distribution, $t_{0.5}$ - half-life, Cl_A - metabolic clearance) was calculated according to the following formulae:

$V_d = D/C_0$; $\Delta = V_d/b.m.t_{0.5} = 0.693/k$; $Cl_A = V_d * k$;

in which:

D = the given dose of antipyrine; b.m. = body mass.

Area under the plasma concentration versus time curves (AUC; $0 \rightarrow \infty$) was calculated according to the log-linear trapezoidal rule (T e u n i s s e n et al. 1985).

In control calves and "experiment I" group, the urea concentration and total protein content in plasma were determined every 48 hours throughout the experiment. In control calves and in those of the "experiment II" group, glucose concentration in whole blood were also determined. For statistical analysis the paired Student t-test was used.

Results and Discussion

Total protein content in plasma of control and "experiment I" calves did not differ significantly, fluctuating between 64.8-68.2 g/l (control group) and 63.8-68.2 g/l ("experiment I" group). No influence of the increased content of protein in diet on urea concentration in the plasma was observed (3.10-3.61 mmol/l - control group; 3.05-3.48 mmol/l - "experiment I" group), see Table 1.

Blood glucose concentration in control and "experiment II" calves did not differ significantly, fluctuating between 4.00-4.47 mmol/l (control group) and 4.04-4.47 mmol/l ("experiment II" group), see Table 2.

Increased protein content in calves food ration did not cause statistically significant changes of the initial concentration, volume of distribution and antipyrine distribution coefficient (Table 3). This observation is in agreement with data presented by A n d e r s o n et al. (1979) and K a p p a s et al. (1976). They proved in man that "high protein" diet does

Table 1

Urea concentration (mmol/l) and total protein content (g/l) in plasma in calves of the control group "C" (n = 10, $\bar{x} \pm SD$) and in "Experiment I" group („EXP I") (n = 10, $\bar{x} \pm SD$)

Calves group	Day of Life							
	5	7	9	11	13	15	17	19
Urea								
"C"	3.44 0.28	3.61 0.38	3.27 0.20	3.11 0.28	3.28 0.21	3.10 0.26	3.37 0.29	3.52 0.20
"Exp I"	3.25 0.29	3.48 0.33	3.11 0.28	3.05 0.18	3.34 0.20	3.28 0.28	3.30 0.26	3.44 0.22
Total Protein								
"C"	66.3 5.2	64.8 3.1	67.3 4.8	68.0 5.0	65.1 4.4	68.2 5.3	65.8 4.4	67.5 5.4
"EXP I"	65.5 5.8	63.8 3.9	66.4 4.7	67.2 5.0	65.4 3.9	67.8 5.5	66.0 4.8	68.2 5.2

Table 2

Glucose concentration in blood (mmol/l) in calves of the control group ("C") (n = 10, $\bar{x} \pm SD$), and of the "Experiment II" group ("EXP II") (n = 10, $\bar{x} \pm SD$)

Calves Group	Day of Life							
	5	7	9	11	13	15	17	19
"C"	4.25 0.26	4.40 0.31	4.11 0.40	4.08 0.28	4.28 0.31	4.47 0.26	4.11 0.19	4.00 0.24
"Exp II"	4.37 0.33	4.08 0.37	4.47 0.28	4.30 0.23	4.04 0.40	4.20 0.28	4.45 0.36	4.36 0.32

not cause statistically significant changes of V_d and Δ values. Pantuck et al. (1984) did not, however, notice any significant changes of Δ antipyrine in individuals receiving for 48 hours intravenous infusion of amino acid solution. Feldman et al. (1980) and Juan et al. (1986) reported that a 25% increase of protein content in the diet does not cause significant changes in distribution volume of theophylline in children and adults.

Increased carbohydrate content in the diet of our calves did not result in any significant changes of the volume of distribution (V_d) or antipyrine distribution coefficient (Δ) (Table 4). Similar results were obtained in man by Anderson et al. (1979) and Kappas et al. (1976). Similarly, Pantuck et al. (1984, 1989) did not find significant changes of the volume and coefficient of antipyrine distribution in individuals receiving intravenous infusion of glucose or dextrose.

The lack of an effect of increased protein or carbohydrate content in the diet on distribution volume of antipyrine in the examined calves indicated indirectly, that these „experimental diets" do not change significantly this pharmacological substance bound to plasma protein.

