23

PHARMACOKINETICS OF ACICLOVIR (ACV) IN PREGNANCY AND PERINATAL PERIOD

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The use of ACV in pregnancy is not yet recommended for two main reasons : its safety has not been established and the lack of studies on pharmacokinetics. In this paper, we have reviewed data concerning nine pregnant women who was given ACV in the perinatal period. Route of administration and doses were as following : orally (O) 350 mg/8 hours (5), intravenously (IV) 5-10 mg/kg/8 hours (4). Plasma trough (T) and peak (P) levels of ACV was determinated by radioimmuno assay. At birth, plasma ACV levels were achieved in the mother and her offspring. P and T after IV were effective to inhibit viral replication (17-41 µmol/l, 1.22-1.36 µmol/l) and higher than in vitro ID 50 for Herpes viradea viruses (0.1-4 µmol/l) ; whereas T and P ranged from 0.32 to 0, 59 µmol/l and from 1.79 to 3.78 µmol/l after 10 doses given orally. Furthermore steady state plasma level was not achieved even after 10 doses O. The maternal foetal ratio of ACV level was approximately 1. No side effects were noted in newborns.
Conclusion : If this drug is felt to be used in a pregnant woman, IV administration seems to be advisable regarding it's efficacy. O administration requires more data about recommended dosage. Transplacental passage of ACV occurs. Plasma ACV levels in the mother reflect probably foetal ACV level.

24

EXERCISE PERFORMANCE IN VERY LOW BIRTH WEIGHT CHILDREN AT THE AGE OF 7-12 YEARS.

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Fifteen very low birth weight (VLBW) children, nine appropriate for gestational age (AGA, mean birth weight 1302±164 g, gestational age 30±1.5 weeks), and six small for gestational age (SGA, mean birth weigth 1263±117 g, gestational age 35.3±1.5 weeks), were studied at the age of 7-12 years, and compared to twentysix age-, sex-, and height-matched healthy children, who were born at term (mean birth weight 3226±167 g). None of the VLBW children had developed chronic broncopulmonary disease. The habitual level of physical activity was not different in the VLBW and control group. Pulmonary function tests and progressive exercise tests on treadmill were performed. Forced vital capacity, forced expiratory volume at one second and forced expiratory flow between 25% and 75% of vital capacity were in the normal range for all the subjects. No differences were found in maximum oxygen consumption (VO2 max), anaerobic threshold (AT) and maximal heart rate between the AGA (VO2 max = 42.1±8.6 ml/min/kg, AT = 31.2±4.4 ml/min/kg) and SGA children (VO2 max = 43.4±11 ml/min/kg, AT = 34.2±8.5 ml/min/kg) and the respective controls (AGA controls VO2 max = 44.2±12.4 ml/min/kg, AT 31.8±4.2 ml/min/kg; SGA controls VO2 max = 40.7±6 ml/min/kg, AT 29.8±2.2 ml/min/kg). Both in the AGA and SGA subgroups the preexercise VO2 values were comparable to those of the controls. In the SGA subgroup the energy cost of running throughout the test was significantly higher with respect to the controls (ANOVA $p<0.025$), while no difference was found between the AGA and the control children.
In conclusion, children with birth weight less than 1501 g have normal values of aerobic fitness; in SGA children the efficiency of running is slightly reduced.

25

LIDOCAINE ANTICONVULSANT THERAPY in NEONATAL SEIZURES.

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Lidocaine is either a convulsant or an anticonvulsant drug , according to the plasmatic levels. We used its anticonvulsant effect in seizures of various etiology. Lidocaine infusion (L.I.) was efficient in 19/29 full term (FT) and in 10/13 premature babies (PT) with seizures (confirmed by EEG) resisting to Phenobarbital and Diazepam therapy. L.I. was given at decreasing dosage (4 mg/kg/h, day 1; 3 mg/kg/h, day 2; 2 mg/kg/h, day 3; 1 mg/kg/h, day 4). After L.I. beginning :
-seizures were controlled within 30 min. in 23 cases , after 3 to 13 hours in 4 cases;
-background EEG changed in some cases, immediatly or after a delay (up to 24 hours) into a very discontinuous pattern. In 2 cases L.I. alone did not control seizures, but an additional bolus (2 mg/Kg) was efficient . Plasmatic levels (mg/ml) obtained after 24 h of L.I. in 15 cases with seizure control were higher in 4 PT (9.5-10.5) than in 11 FT (3.1-8.9), with a lower clearance in PT. L. half-life varied from 30 min. to 3.6 hours in 6 FT and was 36 hours in one PT. Seizures initially stopped then reappared in 4 cases : plasmatic levels obtained in 2/4 after 12 hours of L.I. were high : 13.4 in a PT and 11.7, suggesting the possible convulsant effect of L. high level.There was however no hemodynamic change. In conclusion: in neonates, L. could help to control seizures resisting to usual anticonvulsant drugs. A bolus of 2 mg/kg followed by a L.I. at 2 mg/Kg/h could avoid to attain convulsant level. Further pharmacological studies shoud help to determine optimal approach.

