29

DOES INDOMETHACIN (I) INCREASE THE RISK OF GENTAMICIN (G) TOXICITY IN VERY LOW BIRTH-WEIGHT INFANTS?.

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To confirm the hypothesis that I modifies G pharmacokinetic with high risk of toxicity, we studied 48 neonates (mean gestational age (GA) 28.3 w., birth-weight 1125 g, postnatal age 4.5 d.) affected by respiratory problems and treated with following schedule of G administration: 2.5 mg(Kg/dose every 24 h for GA <32 w. and every 18 h for GA 32-34 w. Twenty-eight neonates were treated only with G (group 1) and twenty were also treated with I (group 2). The serum G concentrations (immunofluorescence assay) were (mcg/ml):

	through	1••	2••	6••	9••
group 1	1.65±0.74	7.42±2.10	6.00±1.48	3.99±1.33	3.03±0.97
group 2	1.95±1.09	8.04±2.74	5.81±1.63	4.28±1.60	3.89±1.41
P	n.s.	n.s.	n.s.	n.s.	<0.03

•• hours after administration

No differences were found in G half-life (7.35±3.54 vs 8.10±2.88 h), G volume of distribution (0.525±0.127 vs 0.445±0.263 L/Kg), serum creatinine levels (1.13±0.37 vs 1.31±0.42 mg/dl) between the two groups. Thirteen neonates (6 in group 1, 7 in group 2) had through levels >2 mcg/ml; five had peak levels >10 mcg/ml (2 in group 1, 3 in group 2). Our results confirm that I doesn't increase the risk of G toxicity in very low birth-weight infants, at least with the schedule of G administration used in this study.

30

REGULATORY ADAPTATION OF CHOLESTEROL BIOSYNTHESIS AND THE LDL-RECEPTOR PATHWAY IN MEVALONIC ACIDURIA

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HMG-CoA reductase activity, ^{14}C-acetate incorporation into cholesterol and cholesteryl ester formation were studied in fibroblasts from 6 patients with mevalonic aciduria due to mevalonate kinase deficiency (MK^-) in response to different concentrations of LDL and non-lipoprotein cholesterol. Despite a virtually complete deficiency of mevalonate kinase in extracts of fibroblasts derived from the patients, there was still significant activity for the cholesterol biosynthetic pathway, assessed by monitoring ^{14}C-acetate incorporation into cholesterol in intact fibroblast monolayers. In the presence of LDL MK^- cells produced ~30% of the control cell lines and showed a significant increase into the control range after complete withdrawal of cholesterol. Adequate cholesterol biosynthesis was assured by a highly increased and partially unsuppressable HMG-CoA reductase activity in MK^- cells as compared to controls. For patients, the mean activity of HMG-CoA reductase of 63.3 ± 44.1 pmol/min/mg protein (± 1SD, range 37.7-146.2) was significantly higher than the mean value in control fibroblasts of 11.1 ± 3.5 (range 8.0-14.9). In addition, cholestyl ester formation, an indicator of the LDL receptor pathway, was twofold increased in the patients' cells, whereas cholestyl ester formation from non-lipoprotein cholesterol was undistinguishable from controls. Apparently an inhibition of intracellular cholesterol biosynthesis is counteracted by an increased activity of HMG-CoA reductase as well as of the LDL receptor pathway. The increased activity of the LDL receptor in the presence of an excess of exogenous cholesterol proves the existence of a single common regulatory mechanism of cholesterol biosynthesis and the LDL receptor pathway. The latter mechanism, which is demonstrated by this "experiment of nature", should be reponsible for the observed reduction of LDL cholesterol in hypercholesterolemic patients by HMG-CoA reductase inhibitors. However, the long term use of these drugs cannot be recommended in children or pregnant women in view of the severe multisystemic pre- and postnatal pathology of mevalonic aciduria. The exact pathobiochemical mechanisms are still unclear and may involve a shortage of non-sterol isoprenes. (Supported by DFG grant Ho 966/2-2)

31

EVIDENCE FOR DIMINISHED INCREASE OF BODY WEIGHT (BW) IN PREMATURES (PM) DURING PROLONGED SPONTANEOUSLY OCCURRING MAXIMAL RENAL ACID STIMULATION (MAX H^+)

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PM suffering from late metabolic acidosis often show growth failure. In a prospective randomized study in all PM below 1500 g as well as in all PM and newborns after intensive care therapy with max H^+ (urine pH < 5.4 on two succeeding days), the influence of oral alkali therapy on the increase of BW was investigated. Group B received 2 mmol $NaHCO_3$/kg/d for 7 days; group A (controls) was retrospectively divided into A1 (urine pH < 5.4 on 7 days) and A2 (urine pH ≥ 5.4 for ≥ 1 day). The results of net acid excretion (NAE, mmol/kg/d, 1.day) and of increase of BW (g, 1.-7.day) in 2 classes of PM (kg on 1.day) are:

	A1			A2			B			
BW	NAE	BW	n	NAE	BW	n	NAE	BW	n	P≤0.1
1.0-1.4	1.8	120±37	7	1.5	153±53	6	1.5	161±48	8	A1/B
1.5-1.9	1.6	137±67	6	1.9	170±54	4	1.8	193±66	13	A1/B

The diminished increase of BW in PM with max H^+ and similar caloric intake is a strong argument for our hypothesis that prolonged spontaneously occuring max H^+ without manifest metabolic acidosis (blood pH ≥ 7.28; BE > -8 mmol/l) decreases growth velocity.

