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INTERACTIONS OF VINCA ALKALOIDS WITH HEPATOCELLULAR METHOTREXATE TRANSPORT

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Accumulation of methotrexate (MTX) in presence of vinblastine (VBL) and vincristine (VCR) was studied in isolated rat hepatocytes. In accordance with our recent study on vindesine (VDS), we found VBL and VCR to reduce net MTX accumulation significantly 15 min after MTX addition. Drug concentrations of 100 μM VBL and 500 μM VCR led to 67% and 82% reduction of intracellular MTX, respectively. Since MTX efflux was only slightly inhibited by 100 μM VBL, the accumulation data demonstrate that the major effect of VBL is on MTX influx. Dixon plot analysis is suggestive of competitive inhibition of the MTX influx, with K_i values of 55 μM (VBL) and 110 μM (VCR). Since the K_i values correspond grossly to plasma levels obtained in humans shortly after infusions of therapeutic doses of the vinca alkaloids studied herein, the interactions may have implications for combinations of MTX and vinca alkaloids in clinical practice.

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BINDING CHARACTERISTICS OF CYTOTOXIC ANALOG OF LUTEINIZING-HORMONE RELEASING HORMONE (LH-RH) IN MEMBRANE FROM HUMAN AND MXT MAMMARY CANCER

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Specific binding of cytotoxic LH-RH analog, [^{125}I]T-98 (D-Lys^6-LH-RH coupled to glutaryl-2-hydroximethylantrhaquinone) was demonstrated in membrane preparations from human breast (BC) and MXT mammary tumor cells. Ligand binding of T-98 was specific, saturable and dependent on temperature, time, and plasma membrane concentration. Analysis of the binding data showed that in BC, interaction of [^{125}I]T-98 was consistent with the presence of two classes of and in MXT tumor with one class of LH-RH receptors. The rates of association and dissociation were calculated to be 4.757x108 $M^{-1}min^{-1}$ and 0.021 min-1 ($t_{1/2}$=38.7 min) in membranes from MXT cancer, and in BC association rate constants were 2.3x106 M^{-1} min^{-1} for binding to high affinity and 1.8x104 M^{-1} min^{-1} for low affinity binding sites. Dissociation rate constants were K_{-1a}=0.0801 min^{-1} ($t_{1/2}$=63.4 min) and K_{-1b} =0.0467 min^{-1} ($t_{1/2b}$=23.5 min), respectively. [^{125}I]T-98 was not displaced by either unlabeled somatostatin or EGF, but was displaced completely by unlabeled T-98 and [D-Trp^6]LH-RH. High affinity binding of T-98 was in nanomolar concentration range. Binding kinetics and analysis of displacement curves suggest that binding of cytotoxic analog T-98 to the LH-RH receptors on BC and MXT cancers proceeds reversibly like that of their congeners without cytotoxic radicals.

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TAXOL: HIGH ACTIVITY IN HUMAN GASTRIC CARCINOMA CELL LINES

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Taxol is a new agent of a complex chemical structure isolated from the Western yew tree Taxus brevifolia. High activity of taxol was shown in ovarian carcinoma, breast cancer and melanoma. In this trial we studied the cytotoxicity of taxol in two human gastric carcinoma cell lines (HM2 and HM51).

Methods: cell lines were maintained in humidified atmosphere of 95% air/5% carbon dioxide and passaged at 70-80% of confluency by trypsinization. Chemosensitivity was measured with the sulforhodamine B-assay (SRB). Exponential cell growth was shown for both cell lines within 96 h ($5x10^3$ cells/microculture well). Continuous drug exposure was performed with concentrations of taxol between 0.001 uM and 0.5 uM for 24 h and 72 h. The intrinsic cytotoxicities of the solvent agents Cremophor EL (CrEL) and methanol (MOH) were determined for the final concentration used for 0.01 uM taxol. Cytotoxicity was measured after 96 h.

