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CEREBROSPINAL FLUID (CSF) BIOGENIC AMINE METABOLISM IN CHILDREN WITH ACUTE LYMPHOCYTIC LEUKEMIA (ALL). F.S. Silverstein, R. Hutchinson, M.V. Johnston, U. of Michigan, Depts. of Pediatrics and Neurology, Ann Arbor.

Clinical,radiologic and pathologic evidence of central nervous system(CNS)injury may be found in children with ALL who have received CNS prophylaxis with intrathecal(IT) methotrexate (MTX) & craniospinal irradiation. It has been suggested that neuronal susceptibility to MTX is due to inhibition of biogenic amine-dopamine(D) & serotonin(S)-synthesis by this drug(Ca Treat Rep 62:1999).To test this hypothesis, we measured levels of homovanillic acid(HVA) & 5-hydroxyindoleacetic acid(HIAA), stable acid metabolites of D & S,in weekly sequential CSF's from 30 patients (pts) with ALL examined prospectively(Group 1), & in CSF's from 130 pts in remission. Group 1 pts, 22 boys & 8 girls, age 2-15, with normal pre-treatment HVA and HIAA, received 8 doses of IT MTX at weekly intervals. Regression analysis of HVA levels revealed a gradual decline in the first 4 wks(r=-1.4)& a more pronounced increase in the next 4 wks(r=+6.5)(p=.027,t-test comparison of slopes). Similar trends were observed for HIAA. These changes were independent of age, sex, and CSF protein elevation. In contrast,there was little intra-subject variability in levels in the absence of intensive MTX therapy;60 paired CSF's obtained at 3 mo intervals,showed no changes in HVA & HIAA. The data provide evidence for MTX induced alterations in biogenic amine synthesis and/or transport. If the levels reflect altered neuronal activity, these observations may contribute to an understanding of changes in mood, appetite, sleep,& other aspects of behavior which are disrupted during treatment.

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DDAVP INHIBITS PROSTACYCLIN FORMATION: A POTENTIAL MECHANISM FOR BLEEDING TIME (BT) CORRECTION IN HEMOSTATIC DISORDERS. Marie J. Stuart, Carolyn Ganley, Mary Reed, Sherry Boone, Ronald Dubowy, Yamaja Setty, SUNY, Upstate Medical Center, Dept. of Pediatrics, Syracuse, N.Y.

A recent study has shown that DDAVP normalizes the B.T. in plt. functional defects. In vitro evidence also suggests that DDAVP enhances plt-vascular adherence. We assessed the effects of DDAVP on prostacyclin as a possible mediator of these effects. Initial studies on human vessels revealed that incubation of segments with DDAVP ↓ $6KPGF_{1\alpha}$ formation. Values of 3.4±0.8 and 2.5±0.7 pmol/mg were obtained in the presence of 0.1 and 1.0 μg/ml DDAVP, with paired control values of 4.1±1.0 and 4.0±1.1 ($p<0.01$). No differences in $6KPGF_{1\alpha}$ were observed when segments were incubated with DDAVP vehicle alone (0.1μg/ml), although at 1μg/ml a slight↓ in $6KPGF_{1\alpha}$ was seen. Direct assessment of the effects of DDAVP on ionophore (10μM) stimulated release of $6KPGF_{1\alpha}$ from bovine endothelial cell monolayers revealed that at 1μg/ml both DDAVP and its vehicle caused a ↓ in $6KPGF_{1\alpha}$ release (33+18 and 31±16 pmol per 10^6 cells versus control values of 121±46 pmol;$p<0.01$). Finally, changes in plasma $6KPGF_{1\alpha}$ are being assessed in patients (n=5) with plt. functional defects in whom DDAVP has been used as a therapeutic modality to correct their prolonged BTs. A ↓ in plasma $6KPGF_{1\alpha}$ has been observed with mean levels of 0.32 and 0.25 pmol per ml prior to and 90' post DDAVP respectively. These studies, demonstrating an in vitro and in vivo effect of DDAVP on endothelial cell prostacyclin production, suggest a potential, hitherto unrecognized,mechanism for BT correction in hemostatic disorders.

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HIGH DOSE STEROIDS (HDS) IN CHILDHOOD ACUTE IDIOPATHIC THROMBOCYTOPENIA PURPURA. Carlos R. Suarez, Dennis Rademaker, Albert Hasson, Lynn C. Mangogna (Spon. by Lewis E. Gibson) Loyola University Medical Center, Department of Pediatrics, Maywood, IL.

The use of steroids in childhood ITP is controversial. High dose intravenous gammaglobulin (IVG) has become an accepted treatment in ITP. HDS in children with ITP has also been proposed ; we utilized a regimen incorporating HDS (prednisone 4-8 mg/kg/d) based on initial platelet count in nine newly diagnosed untreated children with ITP severely thrombocytopenic (mean platelets 5 X 10^9/L). All cases had positive immunologic evidence of ITP (platelet associated antibodies, serum antiplatelet antibodies), bone marrow compatible with ITP and no clinical or laboratory evidence of other disease.

		Platelets X 10^9/L					Prednisone (mg/kg/d)	
Group	N	Initial	Range	Peak	Last	Follow-up	Initial	Days on HDS
A	4	3.2	1-4	494	282	8.1 mos	8	6.7 + 1.2
B	5	7.8	5-12	386	323	7.0 mos	6	6.4 ± 2.9
Total	9	5.4	1-12	433	304	7.4 mos	6.8	6.6 ± 2.2

All patients are presently in remission; none require treatment. For the total group it took 1.9 days (range 1-3) to reach a platelet count of 20 X 10^9/L and 7.1 days (range 2-23) to reach 100 X 10^9/L. Only one case had a relapse (platelet count 18 X 10^9/L). This happened on day 14 of therapy while on 2 mg/kg/d prednisone and responded to an increase to 4 mg/kg/d within 5 days. No serious toxicity was observed except for weight gain ranging from 3-10% (mean 8%) and 5/9 patients showed periods of hyperactivity and poor discipline. HDS is effective in severely thrombocytopenic children with acute ITP, carries few side effects, influences the natural course of the disease, and is at least as effective as IVG and comparatively more cost effective.