Feeding the calves a "protein-rich" diet for 7 days caused statistically significant decrease of antipyrine half-life (about 50% compared with the control group) (Table 3, Figs 1, 2). It indicates a relatively fast increase of microsomal monooxygenase activity linked by cytochrome P450. Alvares et al. (1986) and Anderson et al. (1984) administering to

Table 3
Pharmacokinetics of antipyrine in calves fed the diet with casein supplement „EXP I" (n = 10, $\bar{x} \pm SD$) and in calves of the control group "C" (n=10, $\bar{x} \pm SD$)

Pharmacokinetic Parameter		Day of Life		
		5	12	19
V_d(l)	"C"	26.6 3.1	29.5 3.4	32.2 3.8
	"EXP I"	27.5 3.3	30.8 2.9	33.0 2.9
Δ (l/kg)	"C"	0.74 0.05	0.72 0.06	0.70 0.04
	"EXP I"	0.73 0.04	0.73 0.05	0.69 0.03
$t_{0.5}$ (h)	"C"	10.6 1.3	10.0 1.1	11.0 1.2
	"EXP I"	10.0 1.0	5.0** 0.5	10.5 1.1
Cl_A (ml/min)	"C"	28.8 3.0	34.0 3.7	33.8 4.0
	"EXP I"	31.0 3.3	63.2** 4.6	35.0 3.1
AUC ($\mu g \cdot h \cdot ml^{-1}$)	"C"	316.5 31.5	298.9 30.0	329.5 31.8
	"EXP I"	300.2 29.5	159.9** 19.5	320.4 33.5

** - significant difference ($P \leq 0.01$), (paired Student t-test)

man diets containing 44% and 50% of protein, respectively, for 14 days observed the antipyrine $t_{0.5}$ decrease of 35% and 20% as compared to the initial values (standard diet). Earlier Anderson et al. (1979) showed, however, that (in man) there is a very high "individual sensitivity" of the MFO system to induction by increased protein content in food ration. These authors did not state any significant differences of half-life of antipyrine in individuals receiving a standard diet (30% of protein) and (for 14 days) "high protein" diet (50% of protein). Feldman et al. (1980) and Juan et al. (1986) administering to children and adults a diet with 25% increased protein content observed significant decrease of theophylline half-life. They also showed interindividual differences of up to 300% of $t_{0.5}$ values of the pharmacological substance. Pantuck et al. (1984, 1989) stated though, that in fact, "high-protein" diet decreased significantly half-life of antipyrine, however, within the examined population there were both individuals reacting to the diet, and individuals that did not react at all or only slightly. In our experimental calves fed a diet with addition of casein, no significant interindividual differences of antipyrine metabolism rate were stated. This indicated that MFO system in calves is characterized by considerably smaller (compared with man) individual differences as far as susceptibility to induction by nutritional factors (increase of protein content in food ration) is concerned.

The explanation of differences between antipyrine metabolism rate in calves receiving a protein-rich diet and in adult man ingesting such diet, is difficult and one has to be very careful. Factors to be taken into account are a great genetic polymorphism of cytochrome

Table 4
Pharmacokinetics of antipyrine in calves fed with food ration with glucose supplement "EXP II" (n = 10, $\bar{x} \pm SD$) and in calves from control group "C" (n=10, $\bar{x} \pm SD$)

Pharmacokinetic parameter		Day of Life		
		5	12	19
V_d(l)	"C"	26.6 3.1	29.5 3.4	32.2 3.8
	"EXP II"	27.1 3.3	30.0 2.9	32.0 2.9
Δ (l/kg)	"C"	0.74 0.05	0.72 0.06	0.70 0.04
	"EXP II"	0.73 0.04	0.72 0.05	0.69 0.03
$t_{0.5}$ (h)	"C"	10.6 1.3	10.0 1.1	11.0 1.2
	"EXP II"	11.0 1.0	15.0** 1.5	11.7 1.1
Cl_A (ml/min)	"C"	28.8 3.0	34.0 3.7	33.8 4.0
	"EXP II"	30.0 3.3	24.3** 2.6	32.0 3.1
AUC ($\mu g \cdot h \cdot ml^{-1}$)	"C"	316.5 31.5	298.9 30.0	329.5 31.8
	"EXP II"	330.2 29.5	449.8** 40.9	340.4 33.5

** - significant difference ($P \leq 0.01$), (paired Student t-test)

P450, and variable eating habits in adult man. These differences may also indicate that the increased protein content in the diet causes a faster and more distinct increase of activity of microsomal hepatocytes monooxygenases linked by cytochromes P450 in individuals in their neonatal period, compared with adult individuals. Unfortunately this suggestion cannot be confronted with data in references, since studies on the influence of protein addition to food ration on hepatic biotransformation rate both in neonates and in adult individuals are not available either in man or in any animal species. While evaluating the present results, one must also consider that the MFO system activity is genetically conditioned and it shows large "species difference" (Penno and Vesell 1983; Kalow 1987; Loft 1990; Pantuck et al. 1991).

