163 CELLULAR PHARMACOKINETICS OF araCTP DURING THERAPY OF REFRACTORY ACUTE LEUKEMIA WITH araC: EFFECT OF m-AMSA:

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The cytotoxic activity of araC is dependent on the intracellular accumulation of the active 5'-triphosphate araCTP. Using HPLC, it was possible to study the pharmacology of araCTP in circulating blasts of patients being treated with high-dose araC (3 g/m² q 12 h x 4-12 doses). The rate of araCTP elimination ($t_{1/2}$) from leukemic cells and the area under the intracelluar araCTP concentration x time curve were strongly correlated with clinical response. Therefore it was of interest to determine whether simultaneous administration of an additional antileukemic drug, m-AMSA, would alter the cellular metabolism of araCTP during combined therapy. Determinations of the $t_{1/2}$ and AUC of araCTP after successive doses of araC alone to 5 patients indicated a slight increase (10-15%) in each parameter. Prospective studies of araCTP metabolism were conducted in the circulating blasts of 6 additional patients who received araC alone followed 12 hr later by simultaneous administration of araC and m-AMSA (30 mg/m² over 1 hr). Thus, the cellular pharmacokinetics of araCTP after araC alone served as the control for the combination. Mean decreases of 9% in the $t_{1/2}$ and 10 % in the AUC were observed. These results suggest that coadministration of m-AMSA with araC may adversely affect the cellular metabolism of araCTP in circulating leukemic blasts.

164 SPONTANEOUS VARIATIONS IN RENAL HANDLING OF URIC ACID

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Spontaneous variations in renal handling of uric acid (UA) were studied in 8 normal male volunteers (age : 32.5 ± 4.6, BW : 68 ± 8 kg, H : 175 ± 6 cm). Over 10 weeks, urine was collected every 12 hours for 6 consecutive days, then once every 2 weeks and blood (b) was drawn at day 1, 5 then every 2 weeks for measurement of night (n) and daytime (d) UA excretion (UA e micromol/min), blood concentration (b UA, micromol/l), fractionnal clearance (f Cl : cl UA/GFR) and intraindividual coefficient of variation (ICV = sd/m)

Results are	b UA	n UA e	d UA e	f Cl
m ± sd	312 ± 45	3.2 ± .2	3.7 ± .2	.09 ± .02
ICV %	8.1 ± 2.1	17.3 ± 7.4	18 ± 8.5	15.7 ± 5.2

Over the range of observed b UA, UA e was positively correlated with filtered UA (= 1.88 + .04 f UA, r = .60, p < .001), f Cl was correlated negatively with b UA (= .007 + 30.27/b UA, r = .69, p < .001) and positively with f Cl for sodium (p < .05), suggesting that spontaneous variations of b UA are partly due to changes in net renal transport of UA and dependent on sodium status.

Conclusion : These variations should be taken in account when evaluating the effect of drugs interfering with UA metabolism.

165 SEX DIFFERENCES IN URIC ACID METABOLISM IN ADULTS: EVIDENCE FOR A LACK OF INFLUENCE OF ESTRADIOL-17β (E_2)

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The lower serum urate concentration of age-fertile women compared to men is thought to be related to a higher renal clearance of urate possibly detrmined by plasma estrogen levels. We assessed renal handling of uric acid in 9 normal age-fertile women compared to 9 age-matched men. Women showed significantly lower serum urate concentrations than men (3.5 ± 0.3 vs. 4.9 ± 0.7 mg/dl, P < 0.001), higher fractional excretion of urate (9.8 ± 1.0 vs. 7.3 ± 0.8 percent, P < 0.001) and lower tubular urate postsecretory reabsorption (P < 0.01). To test the hypothetical uricosuric effect of plasma E_2 we administered estradiol valerate and estradiol benzoate to oophorectomized and age-fertile women, respectively. Plasma E_2 levels and urinary total estrogen excretion increased significantly but failed to substantially modify serum urate or the fractional excretion of uric acid. Furthermore, in 4 normal age-fertile women tubular urate transport was not influenced by plasma E_2 levels. The lower tubular urate postsecretory reabsorption of age-fertile women compared to men is in accordance with their lower serum urate concentration and higher fractinal excretion of uric acid. Plasma E_2 does not influence renal handling of uric acid.