Results: IC_{50} of taxol after 24 h (72 h) incubation time were 37.0 nM (25.0 nM) in MOH and 6.8 nM (5.0 nM) in CrEL for HM2, and 18.0 nM (15.0 nM) in MOH and 2.5 nM (2.5 nM) in CrEL for HM51, respectively. MOH and CrEL induced an inhibition of cell growth of 3% and 15% in comparison to untreated controls, respectively.

Conclusions: taxol is active in the human gastric cancer cell lines HM2 and HM51. IC_{50} of taxol is in the range of plasma concentrations, which are clinically achievable after administration of 40-265 mg/m^2 taxol (0.37-13.0 umol/l peak plasma concentrations). In comparison to methanol, Cremophor EL increases the cytotoxicity of taxol in both cell lines.

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IMPROVED THERAPEUTIC INDEX OF CISPLATIN (DDP) BY PROCAINAMIDE (Pd)

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Both Pd and DDP share the common property of being basic drugs, predominantly eliminated by the kidneys. Concurrent administration of the antiarrhytmic drug Pd (50 mg/kg) protected mice against an otherwise lethal dose of DDP (25 mg/kg), and reduced DDP-induced weight loss. Pd prevented DDP nephrotoxicity measured as BUN elevation as well as tubular degenerative changes detected by light microscopy. Concurrent ip or iv injection of Pd on day 1 significantly increased the survival of mice bearing P388 leukemia (p<.05), producing 53% and 62% cure rate, respectively, compared to 20% maximal cure rate achieved with 16 mg/kg DDP alone. Protection from DDP toxicity may depend on Pd-induced changes in renal reabsorption and tubular secretion of the toxic species derived from DDP.

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SENSITIVITY OF CISPLATIN-RESISTANT L1210 CELLS TO DPR, A NEW Pt-COMPLEX CONTAINING PROCAINE

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The cytotoxic activity of DPR, a new Pt-complex containing cisplatin (DDP) and procaine (Anticancer Res, 12, 2285, 1992), was studied in vitro on sensitive and resistant to DDP L1210 and L1210/DDP cells. Thymidine uptake and AAS were used as methods. The cytotoxic activity on L1210 was similar to that of DDP after 24 h or slightly lower after 2 h exposure. Conversely, on L1210/DDP cells DPR was always more active than DDP. Pt uptake experiments confirmed that L1210/DDP accumulated less DDP-derived Pt than L1210 cells. Conversely, DPR-derived Pt was similarly accumulated in both cell lines. Although L1210 and L1210/DDP cells showed similar efflux rates for DDP or DPR, a more rapid DPR efflux was showed in both cell lines. Our results suggest that the mechanisms responsible for DDP resistance in L1210/DDP are not active on DPR. This implies possible different mechanism of action or intracellular behaviour for DPR.

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LIAROZOLE FUMARATE, AN INHIBITOR OF RETINOIC ACID (RA) METABOLISM WITH ANTITUMORAL ACTIVITY

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Liarozole fumarate exerts antitumoral effects *in vivo* in androgen-dependent and -independent R 3327 rat prostate cancer and in human HL60 promyelocytic leukemia xenografts. These effects of liarozole fumarate may be related to the inhibition of P_{450}-dependent RA breakdown, demonstrated both *in vitro* and *in vivo*. In rats, bearing androgen-independent Dunning prostate carcinoma, endogenous plasma and tumor RA levels increased, whilst cellular proliferation decreased. Concurrently, changes in the pattern of cytokeratins characteristic of differentiation/proliferation were observed.The compound has no *in vitro* cytotoxic properties. In F9 teratocarcinoma cells it enhanced cell differentiation induced by RA and it potentiated the growth inhibitory effects of RA in MCF-7 human breast cancer cells. In mouse skin, liarozole inhibited ornithine decarboxylase activity and tumor promotion elicited by phorbol ester. All these findings support the hypothesis that liarozole inhibits tumor proliferation through the inhibition of RA metabolism.