Feeding the calves for 7 days the diet with 25% increased glucose content caused statistically significant increase of antipyrine half-life (about 50% compared with the values observed in control group) (Table 4, Figs 1, 3). This indirectly indicates a relatively fast decrease of microsomal monooxygenases linked by cytochrome P450 in examined calves. Anderson et al. (1979) and Kappas et al. (1976) have shown, however, that an increased antipyrine half-life of 50% in man requires at least twice as long (usually 14-day long) a period of high-carbohydrate diet administration. The comparison of our results with the above-mentioned ones conducted in adult men (Anderson et al. 1979; Anderson et al. 1984; Krishnaswamy et al. 1984; Anderson 1988) allows to put forward a hypothesis that the increased carbohydrate content in food ration causes a significantly

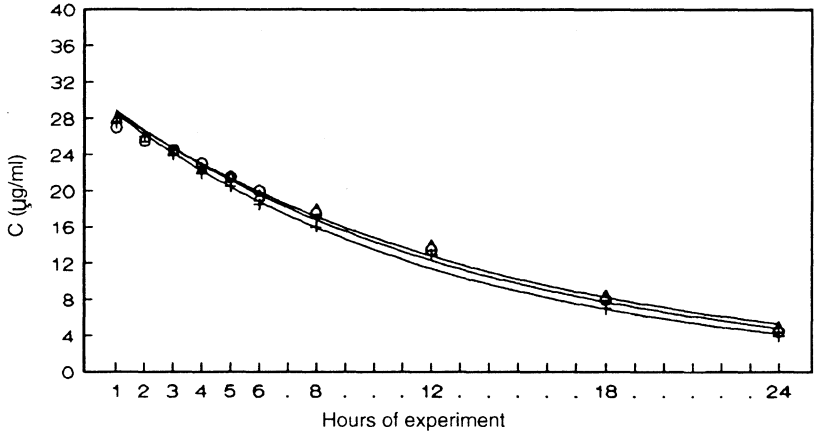

Fig. 1. Antipyrine concentration in plasma of calves of the control group (n = 10, $\bar{x}$). Legend: + day 5, Δ day 12, ○ day 19.

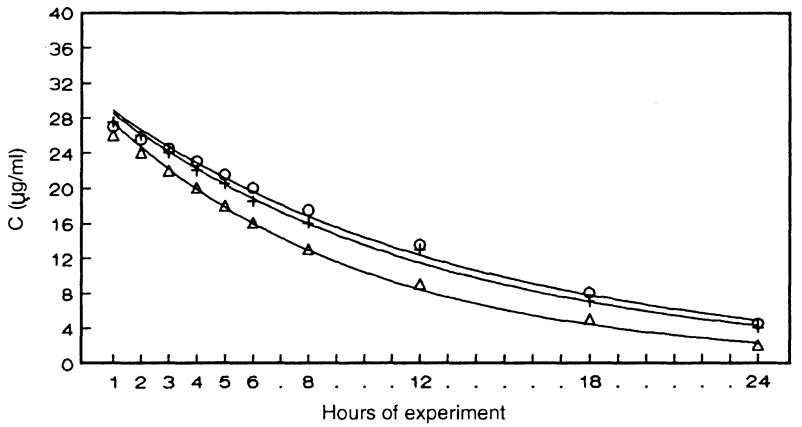

Fig. 2. Antipyrine concentration in plasma of calves fed the diet with casein supplement ("Experiment I" group) (n=10, $\bar{x}$). For legend see Fig. 1.

faster and more distinct decrease of MFO system activity in individuals in the early postnatal period, compared with adult individuals. Reading the results obtained one should, however, consider the existing species differences of microsomal monooxygenase activities (Penno and Vesell 1983; Kalow 1987), therefore confirming the above hypothesis, would require further experiments on the influence of high carbohydrate diet on hepatic biotransformation rate in older calves and adult cattle.

