259 DEVELOPMENT AND TESTING OF AN ALGORITHM FOR RELIABLE CLINICAL IDENTIFICATION OF ADVERSE DRUG REACTIONS. J.M. Leventhal, M.S. Kramer, T.A. Hutchinson, and A.R. Feinstein. (Spon. by H.A. Pearson) Yale Univ. Sch. of Med. Yale-New Haven Hospital, Depts. of Ped. and Med., New Haven.

Despite widespread epidemiological attention to surveillance for adverse drug reactions (ADR's), the results of surveys remain difficult to interpret because identification of ADR's has been a non-reproducible act of unspecified, subjective judgment.

To improve scientific precision in the diagnosis of ADR's, we have developed an algorithm that provides detailed operational criteria for ranking the probability of causation when an ADR is suspected. The algorithm provides a scoring system for six axes of decision strategy: previous general experience with the drug, alternative etiologic candidates, timing, drug levels, and the effects of dechallenge and rechallenge. The sum of the scores is ordinally partitioned to rate the candidate ADR as definite, probable, possible, or unlikely.

The reproducibility and validity of the algorithmic scores were tested with a clinical spectrum of 30 cases of suspected ADR's. Three physicians independently using the algorithm agreed completely in 20 cases; were within one ordinal category of each other in the remaining 10; and scored between 0.911 and 0.956 in the Cicchetti index of pair-wise agreement. The algorithm scorers' consensus agreed with 'truth', as defined by the implicit judgments of 2 experts, in 26 of 30 cases.

The algorithm provides a formal, valid, and reproducible method of identifying the likelihood of an ADR, and can allow accurate assessment of this important, complex clinical phenomenon.

260 STUDIES ON A NEW COAGULATION PARAMETER: DECREASED URINARY γ CARBOXYGLUTAMIC ACID EXCRETION WITH WARFARIN THERAPY. Robert J. Levy, Jane B. Lian, Paul M. Gallop. Spon. by Alexander S. Nadas. Harvard Medical School, Children's Hospital Medical Center, Departments of Cardiology and Orthopedic Research, Boston, Mass.

Warfarin anticoagulation has been previously shown to result from inhibition of post-translational synthesis of γ carboxyglutamic acid (Gla) from glutamic acid residues in the vitamin K-dependent clotting factors. This recently discovered amino acid (Gla) is synthesized in the liver and is known to be excreted in urine largely as the free amino acid. Furthermore, previous work indicates that urinary Gla excretion is chiefly derived from prothrombin breakdown and turnover. The purpose of the present study was to monitor urinary Gla excretion in order to detect any significant differences between normal and anticoagulated patients. Fourteen patients were studied. Seven were on stable Warfarin anticoagulation therapy and 6 were controls. One patient was studied postoperatively during initial anticoagulant treatment. Free urinary Gla was measured in 24 hour collections using 2N KOH hydrolysis and automated amino acid analysis. Normal subjects excreted 18-27 micromoles (μM of Gla)/24 hours (hrs) while anticoagulated patients (Prothrombin time range 20-30 sec. control = 12.0) excreted only 2.7-13 μM/24 hrs. Gla excretion in the patient begun on Warfarin dropped progressively during the first 10 days of therapy (128 μM/24 hrs. to 22 μM/24 hrs.) while Prothrombin time stabilized by day 6 (range 19.0 sec. to 22.9 sec). We conclude that urinary Gla excretion is reduced by Warfarin, and that monitoring urinary Gla may prove useful in regulating anticoagulation.

261 RAPID CONTROL OF NEONATAL NARCOTIC ABSTINENCE UTILIZING A PHENOBARBITAL LOADING DOSE METHOD. Thomas F. Mitros, Leigh Hopkins, Loretta P. Finnegan (Spon. by Leonard J. Graziani), Jefferson Medical College, Department of Pediatrics, Philadelphia, Pa.

Phenobarbital has long been the drug of choice in controlling seizures and narcotic abstinence syndrome (NAS) in newborns. This report describes the relationship between dosage and serum concentration using a high oral loading dose of phenobarbital followed by maintenance dosing to provide therapeutic serum levels more rapidly than with previous methods. Twenty neonates born to narcotic dependent mothers were studied; all had NAS and were evaluated by an abstinence scoring system. When high abstinence scores were reported (>8), all received a loading dose of 16 mg/kg of phenobarbital orally to rapidly achieve an expected therapeutic serum level of 18 mcg/ml. Results showed a serum level of 16 mcg/ml ± 2.6 at 3 hours after the loading dose as determined by the EMIT technique. Serum levels (mcg/ml) at 12 and 24 hours after the loading dose were 18.9 ± 3 and 18.6 ± 3.4. If the infant responded with the expected therapeutic serum level, and if the abstinence score decreased to <8 (defined as control of symptoms), maintenance doses were begun. Daily maintenance dosing of 2 mg/kg/day allowed serum levels to decline at a desirable rate of 20% per day. These infants were more easily controlled and detoxified with the phenobarbital loading dose method than with previously accepted dosing regimens.

