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CROSSVALIDATION OF SERUM TO SALIVA RELATIONSHIPS OF THEOPHYLLINE AND TOTAL METHYLXANTHINES IN NEONATES.

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The relationships of serum (Se) to saliva (Sa) concentrations of Theophylline (Theo) and total methylxanthines (Mx) (Mx = Theo + Caffeine (Caf)) have been established in neonates treated with Theo for apnea (J.Pediatr.96:494,1980). Serum to Sa relationships derived with additional studies have been crossvalidated against the old data. The standard deviations (SD) and correlation coefficients (R) for the Se to Sa relationships are presented below. Data for Mx is presented because of Theo to Caf conversion in neonates.

		Regression Model		Crossvalidation Against Old Data	
New Data Equation		SD	R	SD	R
N = 78					
Theo Se =	1.5 + 1.12 x Sa	2.6	0.92	5.8	0.51
Mx Se =	2.3 + 1.21 x Sa	3.9	0.92	4.7	0.88
		Ratio Model			
Theo Se =	1.35 x Sa	2.9	0.90	3.6	0.85
Mx Se =	1.46 x Sa	4.3	0.90	4.2	0.90

Crossvalidation results indicate that R is high for Mx using both models and for Theo only for the ratio model. The discrepancy between Theo and Mx results may be caused by the wide interindividual differences in conversion from Theo to Caf.

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CROSSVALIDATION OF SERUM TO SALIVA RELATIONSHIPS OF CAFFEINE AND TOTAL METHYLXANTHINES IN NEONATES.

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The relationships of serum (Se) to saliva (Sa) concentrations of Caffeine (Caf) and total methylxanthines (Mx) (Mx = Caf + Theophylline (Theo)) have been established in neonates treated with Caf for apnea (J.Pediatr.96:494,1980). Serum to Sa relationships derived with additional studies have been crossvalidated against the old data. The standard deviations (SD) and correlation coefficients (R) for the Se to Sa relationships are presented below. Data for Mx is presented because of Caf to Theo conversion in neonates.

		Regression Model		Crossvalidation Against Old Data	
New Data Equation		SD	R	SD	R
N = 43					
Caf Se =	1.7 + 1.18 x Sa	3.9	0.97	4.4	0.96
Mx Se =	1.7 + 1.17 x Sa	4.0	0.97	4.8	0.95
		Ratio Model			
Caf Se =	1.29 x Sa	4.2	0.97	6.2	0.93
Mx Se =	1.29 x Sa	4.2	0.96	5.2	0.94

From the high R values for both Caf and Mx it appears that the newly derived relationships crossvalidate well with the old data.

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IS THERE REALLY A GENTAMICIN DOSE SCHEDULE FOR NEONATES?

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Recent evidence suggests the need to modify the gentamicin (G) dose regimen for neonates. To determine the appropriate drug schedule we measured 587 gentamicin serum levels (G.S.L.) on 150 neonates, (G.A. 25-43 wks. and B.W. 680-4820 gms.) admitted to our NICU. When we used the standard dose of 2.5 mg/kg q 12 H our results during the first 2 days of life revealed trough levels >2 ug/ml in 53.6% (42/78), suggesting possible G accumulation, and peak levels >8 ug/ml in 18% (14/78) and <4 ug/ml in 10% (8/78). We then modified the initial dose regimen according to gestational age: <30 wks., 1.5-2.0 mg/kg q 24 H; 30-37 wks., 2.0-2.5 mg/kg q 18 H; and >37 wks., 2.0-2.5 mg/kg q 12 H. Subsequent results showed a marked decrease in babies with elevated trough levels (>2 ug/ml) to 16.6% (12/72). Peak levels >8 ug/ml decreased to 6.8% (5/72). However, peak levels <4 ug/ml increased to 27% (20/72). In addition, 61 of these infants had follow-up G.S.L. determinations which showed that 44.3% (27/61) required further adjustments to their initial dose regimens. Most of these cases had neonatal asphyxia and/or severe cardiopulmonary disorders.

In conclusion, there is really no true gentamicin dose schedule for the neonate. However, until the significance of toxic drug levels for newborns become more clearly defined, we recommend an initial dose based on weight and gestational age which then needs to be adjusted by frequent G.S.L. measurements.

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POTENTIATION OF MAGNESIUM INDUCED NEUROMUSCULAR BLOCKADE BY GENTAMICIN.

