119

BUPRENORPHINE INFUSION IN THE PRETERM NEWBORN

J. Simpson, N.Rutter, and D.Barrett; Nottingham Neonatal Service, City Hospital and Queen's Medical Centre, Nottingham and Department of Pharmacy, University of Nottingham, UK.

Introduction: Buprenorphine is an opiate analgesic used in adults, children and in the newborn.

Aims of study: Investigation of the pharmacokinetics and pharmacodynamics of buprenorphine in the preterm newborn. This has not been studied previously.

Subjects: 12 ventilated, preterm infants (27 - 32 weeks gestation).

Intervention: Buprenorphine administration as a loading dose (3mcg/kg) and continuous infusion (0.72 mcg/kg/hr)

Measurements: Serial blood samples for buprenorphine concentration, blood gases and blood glucose. Heart rate, blood pressure and respiratory rate were measured.

Results: There were significant ($p<0.05$) falls in heart rate and systolic blood pressure from baseline values during buprenorphine infusion. Mean(SD) steady state buprenorphine concentration was 3.6(1.8) ng/ml. Mean(SD) clearance of buprenorphine was 4.3(1.8) ml/min/kg and terminal half-life in excess of 24 hours. Four infants required an increase in the buprenorphine infusion rate and one infant was withdrawn because of inadequate sedation.

Conclusions (1) Buprenorphine infusion in this age group showed increased steady state concentration, reduced clearance and prolonged half-life compared to older children and adults. (2) Buprenorphine in the pre-term newborn appears to be safe but not always effective. (3) There is a non-standard relationship between the pharmacological effect and plasma drug concentration which makes buprenorphine inappropriate for use in neonatal intensive care.

120

NATURAL SURFACTANT (SF) VS. BRIEF LIQUID VENTILATION (LV) RESCUE THERAPY IN VERY IMMATURE LAMBS. Adolf Valls-i-Soler*, Marla Wolfson, Thomas Shaffer. spn. by Juan R Soriano*. Temple Univer. Dept. Physiol-Pediat. Philadelphia USA and (*)Dept. Pediat, Basque Univer. Bilbao,Spain.

In immature lambs prophylactic LV provides better gas exchange than gas ventilation (GV). In 2 groups of age-matched lambs (gest=111±1d), after GV for first 45min of life, lambs were rescued: G-I(n=6) with 200mg/Kg of 14C -DPPC label SF (Curosurf) and G-II(n=6) with brief (5min) LV with oxygenated liquid perfluocarbon. Results are compared to previous studies in lambs with LV (G-III;n=7) and GV (G-IV;n=9) since birth (J.Appl. Physiol. 72:1024; 1992). Oxygenation improved after therapy in both rescue groups, not reaching G-III levels. In G-II paO2 decrease by 2.5h, and in G-I remained unchanged while PIP and PEEP need to be increased to values above those of G-III. In both G-I and II pulmonary compliance similarly increased after rescure and compared to untreated lambs, been less than in G-III. Labeled SF was distributed with >65% of lung sections with an amount within 20% of mean. Bleeding through tracheal tube was seen in 5/8 lambs in G-I immediately after treatment and was not seen in other groups. Gross and microscopic examination of lungs demonstrated evidence of hemmorhage and uneven inflation in all groups but G-III. Even in very immature lambs, both rescue strategies transiently improve gas exchange and pulmonary function; although exposure of immature lung to GV after rescue, impedes a sustained effect of both rescue modalities, been total LV since birth a better alternative.

121

SURFACTANT PROTEIN A (SP-A) AND INFLAMMATORY CHANGES IN TRACHEAL ASPIRATES FROM VENTILATED NEWBORN INFANTS. *Stefaan Van Lierde*, Toyoaki Akino**, Hugo Devlieger*, Ephrem Eggermont** (spn. by Jaak Jacken*); Department of Pediatrics, University of Leuven, Belgium* and Department of Biochemistry, Sapporo Medical College, Japan***.

