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ANALYSIS OF DRUG PRESCRIBING INFORMATION FOR PEDIATRICS AND OBSTETRICS AS PRESENTED IN THE PHYSICIANS DESK REFERENCE. G.C. Rodgers, Jr. and W.A. Carroll, (spon. W.H. Bergstrom). Upstate Medical Center, SUNY, Depts. of Pediatrics, Pharmacology and Pharmacy, Syracuse, New York.

In order to assess the impact of the recent upsurge in pediatric drug research, the 1980 edition of the Physicians Desk Reference was reviewed for data and indications pertaining to pediatric and obstetric usage. A total of 1,133 entries were reviewed. Of these 71.9% were oral preparations, 20% parenteral, 1.6% various other routes of administration and 6.5% included multiple routes. Dosing data based on weight or surface area was provided in 27.8% of entries. Specific pediatric dosing data was provided in 40.9% of entries while pediatric usage was specifically contraindicated in 8.9% of entries. In 39.1% of entries no mention was made of pediatric usage and in 11.1% it was mentioned, but without clear recommendations or data. In 2.6% of entries use in pregnancy was approved while 10.3% contained a definite contraindication for such use. The remaining entries either failed to mention use in pregnancy (31.8%) or mentioned use in pregnancy but without definite recommendation (55.3%). Use in breast feeding mothers was mentioned in 27.9% of entries with data provided in 107 entries and a definite contraindication in 104. Data on overdose management was provided in 29.8% of entries. Marked variability was noted between drug classes and manufacturers in terms of the information provided. It is clear from the above analysis that a continued emphasis is needed by manufacturers on providing solid data pertaining to drug usage in pediatrics and obstetrics.

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USE OF BUTORPHANOL FOR POST OPERATIVE PAIN IN CHILDREN. G.C. Rodgers, Jr., and M. Lasada (spons. by W. H. Bergstrom) Dept. of Peds and Pharmacology, Upstate Medical Center, and Bristol Laboratories, Syracuse, New York.

Butorphanol (B), a new synthetic agonist-antagonist type analgesic, was evaluated in 34 patients aged 4-12 years requiring a parenteral medication for relief of pain following elective surgical procedures. B was administered IM when, in the estimate of the patient or the recovery room staff, an analgesic was required. Doses of B ranged from 0.01 mg/kg to 0.02 mg/kg, with most patients receiving 0.015 mg/kg. Scores of pain intensity (0-3) and relief (0-4) were done prior to dosing and at hourly intervals for six hours following the dose, or until additional medication was required. Surgery included orthopedic (12), abdominal (5), non-cardiac thoracic (3), genitourinary (11) and miscellaneous (2) procedures. There were 19 male and 15 female patients. 16/34 patients continued to experience good pain relief at the end of the six hour observation period. The mean length of time to re-medication was 5.0 hr. with a 6 hr. maximum given. The range was 2-6 hr. At any given dose, pain relief tended to be better and more prolonged in the younger patients. This may derive from the increased sedation seen with B in the younger children. There was no significant difference between the three doses used in degree or duration of analgesic effect. Except for one patient who experienced transient urinary retention, sedation was the only significant side effect seen. This is the first reported dose ranging study of pain therapy in children. B, at a dose of 0.01-0.02 mg/kg, provided good relief of post-operative pain in children.

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6 $\beta$ -HYDROXYCORTISOL: A NON-INVASIVE PROBE TO EVALUATE INHIBITORY EFFECTS OF LEAD (Pb) ON DRUG METABOLISM IN CHILDREN. Paul Saenger, John F. Rosen, Jacob Kream, Morri E. Markowitz, Albert Einstein Coll. Med., Dept. Ped. & CRC, Montefiore Hosp. Med. Ctr., Bronx, N.Y.

6 $\beta$ -hydroxycortisol (6 $\beta$ OHF), a normally occurring polar metabolite of cortisol has been shown to be a sensitive index for hepatic enzyme induction. 6 $\beta$ OHF is formed by the mixed function oxidase system in the liver and excreted by the kidney. Pb is known to inhibit hepatic microsomal activity. In order to measure inhibitory effects of lead on drug metabolizing enzyme activity 6 $\beta$ OHF excretion was measured in 11 children (age 2-9 yrs) with mild to moderate Pb intoxication (nl renal function) prior to chelation therapy. Correlations were examined between 6 $\beta$ OHF and blood Pb, erythrocyte protoporphyrin (EP) and urinary Pb excretion (after a CaNa<sub>2</sub>EDTA provocative test). 6 $\beta$ OHF excretion in normal controls was 0.23  $\pm$  0.03 mg/m<sup>2</sup>/24h, but excretion in Pb burdened children was reduced to 0.17  $\pm$  0.02 mg/m<sup>2</sup>/24h; (p<.01). There was a highly significant correlation between 6 $\beta$ OHF and EP, mean 173  $\pm$  20  $\mu$ g/dl (r=-0.73 p<.01) and 6 $\beta$ OHF and urinary Pb, mean 816  $\pm$  134  $\mu$ g/24h (r=-0.85 p<.001) but none between blood Pb, mean 45.2  $\pm$  1.5  $\mu$ g/dl, and 6 $\beta$ OHF (p>.02). The correlation between 17-hydroxycorticoid excretion and EP or urinary Pb was not significant. **Conclusions:** 1) The data show that children with undue Pb absorption may have decreased 6 $\beta$ OHF excretion; 2) 6 $\beta$ OHF may thus serve as a non-invasive probe to assess the chelatable, potentially toxic, fraction of body Pb stores; 3) 6 $\beta$ OHF may also be used as a non-invasive index to evaluate the inhibitory effects of undue Pb absorption on drug metabolizing enzyme activity.