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Aminoglycosides have been reported to precipitate paralysis in myasthenia gravis, infant botulism, and competitive neuromuscular blockade. We investigated the effect of gentamicin on magnesium induced neuromuscular blockade in the rabbit. Three kilogram male rabbits were anesthetized with sodium pentobarbital, intubated and mechanically ventilated with 100% oxygen. Arterial and venous access were obtained via ear blood vessels. Blood pressure, arterial blood gases, end tidal CO₂, rectal temperature, and muscle twitch height were recorded. Baseline serum levels of Mg⁺⁺, Ca⁺⁺, and gentamicin were collected. Mg⁺⁺ was administered by continuous I.V. infusion to maintain a 50% depression in control twitch height for 30 minutes. Gentamicin, 2.5 mg/kg, was given I.V. and an additional 10-20% depression in twitch height was recorded. Control and experimental data follow:

	Ca ⁺⁺	Mg ⁺⁺	Gent.	Muscle Strength % of control
Baseline	10 ± 2.0	2.1	1.03 ± 2.5	50
Control	6.3 ± 2.8	6.1 ± 6.7	13 ± 4.7	34.6
Significance	p < .025	p < .025	p < .01	p < .01

Gentamicin given in clinical doses will potentiate a preexisting magnesium induced neuromuscular blockade.

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ENDOGENOUS OPIATES MODIFY FETAL CARDIOVASCULAR RESPONSES TO STRESS.

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Endogenous opiates are involved in adult circulatory responses to stress and may function by decreasing sensitivity of nicotinic receptors (Nature 283:489, 1980). To examine their role in the fetus, we studied the heart rate (HR) and mean aortic pressure (MAP) responses to maternal hypoxemia in 5 normoxic (N:pO₂>20mmHg, pH>7.38) and 5 chronically stressed fetuses (S:pO₂<20mmHg spontaneously for >24 hours) at 120-130 days gestation. HR and MAP were similar during control recordings in both groups. HR decreased (p<0.001, ANOV) and MAP increased (p<0.001, ANOV) in response to hypoxia in all animals. In N fetuses during hypoxia, naloxone (Nx:1 mg/kg) increased MAP from 55±4 to 61±4 (X±SEM, p<0.001, ANOV) in the 5 minutes following it; but HR did not change. In the stressed fetuses during hypoxia, Nx did not change MAP but HR decreased from 161±12 to 140±13 (p<0.001, ANOV). Blood pH fell 0.09±0.03 and 0.1±0.02 units following Nx in the N and S fetuses respectively (p<0.005, paired t-test). The Nx-induced rise in MAP in the N fetuses is consistent with increased vasoconstriction due to potentiation of sympathetic-adrenal activity and a balanced parasympathetic-sympathetic effect on HR. The lack of a MAP response to Nx in the S fetuses suggests exhaustion of sympathetic-adrenal output which unmasks the parasympathetic effect on HR. These data indicate that endogenous opiates are involved in HR and MAP control in utero, and are consistent with a Nx facilitated increase in ganglionic transmission. (Supported in part by NIH grant HL00756-01.)

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KETOCONAZOLE, AMPHOTERICIN B AND AMPHOTERICIN METHYL ESTER: COMPARATIVE IN-VITRO AND IN-VIVO TOXICOLOGICAL EFFECTS ON IMMUNE FUNCTION.

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We have previously found that antifungal agents used in the treatment of patients with immune dysfunctions have enhanced those abnormalities and may have rendered the patients more susceptible to secondary infections. To examine the role that antifungal agents play in producing such immune dysfunction, we investigated a number of parameters for host defense following in-vitro addition of the antifungal agents ketoconazole, amphotericin B (AMB), and amphotericin B methyl ester (AME). Similar assays were repeated before and after the patients had received these drugs.

Viability by trypan blue exclusion, adherence by glass bead column, chemotaxis by under agarose technique and phagocytosis and killing by NBT, chemiluminescence and acridine orange direct visualization were assayed. In striking contrast to AMB and AME, ketoconazole showed no significant effect on neutrophils. Adherence in the presence of therapeutic plasma levels of AMB and AME were decreased at low drug concentrations while at higher concentrations, adherence was increased. The chemotactic responses of cells incubated with AMB and AME showed marked suppression and phagocytosis and killing appeared slightly decreased as compared to control assays and assays done in the presence of ketoconazole. In summary, our data suggest that ketoconazole is less toxic to functioning neutrophils than AMB or AME and may offer a therapeutic advantage over the latter drug.