Bronchopulmonary dysplasia (BPD) following respiratory distress syndrome (RDS) has been correlated with persistent surfactant deficiency, a prolonged neutrophil influx and a decreased macrophage response in tracheal aspirate contents during the second half of the first week. These variables have not been studied comparing mild (type 1) and severe (type 2) forms of BPD. We prospectively measured SP-A, protein concentration, neutrophil and macrophage counts in 376 tracheal aspirate samples of 105 consecutively ventilated newborn infants in a longitudinal fashion. Fifty-eight patients had RDS (group A), 28 had pulmonary diseases other than RDS (group B) and 19 had no lung disease (group C). At day 1, RDS patients had lower levels of SP-A, protein, neutrophil and macrophage counts than infants of groups B and C. Among patients with RDS, survival without BPD was associated with an increase in tracheal SP-A concentration, neutrophil and macrophage count between day 1 and day 3 to 5; type 1 BPD was associated with an increase in SP-A without a cellular influx, and 'poor outcome' (type 2 BPD or non-survival at day 28) was associated with neither SP-A increase nor inflammatory response. Our findings confirm that a sustained increase in tracheal surfactant concentration and macrophage count is associated with RDS survival without BPD. However, contrary to current understanding, it is suggested that cure of RDS also requires a neutrophil inflammatory response, which is absent in type 1 and type 2 BPD patients and nonsurvivors. The latter two also fail to produce surfactant. Early treatment with corticosteroids may therefore not be appropriate for these infants.

122

ASPIRIN VERSUS INDOMETHACINE TREATMENT OF PATENT DUCTUS ARTERIOSUS (PDA) IN THE PRETERM NEONATE WITH RESPIRATORY DISTRESS SYNDROME (RDS). Bart Van Overmeire*, Frank Brus**, Nynke J.Elzenga**, Albert Okken**. Departments of Pediatrics, University Hospitals of *Antwerpen, Belgium and **Groningen, The Netherlands.

Indomethacine (Indo) is commonly used for treatment of PDA, its main side effect is renal failure. Aspirin (ASA) is an alternative but there are no controlled trials on its efficacy. We randomly assigned 75 premature infants suffering from RDS (mean GA: 29.6 ± 2.5 wks, mean BW: 1295 ± 464 gr) on artificial ventilation at start of study (mean : 3.4 day of life), to either Indo (3 x 0.2 mg/kg/12 hrs) or ASA (4 x 15 mg/kg/6 hrs). PDA and degree of shunting were diagnosed by echocardio-Doppler at start and after 2 and 4 days. Side effects, especially diminution of diuresis, were carefully recorded.

Results: PDA closed in 35/38 patients from the Indo group (93 %) and in 16/37 patients from the ASA group (43 %) ($p<0.001$). No reopenings were observed in both groups. 19 patients needed further treatment with Indo or surgery (17 in the ASA group and 2 in the Indo group). No side effects were seen in both groups except for a decrease of diuresis in the Indogroup during 4 posttreatment days (difference on 2nd posttreatment day: Indo minus 1.06 ml/kg/h vs ASA: plus 0.48 ml/kg/h; $p<0.01$). Fluid management was not different between both groups. Closing of PDA was positively correlated with GA, but not with time of starting Indo/ASA or grade of shunting.

Conclusion: ASA is not as effective in closing PDA as Indo, but has no adverse effect on diuresis.

123

ROLE OF ALLOPURINOL IN REDUCING CEREBRAL HYPOXIC-ISCHEMIC INJURY DURING REOXYGENATION-REPERFUSION. Paul Y K Wu, Won S Park, Frans F Jobsis-Vandervliet. USC Sch. of Med., LAC+USC Med Ctr., Div. of Neonatology, Dept. of Pediatrics, Los Angeles, and Duke Univ., Dept of Cell Biology, Durham, N.C. ,U.S.A.

