266 DOSE DEPENDENT ENZYME INDUCTION IN ANTICONVULSANT TREATED CHILDREN

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The serum activity of gammaglutamyltransferase (GGT) and the urinary excretion of D-glucaric acid (DGA) are significantly enhanced in patients treated with enzyme inducing drugs. However, quantitative data on the correlation between drug dose and increase of these indicators of enzyme induction are sparce and contradictory. The question to be answered by the present study was: Are GGT and DGA measurements suitable to assess the inducing properties of an individual anticonvulsant drug quantitatively? Children on constant single medication for at least two months with primidone (PR), carbamazepine (CBZ) or sodium valproate (VAL) were investigated. DGA was measured colorimetrically, phenobarbital (PB) and CBZ by EMIT, VAL by GC, GGT and Creatinine by standard methods. There was a significant ($p<.001$) positive correlation between the drug dose and the excretion of DGA for all three anticonvulsants studied. The enhancement of DGA by VAL was less pronounced than by PR and CBZ. DGA excretion was closely ($p<.001$) correlated to the serum levels of VAL and PB (from PR), but not of CBZ. DGA excretion was inversely correlated to the level to dose ratio of CBZ, thus reflecting the degree of autoinduction of CBZ breakdown. Except for PR, the data on GGT were, though similar to those on DGA, less conclusive owing to a greater variation of individual values. In conclusion, DGA and GGT are useful quantitative measures of the enzyme inducing properties of PR, CBZ, and VAL. DGA reacts more sensitively and less variably than does GGT. Compared to PR and CBZ, VAL is a relatively weak but distinct enzyme inducing agent. DGA enhancement does not permit to differentiate between autoinduction and heteroinduction.

267 PENICILLIN PROPHYLAXIS (PP) FOR EXPERIMENTAL STREPTOCOCCAL ENDOCARDITIS IS EARLY PENICILLIN TREATMENT

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The aim of PP for endocarditis due to viridans streptococci (VS) is to prevent the onset of bacteremia. However, the incidence of postextraction bacteremia in children with cardiac disease after dental extraction under PP has been shown to be 21% (Hess et al, Ped 71: 554-558, 1983). Since the adherence of VS onto vegetations is recognized as an initial step in the pathogenesis of endocarditis, we studied the effect of P on adherence of VS in experimental endocarditis. 10^7-CFU penicillin-sensitive VS (MIC .01µg/ml, MBC .02µg/ml) were injected iv 30 min after im injection of procaine penicillin G (PPG) 250 mg/kg into Chinchilla rabbits with a left heart catheter in situ for 24 hrs. The rabbits were sacrificed 5 min, 0.5 hr, 2 hr, 4 hr and 48 hr after the injection of the VS, and the cardiac vegetations, induced by the catheter, were excized and cultured to determine whether or not colonization of the vegetations had been prevented by P. Results were:

culturing after	no. infected/total no.(%)		p value
	PPG	control	
5 min	6/6(100)	6/6(100)	n.s.
0.5 hr	6/6(100)	5/5(100)	n.s.
2 hr	2/6(33)	5/5(100)	p<.025
4 hr	0/6(0)	5/5(100)	p<.005
48 hr	2/22(9)	8/8(100)	p<.001

We conclude that PP does not prevent the colonization of cardiac vegetations by reducing the bacterial adherence, but sterilizes initially infected vegetations. Therefore, PP for experimental streptococcal endocarditis is in fact early treatment.

268 CARDIOVASCULAR AND RENAL RESPONSE TO DOPAMINE IN PRETERM NEONATES WITH CIRCULATORY FAILURE

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49 preterm infants (BW: 1700±385 g; GA: 31,8±1,8 w; PA: 9,8±6,8 h) were treated with dopamine (D) because of peripheral circulatory disturbance. A dosis of 2 µg/kg/min D was administered in mild circulatory failure but in normal BP at 31 neonates. No sign of alpha- and beta adrenerg receptor stimulation was found , i.e. BP, HR and pulmonal resistance remained normal. On the other hand diuresis, Na-P-excretion, FENa and Ccr increased significantly (+106%, +73%, +185%, +140%, +21%), on the basis of renal dopaminergic receptor stimulation. - A dosis of 4 µg/kg/min D was infused in 18 neonates with severe arterial hypotension but with normal CVP. BP normalised within 2 hours (28/11±7/4 vs 54/27±12/9 mmHg), while HR and paO2 did not alter. An improvement of renal functions was also found from oliguric level to that one observed during infusion of 2 µg/kg/min D. - Administration of 8 µg/kg/min D caused an even more pronounced and also lasting BP elevation (62/30±10/9 mmHg) and a significant increase in HR, too (132±9 vs 164±13 1/min). On the basis of our data we conclude: 1. the dopaminergic receptor system is fully developed even in very preterm neonates, 2. on the basis of alpha receptor predominance, alpha-adrenerg stimulation can occur at lower dopamine dosis, too.

