PARVALBUMIN PLAYS AN ESSENTIAL ROLE IN THE HYPERCALCIURIA INDUCED BY LOOP DIURETICS.

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Loop diuretics such as furosemide increase urinary Ca2+ excretion, which can lead to kidney stones and/or nephrocalcinosis. This hypercalciuria has been attributed to an impaired paracellular reabsorption of Ca2+ secondary to the inhibition of the Na+-K+-2Cl- cotransporter in the thick ascending limb (TAL) of Henle's loop. However, the possible implication of the transcellular Ca2+ reabsorption in the distal convoluted tubule (DCT) remains unclear.
Parvalbumin (PV) is an intracellular, high-affinity Ca2+-binding protein that is expressed in muscles but also in the DCT of the mammalian nephron, where its role is unknown. To gain a better understanding of the potential role of PV in the renal handling of Ca2+, we used knockout mice for PV (PV-/-) that have been generated by homologous recombination. These mice develop and grow normally, with no significant alterations in their renal structure and function under standard housing conditions. The mice were kindly given by B. Schwaller from the Institute of Histology and Embryology of the University of Fribourg, and by Hoffmann-La Roche AG, Basel.
Immunostaining and immunoblotting analyses verified the correct expression of PV in the kidneys of wild-type mice (PV+/+), and its absence in the PV-/- mice. Seven pairs of PV+/+ vs. PV -/- mice (males, aged 15 weeks) were studied for 6h in metabolic cages to assess diuresis and renal handling of ions at baseline and following a single injection of furosemide (10 mg/kg, SC). At baseline, mice were similar in terms of body weight and urinary excretion of Na+ ; however, PV-/- mice showed a significant increase in diuresis (+60%, vs. PV+/+) and kaliuria (+23%), and a trend for lower urinary Ca2+ excretion (-27%). Treatment of PV+/+ mice with furosemide led to the expected increase in diuresis (+76%, vs. untreated), with a significant increase in the urinary excretion of Na+ (+446%), K+ (+77%), and Ca2+ (+83%). Furosemide in PV-/- mice induced a similar effect on diuresis (+66%, vs. untreated), Na+ (+225%), and K+ (+22%) excretion but, surprisingly, no increase in urinary Ca2+ excretion (-4%). These observations were confirmed in female PV mice.
These data show that the loss of PV in the DCT is associated with discrete perturbations at baseline, but is critical to mediate the hypercalciuria induced by loop diuretics. Our results also indicate that PV-deficient mice will be a useful model for deciphering the mechanisms of transcellular Ca2+ handling by the distal nephron.

3

HEALTH AND ECONOMIC OUTCOMES OF CRITICALLY ILL PATIENTS WITH NOSOCOMIAL CATHETER-RELATED BLOODSTREAM INFECTION (CR-BSI).

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Objective. To evaluate mortality and excess length of hospitalization in ICU patients with nosocomial CR-BSI.
Methods. A retrospective matched cohort study (Jan 1992 Dec 2002) was performed in which all ICU patients with CR-BSI were defined as cases (n=192). Cases were matched with control subjects (1:2-ratio), (n=384) on basis of the acute physiology and chronic health evaluation (APACHE) II system: an equal APACHE II score (±4 points) and diagnostic category. As expected mortality can be derived from this severity of disease classification system, this matching procedure results in an equal expected mortality for cases and controls. In addition, control subjects were also required to have had an ICU stay at least as long as the matched case s length of stay before the onset of the CR-BSI. Continuous variables are described as median [interquartilerange] and categorical variables as %. Results. 51.6% of CR-BSI were due to coagulase-negative Staphylococci, 26.1% due to other gram-positive bacteria (11.5% S. aureus), 29.2% due to gram-negative bacteria and 10.9% due to Candida species. 19.2% of CR-BSI were polymicrobial. 87% of the catheters were removed within 24h.
There was no difference between cases and controls in age (respectively 55 year [39-66] vs. 56 [42-68]; P=0.292), incidence of acute respiratory failure (respectively 89.1% vs. 83.6%; P=0.081) and hemodynamic instability (respectively 74.0% vs. 66.4%; P=0.070). Cases had more acute renal failure (26.0% vs. 15.4%; P=0.003). Despite having a higher morbidity, mortality in cases was not different from control subjects (respectively 27.1% vs. 28.1%; P=0.844). Cases had a longer ICU stay (31 days [17-49] vs. 18 days [8-31]; P<0.001), a more extended period of mechanical ventilation (24 days [15-38] vs. 14 days [6-24]; P<0.001) and a longer length of hospitalization (55 days [28-108] vs. 34 days [16-75]; P<0.001). From this, a median excess ICU stay of 13 days was calculated (from 18 through 33 days) whereof 10 days on mechanical ventilation (from 14 through 24 days). The median excess in hospital stay averaged 21 days (from 34 through 55 days).
Conclusions. We found that, after careful adjustment for severity of underlying disease and acute illness, CR-BSI does not adversely affect the clinical outcome in our ICU population. Yet, CR-BSI carries an important economic burden as lengths of ICU stay, mechanical ventilation and hospitalization are significantly increased in these patients.