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A REASSESSMENT OF PASSIVE IMMUNIZATION AGAINST VARICELLA. Jean Taylor-Wiedeman, Philip A. Brunell, Clementina F. Geiser, Lisa Frierson, and John Connolly. U.T. Health Science Center, Department of Pediatrics, San Antonio, Texas.

Concern has been expressed about the efficacy of Varicella-Zoster Immune Globulin (VZIG) given intramuscularly (IM) to high risk individuals exposed to varicella. Perceived decreased efficacy may be due to more intensive chemotherapy and/or decreased potency of VZIG. Varicella-zoster antibody titers (VZAT) were determined by enzyme-linked immunosorbent assay for 21 normal adults and 23 susceptibles; the means and standard deviations were 0.600 ± 0.310, and 0.020 ± 0.0153 respectively. The seronegative range was defined as the mean for susceptibles +3 SD, ≤0.066. The peak mean VZAT in 7 seronegative VZIG recipients was 0.123 and, at 4-8 weeks, only 0.066. Thus, the peak VZAT provides minimal levels of antibody. Moreover, a second exposure following the usual incubation period would require an additional dose of VZIG. In contrast, 11 seronegative patients who received intravenous transfusions of platelets, white blood cells in plasma, or plasma alone had peak mean VZAT of 0.310. For 9/9 patients the duration of seropositivity lasted 4 weeks and for 2/5 as long as 12 weeks. Much higher peak titers of antibody were achieved than by IM VZIG ($p\ 0.01 > 0.02$) which might further reduce morbidity. Larger volumes of antibody could be given IV than IM, there is less pain, and thrombocytopenia would not be a deterent. Development of an IV VZIG preparation would appear to have a greater likelihood of reducing morbidity from varicella.

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DESMOPRESSIN (DDAVP) FOR MAINTAINING HEMOSTASIS AT SURGERY IN HEMOPHILIA A AND VON WILLEBRAND'S DISEASE. Indira Warrier and Jeanne M. Lusher Wayne State Univ. School of Medicine, Children's Hospital of Michigan Detroit.

Desmopressin (1-deamino-8-d-arginine vasopressin; DDAVP) results in a transient increase in all F VIII components (VIII:C, VIIIR:Ag, VIIIR:Cof) in normal subjects as well as in those with mild hemophilia A and von Willebrand's disease (vWD). In addition, this synthetic agent effects a transient normalization of the bleeding time (BT) in persons with vWD type I, and partial correction in type IIa. We have given desmopressin to 25 individuals undergoing surgery (14) or extraction of permanent teeth (11). Three subjects had moderate hemophilia A while 22 had vWD type I. Desmopressin was given in a dosage of 0.3 μg/kg, I.V., 30-45 min. prior to surgery. Those undergoing oral surgery were also given EACA, 300 mgm/kg/day for 7-10 days. Hemostasis was maintained in all 25 subjects and none required blood products. Desmopressin appears to be a safe and effective alternative to the use of blood products in certain individuals with mild-moderate hemophilia A and vWD. Patient selection should be made on the basis of 1) the patient's usual baseline F VIII level, 2) nature and extent of surgery to be done, 3) type of vWD (i.e. appropriate tests should be done to exclude vWD types IIb and III), and 4) response to a test dose of desmopressin. Desmopressin is particularly useful for surgical procedures in which it is anticipated that a relatively short-term normalization of F VIII and BT will suffice. If repetitive doses of desmopressin are given, one must be aware of tachyphylaxis, as well as the possibility (albeit slight) of hyponatremia and fluid overload.

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HYPERACTIVE PLATELETS ASSOCIATED WITH STROKE IN CHILDREN. Indira Warrier and Michael Nigro. (Spon. by Jeanne Lusher,) Wayne State Univ. School of Medicine, Children's Hospital of Michigan Detroit.

We have investigated platelet activity in 13 children (mean age 11 yrs.) who had one or more episodes of unexplained stroke, with arteriograms revealing medium size arterial occlusions. Six children had no associated risk factors while 7/13 had one (migraine, hyperlipidemia, mitral valve prolapse, oral contraceptives). Platelet activity was assessed using electron microscopy (whole blood TEM platelet function test) and platelet aggregometry. The TEM platelet function test showed platelet hyperactivity in 11 of 13 subjects, with a marked shift from round or abortive forms to spread forms and increase in spontaneous platelet aggregates.

	Round/Abort.	Dendritic	Spread	Aggregates
Normal (100)	10.2 + 8.5	80.5+ 6.2	9.7+ 5.7	<50
Patients(13)	7.69+ 6.5	43.4±20.6	48.9±25.2	63.5±27.8

In contrast,platelet aggregometry using decreasing concentrations of ADP and epinephrine showed hypo or normo-responsiveness in the majority (11/13) of patients studied. This may reflect in vivo activated & 'exhausted' platelets being refractory to such agonists in vitro.

Seven of 11 children with marked platelet hyperactivity who received small doses of aspirin and persantine had normalization of platelet activity and clinical improvement. We conclude there is a relationship between platelet hyperactivity and stroke in children. Aspirin in small daily doses (80 mg) may prove useful in preventing recurrent micro infarcts.