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THEOPHYLLINE & BRAIN DEVELOPMENT. Ulana M. Sanocka, Ralph B. Dell & L. Stanley James, Div. of Perin. Med., Dept. of Ped., Coll. of P&S, Columbia Univ., NY.

Theophylline (T) inhibits cholesterol synthesis in cultured glial cells. Hence, T usage in premature infants at a time of rapid brain growth may be harmful. We examined the effects of chronic administration of T on brain growth in the newborn rat: cell division (DNA/brain), hypertrophy (protein/DNA) & myelination (glycolipids). 24 Sprague-Dawley rat pups were randomly distributed into 2 groups: 16 experimental & 8 controls. The experimental group received 20 mg/kg/d of T by oral-gastric tube from day 5 to 21 of life (serum T 20-30  $\mu$ g/ml). Control animals received saline. Drug dose & frequency of administration was increased during the study period to offset effects of maturation on the pharmacokinetics of T. Rats were decapitated on day 21 & brains were weighed & analyzed. As shown in the table below, we observed no statistically significant differences in total body & brain weight, brain DNA, RNA, protein, cholesterol or glycolipid content between the control & drug treated rats.

	Brain Body Wt.	DNA (mg)	Protein DNA	Cholesterol (mg)	Glycolipid ( $\mu$ moles)
Control	.028 $\pm$ 0.004	2.02 $\pm$ 0.14	47.04 $\pm$ 4.77	15.78 $\pm$ 1.50	4.62 $\pm$ 0.31
Exp	.028 $\pm$ 0.005	1.98 $\pm$ 0.27	45.78 $\pm$ 4.84	15.26 $\pm$ 0.97	4.60 $\pm$ 0.50

Thus biochemical measurements of brain cell number, cell size & myelination do not indicate that brain growth & development in the rat is adversely affected by T even when it is administered during the presumed period of maximal vulnerability.

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GENTAMICIN KINETICS IN VERY LOW BIRTH WEIGHT NEONATES Malini Satish, Tom Thompson, Venkatesan Krishnan, Gerald Katzman, Jose Urrutia, Irwin Weinfeld, Sidney Kripke, P.L.S. Amma. (Spon. by M. G. Robinson) Medical College of Ohio, The Toledo Hospital, Dept. of Peds., Toledo, Ohio.

Gentamicin kinetics were studied in 12 neonates of gestational ages (GA)  $\leq$  34 wks. (27-34 wks.), of birth weight (700-1500) and compared to 5 neonates of GA > 34 wks. (2440-4890). Timed peak and trough levels were drawn following the first dose of Gentamicin of 2.5 mg/kg I.V. over one half hour. All determinations were done in the first week of life.

G.A.	# Neonates	Volume Dst. (Vd)		Elimination Constant (Ke)		Half life (t <sub>1/2</sub> ) hrs.	
		$\bar{X}$	S.V.	$\bar{X}$	S.V.	$\bar{X}$	S.V.
<34 wks.	12	0.43	0.03	0.018	0.0003	10	7.84
>34 wks.	5	0.29	0.0024	0.108	0.0022	7.5	12.25
t		student 't' test t <sub>15</sub> = 18		9.76		3.16	
p value		<.001		<.001		<.01	

We conclude that during the first week of life in the neonates <34 wks. G.A. the Vd is significantly higher, Ke is significantly slower and t<sub>1/2</sub> is significantly longer than the neonates of >34 wks. G.A. We found no relationship between half life of Gentamicin and Serum BUN and creatinine values. This has obvious clinical implications in deciding dosage intervals.

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THE EFFECT OF CALCIUM CHELATION ON LYMPHOCYTE NA AND K PERMEABILITY. G.B. Segel, M.A. Lichtman, and M.R. Quastel, University of Rochester, Rochester, N.Y.

Ca chelation prevents the proliferative response of lymphocytes. Lymphocyte proliferation is critically dependent on membrane adaptations including a doubling of Na and K pumping. Thus calcium chelation could disrupt the membrane and prevent the compensatory increase in active transport of Na and K. We examined the leak and pump of Na and K under conditions of Ca deprivation. Lymphocytes were studied in a medium containing EGTA so as to quantitatively reduce ionized Ca, as measured by a Ca electrode. The membrane permeability to Na and K increased when Ca activity was less than 10  $\mu$ M. When Ca activity reached 0.1  $\mu$ M, K and Na leak reached a maximum of 3 times control values. As leak increased, active transport increased to maintain an internal Na and K close to normal values. Intracellular Na was increased from 15 to 27 mM, and K was reduced from 145 to 137 mM in the presence of 0.1  $\mu$ M ionized Ca. The 3-fold increase in Na and K transport at 0.1  $\mu$ M ionized Ca was shown to be the result of the 12 mM increase in Na since a 3-fold increase in Na and K transport occurred when cell Na was increased to 25 mM by other means. Replacement of Ca completely reversed the increased membrane permeability. Thus, 1) the chelation of extracellular Ca does not restrain the ability of the Na,K-pump to compensate for increased leak and 2) Ca chelation does not block lymphocyte proliferation by inhibition of Na and K transport but does produce a dramatic increase in membrane permeability.