4

OBSERVATION AND COMPARISON OF REPEATED UPRIGHT CYCLE ERGOMETER TESTING IN PATIENTS WITH THE CHRONIC FATIGUE SYNDROME

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Background : Exercise testing is a common tool in the clinical evaluation of patients with the chronic fatigue syndrome (CFS), however all CFS patients experience a total loss of strength during several days after the examination.
Objective : To evaluate and compare exercise capacity data of two consecutive bicycle ergometric tests performed with an interval of twenty-four hours.
Methods : Heart rate at rest, peak heart rate, and exercise capacity of eighty-one CFS patients (fulfilling the 1994 case definition)during two consecutive exercise tests were collected and analysed. Tests were started at 50 Watt, with an increase of 10 Watt per minute untill exhaustion. It was assumed that maximal effort was performed if 85% or more of the age-predicted maximal heart rate (220-age) was reached. For statistical analysis SPSS version 11.5 was used.
Results : Forty-nine patients performed maximal effort in the first test, forty-one patients in the second test. Fourteen patients could not reproduce their maximal effort after an interval of twenty-four hours. Maximal exercise capacity was significantly lower in the second test (109.9±37.73 Watt versus 114.7±37.72 Watt; P<0.001). Heart rate at rest was significantly higher starting the second test (95.4±16.91 beats/min versus 92.1±15.80 beats/min; P=0.038).
Conclusion : Significant differences in heart rate at rest and in exercise capacity between two consecutive bicycle ergometric tests were observed in CFS patients.

5

FOLLOW-UP OF IRON AND RED CELL PARAMETERS AT rHuEPO INITIATION: IMPACT OF ERYTHROPOIETIC STIMULATION ON RED CELL PARAMETER DETERMINATION.

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Background Initiation of rHuEPO therapy is associated to erythropoietic stimulation and reticulocyte production. We have previously shown that the percentage hypochomic RBC (%HYPO) was correlated to the reticulocyte count. The aim of this study was to assess whether %HYPO is specific for iron deficiency in a situation of erythropoietic stimulation with appropriate iron supply.
Methods Six patients, free of inflammation and transfusion, completed the follow-up. They were included when the Hb level was lower than 10.5 g/dL so that the administration of rHuEPO was indicated. rHuEPO was administered intravenously at the dose of 200 UI/kg/week in three doses. Iron supplementation was initiated at the start of rHuEPO therapy at the dose of 100 mg IV iron sucrose (Venofer®) once weekly. Iron and red cell parameters were measured weekly for 12 weeks before the first dialysis session of the week.
Results The treatment schedule was efficient for the correction of anemia. The Hb level was 12.1±0.6 at the end of follow-up versus 8.3±1.2 g/dL before rHuEPO administration. The reticulocyte crisis occured at day 7. Despite IV iron supplementation, ferritin and TfSAT decreased from 241.2±130.4 to 112.0± 30.1 ng/mL and from 18±3 to 15±3 %, respectively. All along the follow-up, CHr remained constant (31.8±2.1 vs 32.4±0.7pg; p=0.56). However, a progressive increase of %HYPO was observed (7.2±4.1 vs 1.7±0.8 %; p<0.05). This evolution is due to a slight decrease in Hb concentration (CHCM: 32.3±0.5 vs 33.0±0.7 pg/mL; p=0.14) which is due to increased RBC volume (90.1±2.5 vs 85.7±2.4 fL; p<0.001) and stable Hb content (CH: 28.6±2.0 vs 28.7±0.8; p=0.89). The evolution of reticulocyte and RBC volume and Hb concentration was similar.
Conclusion Based on CHr follow-up, 100mg IV iron sucrose per week at rHuEPO initiation prevents iron deficient erythropoiesis. Despite CHr stability, %HYPO increased. This can be explained by the reticulocytosis (larger cells with similar Hb content) interfering with red cell parameter determination. This may lead to overtreatment by IV iron with the risks of complications it may carry.

6