26

Phagocytic functions and TNF secretion of human monocytes exposed to natural porcine surfactant (Curosurf)

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In this study we have analyzed various phagocytic functions and TNF secretion of human monocytes exposed to either biochemically well defined porcine surfactant or a purified phospholipid preparation. Adherence, random migration and chemotactic response to zymosan activated serum and formyl-methionyl-leucyl-phenylalanine was normal in surfactant treated monocytes; surfactant was not a chemotactic stimulus. In contrast, phagocytosis of S. aureus by monocytes exposed to surfactant (100 µg/ml) and phospholipids (100 µg/ml) was slightly impaired (surfactant: t_{30} 48.5 ± 11 %, t_{60} 73.3 ± 10.1 %; phospholipids: t_{30} 47.3 ± 2.5 %, t_{60} 68.0 ± 6.6 %; controls: t_{30} 66.6 ± 9.9 %, t_{60} 81.0 ± 6.6 %, $p<0.05$ at t_{30} for both, $p<0.05$ at t_{60} for phospholipids. Due to the smaller number of S. aureus ingested, bactericidal activity of surfactant/phospholipid treated monocytes was slightly reduced when compared with controls (surfactant $t_{60} < 0.05$, phospholipids $t_{60} < 0.01$). Surfactant and phospholipids had no bactericidal activity. Uptake of candida was identical in surfactant/phospholipid treated monocytes and untreated controls; the same was true with the number of candida per cell ingested. Phagocytosis-associated chemiluminescence and production of superoxide anion by monocytes of either source in response to phorbol myristate acetate and opsonized zymosan was also identical. Surfactant and phospholipids, however, effectively suppressed TNF secretion by resting and by LPS-stimulated monocytes in a dose dependent fashion. TNF is an important mediator of inflammation (LPS-stimulated monocytes controls: 3004 ± 570 pg/ml, LPS + surfactant (500 µg/ml): 426 ± 162, LPS + phospholipids (500 µg/ml): 28 ± 9.6; $p<0.001$ for both). These data suggest that surfactant and phospholipids by suppressing monocytes TNF secretion may have an important role in down regulating inflammatory reactions in the lung.

27

Activity of Elastase and α_1-proteinase inhibitor in bronchial secretions of premature infants suffering from severe respiratory distress syndrome (RDS) treated with a natural porcine Surfactant (Curosurf)

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Proteolytic enzymes, especially elastase (E) released from neutrophils, seem to play a role in the pathogenesis of bronchopulmonary dysplasia (BPD). In some trials the combined incidence of death and BPD was shown to be reduced after surfactant replacement therapy in severe RDS.
In a prospective study we have analyzed activities and concentrations of free elastase (E), α_1-proteinase inhibitor (α_1-PI) and the enzyme inhibitor complex (E-α_1-PI) in bronchial secretions of 52 premature infants suffering from severe RDS following surfactant replacement therapy. Within a randomized trial "single versus multiple doses of surfactant (Curosurf)" the enzyme inhibitor potential of patients with severe RDS was analyzed during the first 10 days of life.
Results In 28/52 infants free elastase (E) was found in bronchial secretions (concentrations 0,8 - 162 µg/mg albumin). In these patients no free activity of α_1-PI could be detected, however, E α_1-PI was identical in all patients. Elastase was present especially in bronchial secretions of immature and low birth weight infants. 21/28 infants in whom free elastase was detected had an gestational age <30 weeks. No differences in concentrations of free elastase were found between premature infants who received a single dose and those who received 3 subsequent doses of surfactant.
Conclusions In all 52 cases the enzyme inhibitor complex (E α_1-PI) could be demonstrated. The was no correlation between the concentration of E α_1-PI and the activity of free elastase. Multiple treatment did not influence the imbalance between the activity of the enzyme and activity of α_1-PI. We need more knowlegde about factors that might influence the influx of neutrophils and the consecutive release of elastase into the bronchoalveolar space.

28

RANDOMIZED EUROPEAN MULTICENTER TRIAL OF SURFACTANT REPLACEMENT IN NEONATAL RESPIRATORY DISTRESS SYNDROME (RDS): SINGLE VERSUS MULTIPLE DOSES OF CUROSURF

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There is now convincing evidence that the severity of neonatal respiratory distress syndrome can be reduced by surfactant replacement therapy; however, the optimal therapeutic regimen has not been found. The aim of this randomized European Multicenter Trial "Single versus multiple doses" was to reduce the incidence of RDS-associated pulmonary complications as well as mortality in patients receiving multiple doses of surfactant. In this trial, preterm infants (birthweight 700-2000 g) with severe RDS requiring artificial ventilation with $FiO_2 \geq 0.6$ were randomized into two groups at an age of 2-15 h. Exclusion criteria have been recently published (Pediatrics 1988, 82, 683-691). Both groups received immediately after randomization the usual dose of Curosurf (200 mg/kg). In infants randomized to receive multiple treatment, two additional doses of Curosurf (100 mg/kg) were instilled into the airway at the age of 12 h and 24 h, provided that the patient still needed artificial ventilation with an $FiO_2 > 0.21$. Interim analysis (n=245) showed a reduction of pneumothorax incidence (17% vs. 8,3%); single vs. multiple doses; additionally, the incidence of BPD (17% vs. 10%) and mortality (23% vs. 14%) was reduced in multiple treated patients. Final data of approximately 300 patients included in this trial - which will be finished in april 1990 - will be presented.