Working Group on Paediatric Pharmacology—WGPP

Abstracts for Oral Presentations

260 ANTIASTHMATIC DRUGS AND THEIR EFFECTS ON ß-ADRENOCEPTORS OF LYMPHOCYTES FROM ASTHMATIC CHILDREN.

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Because of the lack of direct measurement of sympathetic activity, lymphocytes (LY) which contain the same ß-adrenoceptor (R)-subtype as the bronchial tree have been introduced as an easy available in vitro model to study ß-adrenoceptors (R). Although widely used in prevention of bronchial asthma the mode of action of most antiasthmatic drugs, including prednisolone (PRED), sodium comoglycate (SCG) and ketotifen (KET) remains to be obscure. Since some of these drugs have been reported to influence the adrenergic system in different tissues we have investigated the effects of fenoterol (FENO), PRED, SCG and KET on R of LY. Number and affinity have been quantitatively determined by binding with the radioligand ^{125}[I]-Cyanopindolol.- FENO(4x0.4mg per inhal./d) down regulated the number of R to 40%. PRED (2mg/kg/d) and SCG (4x2mg per inhal./d) were able to prevent this down regulation.In addition PRED increased the basal number of R, whereas SCG did not. A one week treatment with KET (0.2 mg/kg/d) had no influence on R. Since down regulation produced by ß-sympathomimetics is suggested to be due to an internalisation of the drug-R-complex from the cell surface into the cytoplasma PRED and SCG may evoke some of their effects by inhibiting this process.PRED may have a further different mode of action, perhaps on the R-synthesis.

261 PROPRANOLOL INHALATION IN CHILDREN WITH ASTHMA.

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Inhalation of propranolol (P), a non-selective beta blocker, induces a bronchial constriction in many patients with asthma. In adults P challenge has been used for estimation of hyperreactivity. Untill now no reports are available on P challenge in children. In 65 children with asthma aged 8-14 yr we consecutively performed a histamine provocation test and after recovery from bronchoconstriction a P challenge. In 45 children P challenges were performed in the same way as in adults, with dosages increasing in steps of 0,25 mg from 0,25 to 1,5 mg. In 20 children a modified method was used, doubling the concentration of P at each inhalation (0,1-1,6 mg%). In another 20 children the course of FEV_1 after P challenge was studied. The aim of the study was to investigate the feasibility of P challenges in children and to establish the relation with histamine provocation tests. The findings are: - P threshold was found in 60% of the children with a response to histamine. This is in agreement with findings in adults. - The correlation between histamine and P thresholds is slight (r=.34). - Most children have an increase of bronchoconstriction 15 min. after challenge with P. - Severe bronchoconstriction induced by P can be blocked by inhalation of ipatropiumbromide. - Recovery after P challenge is slow and lasts for more than 2 hrs. - P challenge is less suitable for clinical estimation of hyperreactivity. It can be applied for research on basic mechanisms of patterns of bronchial constriction in patients with astma.

262 EFFECT OF KETOTIFEN ON IN-VITRO BRONCHOCONSTRICTION

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Ketotifen has been used in the treatment of asthma for over six years, but its place in management remains controversial. We aimed to reappraise the efficacy of ketotifen at concentrations of 10^{-4} and 10^{-6}M, on two in-vitro models of bronchoconstriction: actively sensitized guinea pig tracheal strips (G.P.T.), and passively sensitized human bronchial muscle strips (H.B.M.). Experiments were performed on matched pairs of tissues. An initial maximal acetyl choline induced response was obtained for each tissue, and all other contractions expressed as a percentage of this. Cumulative dose response curves[C.D.R.C] to histamine or acetylcholine were constructed, and repeated with or without ketotifen. Maximal antigen induced contractions were also compared. Results were analysed using paired t-tests. Contraction of G.P.T. by histamine and acetylcholine was inhibited by ketotifen, but antigen challenge was not affected. Contraction of H.B.M. by acetyl choline and antigen was inhibited by ketotifen. We were unable to obtain reproducible histamine C.D.R.C.'s for H.B.M. In both models the effect of ketotifen was dose related, with attenuation or loss of efficacy at 10^{-6}M, a level close to that attained in clinical practice. These results support the concept of dose dependancy of clinical efficacy of ketotifen, and suggest that therapeutic trials of even higher doses may be warranted.