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262 ALPHA-METHYLDOPA METABOLISM IN HYPERTENSIVE AND RENAL INSUFFICIENT CHILDREN: IDENTIFICATION OF A NEW METABOLITE. R.F. O'Dea, M.J. Cooper and B.L. Mirkin. Univ. of Minn. Med. Sch., Dept. Peds. & Pharmacol., Div. Clin. Pharmacol., Minneapolis, Minnesota.

Despite extensive clinical use, the basis for the antihypertensive action of alpha-methyldopa (α-MD) has remained undefined. Alpha-methyldopamine (α-MDA), the decarboxylated product of α-MD, has been suggested as a possible mediator of these effects in the CNS. A sensitive and specific high-pressure liquid chromatographic system coupled to an electrochemical detector has been developed for the assay of α-MD, its metabolites and their sulfated conjugates in biological specimens. This technique has routinely detected 0.1 μg/ml of aromatic amine. In 7 hypertensive pediatric patients receiving α-MD therapy, the serum levels of α-MD and its 3-O-SO_4 conjugate were significantly elevated in subjects with impaired renal function (creatinine>2.0). The presence of α-MDA and its 3-O-SO_4 conjugate has also been demonstrated in serum. In renal dysfunction there is a 6-10 fold elevation of both α-MDA and its sulfated conjugate. The ratio α-MDA-3-O-SO_4:α-MDA (7-10) is significantly higher than the comparable α-MD-3-O-SO_4:α-MD ratio (2-4) in all patients. The accumulation of the presynaptically-active α-MDA and its sulfated conjugate in hypertensive patients with renal dysfunction may modify the response of these patients to α-MD. Studies in progress will attempt to define the mechanism of action of α-MD and relate its therapeutic effectiveness to metabolic products of this agent. (Supported by USPHS Grant #HD-08580).

263 *FUROSEMIDE PHARMACOKINETICS IN THE PREMATURE NEWBORN* *Robert G. Peterson, Barry H. Rumack, John G. Brooks (Spon. by F. C. Battaglia) Univ. of Colorado Med. Ctr. Department Pediatrics, Denver.*

Serial plasma levels of furosemide were measured in 14 premature newborns by high-pressure liquid chromatography following an intravenous dose of 1 mg/kg. All neonates were less than 21 days of age with birth weights ranging from 700 to 2500 grams. The half-life for furosemide calculated from the elimination rate constant was 19.95 ± 3.0 hours (mean ± s. err.) in these infants. The plasma clearance was determined to be 10.58 ± 2.1 ml/kg/hour. Equilibrium dialysis revealed more than 90% protein binding of furosemide by the newborn. The volume of distribution measured from the kinetic data was 0.24 ± .03 L/kg and is consistent with extensive binding of furosemide within the vasculature. Several infants were re-studied and found to have an adult half-life by four months of age.

No correlation was observed between birth weight or postnatal age and the elimination of furosemide within the group studied.

These data are very different from those reported for either adults or older children and indicate that the frequency for administration of furosemide to the newborn within the first three weeks of life should be no more than twice daily if drug accumulation is to be avoided. Furthermore, the prolonged half-life of furosemide in the newborn may contribute to altered elimination or toxicity of other drugs (e.g., aminoglycosides) in this age-group.

264 ONSET AND DURATION OF THE GROWTH HORMONE EFFECT ON AMOBARBITAL METABOLISM. Geoffrey P. Redmond, Jennifer J. Bell and James Perel, Dept. of Pharmacol., Univ. of Vermont Coll. of Med., Burlington and the Depts. of Ped. and Psychiat., Columbia Univ. Coll. of Physicians & Surgeons, NY

We previously reported that human growth hormone (hGH) alters drug metabolism when administered to growth hormone deficient children. Six weeks of t.i.w. administration of 2U i.m. was found to increase half-life ($t_{\frac{1}{2}}$) of amobarbital from 13.9 hrs to 22.8 hrs. Further investigations on hGH deficient children were undertaken to elucidate the possible role of hGH in regulation of hepatic drug oxidation. Amobarbital was again chosen as a representative substrate. Pharmacokinetic parameters (V_d, $t_{\frac{1}{2}}$, Cl) were determined on the basis of at least 3 blood level measurements following a single 3 - 5 mg/kg oral dose. In three children amobarbital was given before and 12 hrs after a single injection of 2U of hGH. No significant change in V_d, $t_{\frac{1}{2}}$ or Cl was found. One subject was restudied at 6 weeks and found to have the characteristic prolongation of $t_{\frac{1}{2}}$ at that time. Two children were studied before and after 4 injections of hGH on alternate days. One showed no change in drug elimination; the other showed a very slight increase in $t_{\frac{1}{2}}$. All children who showed a prolongation at 6 weeks and who were restudied 12 or more months later continued to have a long $t_{\frac{1}{2}}$. Conclusions: (1) The hGH inhibition of amobarbital metabolism is reproducible; (2) the effect is not evident at 2 weeks but is complete by 6 weeks, at least on current treatment schedules and (3) the effect persists for one year of treatment or longer; diminution of the effect has not been observed.