269 PROSTAGLANDINS AND AMINOGLYCOSIDE NEPHROTOXICITY.

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PGs renal metabolism was studied during gentamicin (G) induced renal failure in CD-COBS rats (200g.b.w.) to assess the role of arachidonic acid metabolites inb the development of the damage. The animals divided in 4 groups received G 80mg/Kg, acetylsalicylic acid (ASA) 200mg/Kg, both drugs or saline in a single daily ip administration. G. reduced the clearance of creatinine by 30 at 10 days ($p<.05$). ASA alone did not cause any significant change while its combination with G woresened the renal failure (CrCl G+ASA 50% of controls at 10 days $p<.05$) G alone caused a reduction in the maximal concentrating capacity after DDAVP whichwas worsened by ASA: Uosm max (mosm/kg, mean ± SE) = Control 3500 ± 150, G: 2500 ± 180*, G ASA: 1500 ± 100*. *= $p<.05$.

PGs metabolism was studied on the tissue homogenate after solvent extraction and quantified by GLC-Mass spect. PGE_2 PGD_2, 6 Ke to PGF_1 and $Thromboxane B_2$ were measured. ASA caused a 70-90% inhibition in all PG synthesis for 24 hrs after a single or multiple injections. In the group PGE_2 synthesisspecifically increased (at day 10: 130±20 ng/g tissue controls 62±12, $p<.05$). This rise was prevented by ASA. No change was found for the other PGs metabolites.

Conclusions PGE_2 has a vasodilatory effect on the Kidney, its increased synthesis during aminoglicoside induced toxicity is protective. Inhibition of PG synthesis by non-steroid anti-inflammatory drugs prevents the compensatory mechanism.

This interaction should be considered in septic neonates treated for the patency of the ductus arterious.

270 ALPHA 2 renal adrenoreceptors in young hypertensive rats (Milano strain)

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Alpha 2 renal adrenoreceptors play an important role in the control of sodium homeostasis. Since the kidney has a major role in the development of hypertension in the genetically hypertensive Milano strain of rats (MHS) it is important to determine the possible defect in the receptors regulating the transport of sodium in these animals.

Alpha 2 adrenoreceptors were studied in renal outer and inner cortex and medulla (OC, IC and M) of young (7 weeks, 200 g b.w.) MHS and in their normotensive controls (Milano normotensive strain ,N) Kd and Bmax were calculated by Scatchard analysis of ^3H rauwolscine binding. Non specific binding was defined as the displacement of 10 uM phentolamine.

Results (each data represents mean + SD of 4 experiments)

	B max		Kd	
	MHS	N	MHS	N
OC	150(5)	149(17)	7(3)	4(1)
IC	118(24)	155(9)**	5(1)	5(1)
M	121(27)	136(27)	7(2)	5(1)

** p .05 by the t Student test

Since in other experiments we did not find differences in the beta receptors, we conclude that the alpha2 system of IC is specifically involved in the development of hypertension in MHS rats.

WGPP—Abstract for Poster Presentation

271 THEOPHYLLINE METABOLISM DURING POSTNATAL DEVELOPMENT

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Few data exist regarding theophylline (T) biotransformation in early postnatal life. In this study T metabolism was characterized in the rat with emphasis on its changes during postnatal development. Liver slices were prepared from Charles River rats and incubated in Krebs-bicarbonate buffer with (8-^{14}C) T under 95% O_2-5% CO_2 in a metabolic shaker at 37°C. T metabolites were analysed by tlc and hplc. T and 6 main metabolites were recognized in adult liver: 1 methyluric acid; 1 methylxanthine; 1,3 dimethyluric acid; caffeine, a uracil derivative and an unknown polar compound. Preincubation with caffeine and theobromine inhibited T metabolism. SKF 525-A and allopurinol inhibited overall T metabolism; in particular allopurinol inhibited formation of 1 methylxanthine. The specific activity of the enzyme system was 3.9 ± SE 0.4 nm (gm liver)$^{-1}$. hr^{-1} in the 4-day-old and increased to a peak of 25.3±1.7 in the 28-day-old rat; Km was similar (67.5 vs. 132.1 µM) but Vmax was two-fold greater in the 28-day-old (23.9 vs. 52.1 nmol [gm liver]$^{-1}$. hr^{-1}). T and the same 6 metabolites were identified in young and adult rats but the developmental pattern was not uniform. Peak age related activity and involvement of mixed function oxidase system are common features to caffeine (Bioch. Pharmacol. 30: 3145, 1981) and T biotransformation, Xanthine oxidase was involved in T metabolism. As opposed to previous suggestions formation of caffeine from T was not dependent on lack of activity of other pathways.