79

DOSING TOBRAMYCIN IN CHILDREN WITH CYSTIC FIBROSIS USING SERUM CONCENTRATIONS. I. PHARMACOKINETICS.

*Driessen, O., **Horrevorts, A.M., **Kerrebijn, K.F., *Hermans, J. and **Michel, M.F.
*Depts. of Pharmacology and Medical Statistics, Univ. of Leiden, Leiden, The Netherlands. **Depts. of Pediatrics and Clinical Microbiology, Erasmus University Rotterdam, Rotterdam, The Netherlands.

In 15 patients (8 to 22 years of age) with cystic fibrosis (CF) the plasma concentration time profile of tobramycin was carefully monitored by sampling plasma 15 times during 8 hours. The obtained data were well fitted by a two-compartment open model. It appeared that the concentration-time curves and some of the derived pharmacokinetic parameters were clearly age-dependent [1]. $T_{\frac{1}{2}\alpha}$, $T_{\frac{1}{2}\beta}$ and the area under the concentration-time curve per unit of dose were inversely correlated with age and body weight. Using the experience obtained in such patients a single tobramycin dosage scheme for CF patients of all age groups was formulated, intending not to overshoot a plasma level of 2 µg/ml tobramycin at the end of the dosage interval, whereas the period in which a plasma level less than 1 µg/ml existed would be minimal. We were of opinion that by such a scheme CF patients would be treated optimally, while avoiding toxicity. This scheme is adapted to the pharmacokinetic behaviour of individual patients by measuring two points of the concentration-time curve of tobramycin in a patient and subsequently adjusting the dosage interval to individual needs. The therapeutic gain obtained with the scheme is the subject of part II of this study.

[1] Pharmacokinetics of tobramycin in patients with cystic fibrosis; implications for the dosing interval. Chest 88 (1985) 260-264.

80

DOSING OF TOBRAMYCIN IN CHILDREN WITH CYSTIC FIBKOSIS USING SERUM CONCENTRATIONS: II.PHARMACODYNAMICS.

*Horrevorts, A.M., **Driessen, O., *de Witte, J., *Michel, M.F. and **Kerrebijn, K.F. *Depts. of Clinical Microbiology, Respiratory Diseases in Children, Erasmus University, Rotterdam. **Dept. of Pharmacology, State University, Leiden, The Netherlands.

The efficacy of chemotherapy in treating acute exacerbations of chronic respiratory infections in patients with cystic fibrosis (CF) is sometimes poor. This cannot always be adequately explained by the severity of the disease or the susceptibility of the bacterial flora to the drugs used. After 10 days of treatment+, pulmonary function did not improve in 16 patients with CF, despite tobramycin-sensitive micro-organisms and adequate 1-hour peak (between 5-8 mg/l) and safe 8-hour trough (< 2 mg/l) serum tobramycin concentrations. It appeared that in these patients an 1 mg/l serum tobramycin level was attained within 3-6 hours after a dose. In order to ensure sufficiently protracted serum concentrations which may be expected therapeutically active, in 9 out of the 16 patients, we adjusted the dosing interval to a minimum trough level of 1 mg/l. In the other 7 patients, no alteration in the dosing interval was made. In the patients in whom the dosing interval was shortened, pulmonary function was significantly more improved than in the patients in whom the dosing interval was unchanged ($P < 0,02$). Toxic side effects of tobramycin were not observed. It is concluded that the use of more frequent dosages of tobramycin may be necessary in treatment of patients with CF.

+ Tobramycin: 10 mg/kg/day in three divided doses at 8-hr intervals; Ticarcillin: 600 mg/kg/day.

81

A NOVEL FORM OF DRUG-INDUCED CARNITINE INSUFFICIENCY

Melegh B., Kerner J., Department of Pediatrics and Biochemistry, University Medical School of Pécs, Pécs, Hungary

Pivalic acid is widely used in pharmacology to facilitate drug absorption. As a fatty acid it may react with carnitine /C/ but further degradation via beta oxidation is impossible due to its structure. It is possible therefore, that pivalate containing drugs can cause C insufficiency. Urinary excretion of C /o to 7 days daily/ and fasting plasma levels of C, beta hydroxybutyrate /BHB/, FFA, triglycerides /TG/ and glucose /BG/, /day o and 7/ were measured in 7 children during pivampicillin treatment /2g/day/. Drug administration was followed by a prompt and sustained increase in total C excretion /o.27±o.o7 vs 1.24±o.18 mmol/day, day o vs 1, means±SEM, $p < o.o5$/ which was mainly due to a rise in acyl C excretion, the excretion of free C declined. The plasma level of total C /42.7±5.4 vs 26.2±2.1 umol/l, $p < o.o5$/, BHB /o.27±o.13 vs o.o4±o.o2 mmol/l, $p < o.o5$/ and urea /4.61±o.25 vs 3.74±o.2 mmol/l, $p < o.o2$/ decreased and acyl C increased /11.6±1.9 vs 17.7±1.7 umol/l, $p < o.o5$/ with no change in TG, FFA and BG levels.