32

VALIDATION OF"SPOT" URINE ANALYSES IN ASSESSING SODIUM OUTPUT IN INFANTS.

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The urinary sodium concentration(UNa) and sodium/potassium ratio(Na/K)are frequently used to assess sodium status in infants with abnormal sodium losses. However,24hr urine collection in infants is difficult and prone to error and we therefore studied the validity of using spot urine samples, comparing values for "spot" UNa and Na/K with 24hr urine collections and 24ht fractional sodium excretion(FeNa). Twenty infants(median age 24 ds,ranged 6-150d;mean weight 2.6 kr SD 0.65 kg)were studied,all receiving parenteral or enteral nutrition.Plasma levels of sodium, potassium and creatinine were all within the normal range. Urine was collected using a specially designed metabolic cot. Collections were made at 2 and 4hr, and then regularly during the next 20hrs. One ml aliquotes from the 0-2 and 2-4hr urine collections were analysed separately(spot 1 and spot 2);all remaining urine collected was pooled(24hr urine). - UNa in both spot samples correlated positively and significantly with UNa in 24hr urine(r_1= 0.67,$p<0.01$;r_2=0.62,$p<0.01$).Furthermore,Na/K in both spot urines correlated with Na/K in 24hr urine(r_1=0.76,$p<0.001$;r_2=0.78, $p<0.001$) and FeNa(r_1=0.47,$p<0.05$;r_2=0.61,$p<0.01$).

Conclusion: The sodium concentration and sodium/potassium ratio in spot urines accurately reflect values derived from 24hr urine collection and may be used to assess sodium balance in infants.

33

POSTNATAL TIMECOURSE OF RENAL BLOOD FLOW(RBF)VELOCITY IN HEALTHY TERM NEONATES.

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The normal adult values for RBF cannot be used in infants.In order to establish standard values for the postnatal timecourse of RBF,25 healthy neonates were investigated by means of an ultrasonic doppler color flow technique at birth,at 6 and 12 months.The measuraments were done in double by 2 invastigators.The flows were repeatedly recorded at the level of the main renal and the segmentary arteries on both kidneys over 3-4 sistolic-diastolic cycles during an examination time of approx.30 min..The measured items were:

		Birth(B)	6 months	12 months
RESISTANCE	R.Renal Artery	0.69±0.14	0.70±0.05	0.62±0.04
INDEX(RI)	L.Renal Artery	0.71±0.11	0.71±0.06	0.63±0.06
	P	B vs	NS/NS	<0.05/<0.01
A/B RATIO(+)	R.Renal Artery	3.94±1.75	3.53±0.67	2.65±0.39
	L.Renal Artery	4.19±2.38	3.83±0.93	2.85±0.45
	P	B vs	NS/NS	<0.02/<0.05

(+) A maximum,B minimum values over the cardiac cycle

Our results show that:normal values for infants are often in the pathological range for adults,the postnatal decrease of all indexes significantly correlates with postnatal age,the RI correlates the best with postnatal age and may be the most sensitive predictor of pathological changes.

34

THERMOGENIC EFFECT OF EPHEDRINE AND AMINOPHYLLINE IN OBESE CHILDREN.

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Several studies have demonstrated the thermogenic effect of ephedrine and methylxanthines. However, no data are available on the thermic effect of these drugs in children.In the present study we investigated the thermogenic effects of 1 mg/kg lean body mass (LBM) (group 1,n=5) or 2 mg/kg LBM (group 2,n=7) ephedrine and 3 mg/kg LBM (group 3,n=6) or 6 mg/kg LBM (group 4, n=5) aminophylline in 10 obese boys and 13 obese girls.Their age (mean±SE), body weight, body fat and LBM were 12.1±0.6 yr,78.4 ±5.2 kg, 38.8±0.8 % and 48.1±3.3 kg, respectively. Resting metabolic rate (RMR) was measured by Kipp and Zonnen indirect calorimeter after an overnight fast for 45 min and for 180 min after the administration of the drugs. RMR rose after the consumption of the drugs by 3.9±0.7 %, 7.5±1.2 %, 10.8±2.2 % and 20.0±2.5 % in group 1,2,3 and 4, respectively ($p<0.05$, group 1 vs 3 and 2 vs 4). Heart rate was increased significantly by both drugs. Systolic blood pressure was elevated only by ephedrine.

Conclusion:The thermogenic effects of ephedrine and aminophylline are dose dependent. Aminophylline is a much more effective thermogenic drug in children than ephedrine and it does not increase blood pressure. Before it could be recommended as an aid for the treatment of extremely obese children, a chronic energy balance study is needed.