166 URIC ACID METABOLISM IN PSORIASIS

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Enhanced epidermal turnover is believed to increase uric acid synthesis in psoriasis. Fifteen patients with psoriasis (less than 30% skin surface involvement) showed normal serum urate concentrations and urinary hypoxanthine and xanthine excretion but increased uric acid excretion (patients vs. controls, 3.2 ± 0.1 vs. 2.0 ± 0.1 mmol/g creatinine, P<0.01). The reanl physiological response to RNA loading is to increase uric acid excretion due to reduced tubular urate postsecretory reabsorption. To test whether increased uric acid excretion in psoriasis indicates enhanced purine nucleotide degradation we examined the intrarenal handling of uric acid and the capacity of the nucleotide catabolic pathway to accelerate in response to fructose infusion. The probenecid test evidenced a significantly diminished tubular urate postsecretory reabsorption in psoriatic patients. Intravenous fructose promoted a mean increase in hypoxanthine and xanthine excretion, with respect to mean baseline values, of 1257 and 1387 percent vs. 342 and 380 percent in patients vs. controls, respectively (P<0.001) These data indicate accelerated purine nucleotide degradation in psoriasis. A diminished tubular urate postsecretory reabsorption with normal serum urate levels may reflect increased uric acid synthesis.

167 CELL CULTURE MODELS FOR THE STUDY OF PURINE METABOLISM IN HUMAN PLACENTAL TISSUE.

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Study of placental metabolism is hampered by the presence of many cell types and by changes in their relative abundance with gestation. We assessed cell type distribution, growth, and synthetic functions in cultures from 1st (legal terminations) and 3rd (cesarean sections) trimester placentae, and in a choriocarcinoma cell line (BeWo). Monolayer cultures were started after collagenase/DNAase digestion. Cells were typed with antibodies to cytokeratins (epithelial, ie. trophoblastic) and vimentin (mesenchymal, ie. fibroblastic cells). Specific function was assessed by production of chorionic gonadotropin (hCG). In 3rd trimester cultures, 70-95% of cells were trophoblastic, did not grow in culture, and there was no fibroblast overgrowth. They produced 3-10 times more hCG than BeWo cells but only 1/10 as much nucleotides from adenine. In 1st trimester cultures, 60-90% of cells were trophoblastic, showed an increase in protein and DNA between days 5-7, and fibroblast overgrowth by day 14. Production of hCG was maximal during the first 5 days and significantly higher than in 3rd trimester cultures. In conclusion, primary placental cultures retain their trophoblastic character only during the first 3-5 days. Gestational age has a major influence on their growth and synthetic capabilities.

168 INVOLVEMENT OF SUBSTRATE CYCLES IN THE REGULATION OF PYRIMIDINE dNTP POOLS IN 3T6 MOUSE FIBROBLASTS.

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The in situ activities of some enzymes involved in the synthesis of pyrimidine dNTPs and DNA as well as the turnover of dNTP pools were measured in rapidly growing 3T6 cells from the flow of isotope from labeled nucleosides via nucleotides into DNA and excretion products in the medium during steady state conditions. The effects of inhibitors of ribonucleotide reductase, thymidylate synthetase or DNA-strand elongation were also determined. In non-inhibited cells as much as 28% of dCDP synthesized was degraded and excreted (mostly deoxyuridine) into the medium. Hydroxyurea, but not amethopterin or aphidicolin stopped the turnover of dNTP pools. In the latter case all dNTPs were excreted as deoxynucleosides, while with hydroxyurea there was a stimulation of uptake of deoxynucleosides from the medium. This stimulation also occurs in the presence of dipyridamole, an inhibitor of nucleoside transport, and therefore appears to involve an intracellular event. We propose that substrate cycles between deoxyribonucleosides and their monophosphates, involving the activities of kinases and phosphatases, normally participate in the regulation of pyrimidine dNTP pool levels. Inhibition of ribonucleotide reductase stimulates their anabolic activity while inhibition of DNA-strand elongation or thymidylate synthetase stimulates catabolism.