Conclusions: 1., Decreased availability of free C may cause carnitine insufficiency /increase of the acyl:free C ratio/ and as a consequence ketogenesis and urea synthesis may be impaired; 2., Increased excretion of acyl C, on the other hand, may represent a novel xenobiotic function.

82

PHARMACOKINETICS OF NETILMICIN IN NEONATES.

E. Autret, C. Lionnet, J. Laugier, M. Breteau. Hôpital Gatien de Clocheville, 37000 Tours, France.

Studies in animals and in adults have shown that netilmicin (NM) is as effective but less nephrotoxic or oxotoxic than other aminoglucosides. There are few data on the use of NM in neonates, which can help the neonatologist to predict situations during which NM monitoring will be necessary.

54 pharmacokinetic (PK) NM studies were performed: in 31 fullterm and 14 preterm babies. 3 mg/kg/12 h of NM was administered by 30 mn infusion in 40 cases and by IM route in 14 cases. Serum concentrations were analyzed by fluorescence polarization. For IV and IM route the mean peak serum level was 5.57 mg/l and 6.34 mg/l, recpectively, the mean through level was 1.66 mg/l and 2.36 mg/l. Mean concentrations were significantly higher with the IM than with the IV route because of the slow IV administration. In the 9 children with two successive pharmacokinetic studies the mean plasma levels were significantly higher during the second study, suggesting an accumulation of NM. The serum half life was higher:

1) in preterms (7.19 h) than in fullterms (5.84 h).
2) in neonates with proven infections (8.5 h) than in those with suspected infections (5.4 h) suggesting poor hemodynamic conditions in those babies with diminution of clearance of NM.

Our study shows that 3 mg/kg by 30 mn IV infusion of NM is safe in neonates without dangerous peak levels: it will be useful to monitor NM levels in preterm babies, neonates with proven infections and during treatment longer than 7 days.

83

RELIABLE NON-INVASIVE MONITORING OF THEOPHYLLINE THERAPY IN INFANTS AND CHILDREN: MEASUREMENT OF SALIVA THEOPHYLLINE CONCENTRATIONS.

Aviram, M; Tal, A; Ben-zvi, Z; and Gorodischer, R. Soroka University, Hospital, Beer-Sheva, Israel 84101

The use of saliva (Sa) theophylline (Th) for monitoring Th therapy is not routinely used in infants and young children due to the inapplicability of the usual technique (chewing on a piece of paraffin) to obtain stimulated Sa in this age group.

Simultaneous blood and Sa samples were obtained in 57 infants and children (age: 3 mo-14 ys; mean: 3.3ys) under Th therapy. Th was given po (slow release preparations or elixir) or i.v. Mean± SD dose was 21.3±6.4 mg/kg/day. Sa secretion was stimulated by placing citric acid crystals on the tongue. Plasma (Pl) and Sa Th was analysed by competitive fluorescence polarization immunoassay (TDx).

Mean± SD Pl/Sa Th concentration ratio was 1.78±0.25 within a wide Pl Th concentration range (3.1-32.1 mcg/ml). Good correlation existed between both determinations (r=0.98). Interindividual coefficient of variation (CV) was 14%; mean intraindividual CV was 5.2%. Mean estimated/actual Pl Th ratios determined in the following 48 samples studied was 0.98±0.11, CV 11.2%.

Th measurements in citric-acid stimulated saliva represent a convenient, non-invasive and reliable method for monitoring theophylline therapy in infants and children.

84

IS THE YOUNG RAT PROTECTED TO NEPHROTOXIC DRUGS BY ITS HIGH KIDNEY WEIGHT RELATIVE TO BODY WEIGHT?

H.T.M. Jongejan, A.P. Provoost, O. Adejuyigbe, E.D. Wolff, Depts. of Pediatric Surgery and Pediatrics, Erasmus University, Rotterdam, the Netherlands.

We compared the nephrotoxicity and renal accumulation of two aminoglycosides, Gentamicin (Gm) and Amikacin (Ak), and of Cisplatin (Cp) in young (BW ±50g) and adult (BW ±300g) rats. The glomerular filtration rate (GFR) was measured regularly as the plasma clearance of Cr-51 EDTA, with a method allowing repeated use within the same animal. The aminoglycosides were administered s.c. for 14 days (60mg Gm and 180mg Ak per kg/day). Cp was given as a single i.v. injection (5mg/kg). Measurements of the acute effects of the drugs, i.e. on day 14 for the aminoglycosides and on day 4 for Cp, revealed that the decrease in GFR was significantly less in young rats than in adults for all drugs. The GFR recovered completely in the young, while a permanent impairment remained in adult rats treated with Gm or Cp. Measurement of renal drug levels showed that these were significantly lower in young rats than in adults. This was not due to a diminished uptake (as a % of the injected amount), but to the heigh kidney weight relative to body weight in young rats. Per 100g BW the wet kidney weight of young rats was 190% of that in adults. The renal drug concentration in young rats was in average only 55% of that in adult rats. We conclude that if 1) drugs are administered relative to BW and 2) they have to accumulate in the kidney to become nephrotoxic, the young rats are at least partially protected because of their high relative kidney weight.