Significant increase of antipyrine values, observed in this experiment, as well as metabolic clearance and decrease of area under the antipyrine elimination curve (Table 3) in calves in "experiment I" points out indirectly a significant increase of monoxygenase ativity of hepatic microsomal cytochrome P450. Similar results were obtained in men receiving a high-protein dietin the study of Anderson et al. (1984) and Pantuck et al. (1984, 1989). These authors also proved that the induction of MFO system depends on the amino acid composition of the proteins in the diet. The significant decrease of values

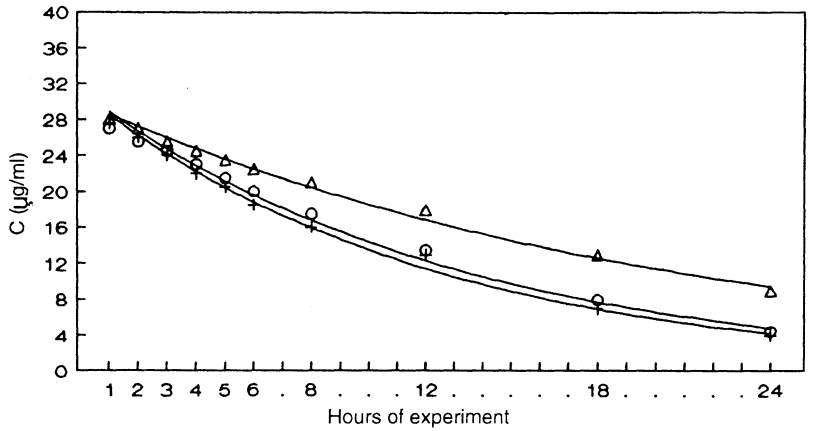

Fig. 3. Antipyrine concentration in plasma of calves fed the diet with glucose supplement ("Experiment II" group) (n = 10, $\bar{x}$). For legend see Fig. 1.

of antipyrine metabolic clearance and the increase of the AUC (Table 4) in calves receiving the diet supplemented with glucose indicates indirectly significant decrease of MFO system in the animals. Anderson et al. (1979, 1984) and Pantuck et al. (1984, 1989) obtained similar results in men receiving a high-carbohydrate diet. Feldman et al. (1980) stated, however, a large (reaching 300%) interindividual difference of theophylline metabolic clearance rate in individuals receiving diet with carbohydrate supplement. The results obtained in these studies are in conflict with the results of experiments carried out by Feldman et al. (1980). In calves (both the control group and the "experiment II" group) interindividual differences of Cl_A values did not usually exceed 10%. This phenomenon was also observed in our previous experiments (Janus 1992; Janus et al. 1992). The presented results, showing indirectly that hepatic microsomal P450-dependent monooxygenase activity decreases significantly under the influence of increased carbohydrates content in food ration of calves, correspond with results of other experiments carried out in man and laboratory animals (Brandt et al. 1965; Strother et al. 1971; Hartshorn et al. 1979; Krishnaswamy et al. 1984; Peraino et al. 1986). The mechanism that allows carbohydrates to inhibit the hepatic biotransformation rate in different animal species has not been so far explained. Perai no et al. (1986) stated that the decrease of activity of enzymes of MFO complex is caused by deposition of glycogen within endoplasmic reticulum, which again supresses the synthesis of many enzymes responsible for biotransformation process. Alvares et al. (1986) report, however, that glucose producing during decomposition of carbohydrates, decreased significantly the activity of d-aminolevulinate synthase the enzyme limiting hem synthesis in liver. Since a significant part of hem being produced in this organ is used to cytochrome P-450 synthesis, a hypothesis saying that significant decrease of MFO activity is caused by (at least partially) decreased hem synthesis rate, seems likely. The values of half-life of antipyrine, metabolic clearance and AUC did not differ significantly from the values observed in control group after 7 days from the end of feeding the calves with diet enriched by casein or glucose addition (Tab. 3,4). In conclusion,it should be stated that a 25% increase of protein or carbohydrate content in food ration for calves influenced significantly the hepatic biotransformation rate.The results obtained also point out that a high-protein diet significantly increases, and a high-carbohydrate diet

significantly decreases the metabolism of drugs in calves, provided they undergo the same biotransformation process as antipyrine does (e.g. aminopyrine, phenacetin, phenytoin, theophylline, metronidazole).

Rychlost jaterní biotransformace u telat kremných dietami s přídavkem proteinů anebo sacharidů

Cílem práce bylo hodnotit rychlost jaterní biotransformace u telat v neonatálním údobí pomocí farmakokinetiky antipyrinu. Telata byla krmena dietami s přídavkem kaseinu anebo glukozy. Bylo zjištěno, že zvýšený obsah proteinů významně ovlivnil aktivitu monooxygenázy. Zvýšený obsah sacharidů vyvolal opačný účinek na aktivitu systému cytochromu P450. Z výsledků vyplývá, že vysokoproteinová dieta by zvyšovala intenzitu metabolizmu jiných látek, a vysokosacharidová dieta by ji snižovala v případě, že by šlo o látky s takovým procesem biotransformace jako má antipyrin.

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