Oxidation of hypoxanthine (HX) by xanthine oxidase (XO) has been hypothesized to be a potential source of oxygen-derived free radicles (O_2^-) during reoxygenation-perfusion of hypoxic-ischemic organs. Allopurinol (Al), a XO inhibitor, can reduce reperfusion injury. During hypoxia-ischemia, components of the mitochondrial electron-transport chain become reduced. With reoxygenation-reperfusion O_2^- are generated. A Near Infrared Spectroscope (Niroscope) was used to continuously monitor changes in cytochrome aa_3 ($Cytaa_3$), blood volume (BV), saturated Hb (HbO) and desaturated (Hb-) in 24 rats. The rats were divided into 2 groups (Gp). **Gp1** (12), Wt=286±38g (m±SD) received Al (dose 200 mg/kg IP) and was subjected to 1/2 hr period of 9.7%O_2 followed by 100%O_2. **Gp2** (12), Wt=282±41g (m±SD) was subjected to the same 2 periods of FiO_2 but without prior Al. **Results: Gp1**.With administration of 9.7% O_2, $Cytaa_3$ became more reduced, by as much as 100% of total labile signal (TLS), with concomitant fall in BV and HbO and rise in Hb-. With administration of 100% O_2, $Cytaa_3$ became more oxidized with concomitant rise in BV and HbO and fall in Hb-. **Gp2**. During the hypoxic period (9.7%O_2) the changes in $Cytaa_3$, BV, HbO and Hb- were similar to those obtained in Gp1. However on reoxygenation with 100% O_2 the $Cytaa_3$ remained reduced despite increases in BV and HbO and fall in Hb-. To evaluate the role of HX and XO in these changes,an additional 6 rats on 100% O_2 were infused with 1. HX (dose calculated to provide a plasma concentration 30 µM/dl). 2.HX with Arabinose (dose 2-4 ml of 1.6 M Sol.) 3. HX + XO (1 unit). Infusion of HX, and XO, with or without arabinose, did not result in any change in $Cytaa_3$. Our results suggest that allopurinol protect the mitochondrial electron-transport chain from O_2^- during reoxygenation-reperfusion following cerebral hypoxic-ischemic injury probably by scavenging O_2^- rather than by inhibition of xanthine oxidase.

124

CEREBRAL DOPPLER CAN SERIOUSLY MISREPRESENT FLOW CHANGES. Marianne Thoresen* and Kirsti Haaland*, (spn by Andrew Whitelaw) Dept. of Experimental Medical Research, University of Oslo, Ullevål Hospital and *Dept of Pediatric Research, Rikshospitalet, Oslo.

Doppler ultrasound has been widely used to investigate the mechanisms of cerebral ischaemia in sick newborns. If the diameter of the vessel is constant, then changes in cerebral blood flow velocity (CBFV) reflect true changes in volume flow. Even if vessel diameter increases by distention under increased pressure, it is widely assumed that the changes in CBFV will be in the same direction as true changes in flow.

4 newborn piglets underwent simultaneous measurements of cerebral blood flow by electromagnetic flowmetry (EM) on the common carotid artery (extracerebral branches were ligated) and Doppler CBFV. The two methods agreed well under normal conditions ie within moderate CO2 and blood pressure changes. Pathological changes were induced by infusion of 6 - 11 ml/kg of a) blood which had been infected, b) blood which was incompatible (human) c) blood which was chilled to 4 °C d) blood heated to 45 - 50 °C.

Incompatible blood resulted in a 75% increase in EM CBF but only 10% increase in Doppler CBFV. Cooled blood gave Doppler changes that were greater than the EM changes and heated blood gave Doppler changes that were smaller than the EM changes. Infected blood resulted in a decrease in Doppler CBFV of 50% while the EM CBF increased by 30%.

These findings could be explained by vasoactive substances changing the diameters of large arteries. It is therefore possible that Doppler CBFV measurements in critically ill infants with eg sepsis might be misleading.