263 THEOPHYLLINE, SAFELY AND EFFECTIVELY HASTENS WEANING FROM VENTILATION IN PRETERM NEWBORNS.

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Methylxanthines have been used for many years to treat neonatal apnoea in preterm infants. Preliminary evidence suggests they may also have a role in weaning such infants from artificial ventilation (IPPV). This was investigated in a double blind randomised trial giving theophylline orally to preterm infants ($\bar{x}$ GA 28.5 weeks), using a loading dose of 5 mg/kg and a maintenance dose of 5 mg/kg/24 hrs in four divided doses. Control infants received a placebo solution which was indistinguishable from the active preparation. Forty infants were entered into the study and the two groups were well matched for gestational and postnatal age, sex, type and place of delivery.

Administration of theophylline caused both a significant improvement in compliance ($p< 0.05$) six hours after commencing treatment and hastened weaning from IPPV, ($p< 0.01$) compared to the controls. Its use was not associated with an increased incidence of side-effects, in particular no fits, gastric irritation or fluid and electrolyte inbalance was seen.

We conclude that the use of oral theophylline is a safe and effective method of hastening weaning from IPPV in preterm neonates.

264 HAEMODYNAMIC EFFECTS OF BETA-2-RECEPTOR STIMULATION IN CHILDREN: K-H Lundell, K-G Sabel (introduced by R Olegård) Dept of Paediatrics, University of Göteborg,Sweden.

Terbutalin (Te) increases PaO2 in hypoxic newborns with respiratory disorders. The haemodynamic effects of Te have not been investigated in infants previously.The hypothesis that Te reduces pulmonary vasoconstriction and increases cardiac output was investigated in infants with symtomatic ventricular septal defect (VSD) and postoperative children (PO) with suspicion of persistent pulmonary hypertension. Methods: During diagnostic heart catheterization main pulmonary artery (MPA), left atrium and systemic artery (BP) pressures as well as pulmonary flow (Qp) by thermodilution technique were determined before and after the injection of 10 ug/kg Te in the right atrium. Pulmonary vascular resistance (Rp) was expressed in UM^2 (mean pressure gradient over pulmonary vascular bed divided by Qp in L/min per M^{2}BSA) Results: In the VSD group (n=21) all but one had pulmonary hypertension. After Te systolic and mean MPA pressure decreased slightly ($p< <0,05$). Qp increased ($p<0,01$). Heart rate increased markedly and stroke volume decreased. Mean Rp decreased ($p<0,01$). BP dropped at 2 min and was restituted at 5 min. In the PO group all 12 had pulmonary hypertension. After Te MPA systolic pressure increased slightly ($p<0,05$) while diastolic and mean pressures were unchanged. Qp increased ($p< <0,01$). Mean Rp fell after Te ($p<0,02$). BP dropped at 2 and 5 min and was back to initial level at 10 min. No complications of Te injection were detected. Conclusion: The betareceptor stimulator Terbutalin reduces pulmonary as well as systemic vascular resistance and increases cardiac output. The drug may have diagnstic and therapeutic usefulness in conditions with pulmonary vasoconstriction and low cardiac output in early life.

265 CYTOSTATIC AGENTS AND BODY FLUID VOLUMES IN THE HEALTHY DOG. S.S.N. de Graaf, J.A. de Vries, W.G. Zijlstra (introduced by J. Fernandes). Dept. of Pediatrics, University of Groningen, The Netherlands.

We hypothesized that cytostatic agents per se, apart from the malignancy, may have an effect on body water distribution. The influence of high dose methotrexate (HDMTX) and doxorubicin on body fluid volumes in the dog was investigated. Firstly, total body water (TBW), extracellular water (ECW), body weight and plasma osmolality were measured in six healthy mongrel dogs with permanent catheters in aorta and pulmonary artery, before and after infusion of isotonic saline and HDMTX (dose=250 mg/kg in isotonic solution), respectively. TBW and ECW were determined simultaneously, using a double indicator (D_2O/ferrocyanide), single injection technique. D_2O was determined in red cells by an infrared spectrophotometric method; ferrocyanide (hexacyanoferrate II, $Fe(CN)_6^{4-}$) levels were spectrophotometrically assessed in plasma. One hour after HDMTX infusion we observed a increase in mean ECW from 225 to 244 ml/kg body weight ($p=0.011$, paired Student's t-test); this is an increase of 8.4 %. Mean TBW remained the same. The increase in ECW could not be explained by a simple volume effect as an equal volume of saline did not yield a significant change in extracellular fluid volume. Plasma osmolality decreased only 1% and therefore a simple osmotic mechanism was unlikely to have caused the observed fluid shift. No other drugs, known to influence water distribution, e.g. barbiturates, were administered. Results suggest a water shift across the cell membrane due to an effect of HDMTX. Similar experiments using doxorubicin (1 mg/kg) did not show any significant change in either TBW or ECW.