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GF120918 (GG918) tissue distribution in tumor bearing mice, favorable tumor retention of a potent P-glycoprotein blocker

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GF120918 (GG918), an acridinecarboxamide, has demonstrated a high affinity for P-glycoprotein (P-gp) and the ability to reverse P-gp-mediated multidrug resistance in doxorubicin resistant cell lines. In addition, mice bearing C26 colon carcinomas demonstrated significant tumor reduction with DOX and GF co-administration, which was not seen by single agent administration of GG918 or DOX. The goals of this study are to demonstrate that GG918 is distributed to the tumor, estimate relative distribution of radioactivity in normal host tissue and estimate GG918 residence time in the tumor. GG918 was prepared as two separate radiolabeled isotopes; a ^{14}C isotope labeled on the acridone ring and a ^{3}H isotope labeled on the tetrahydoisoquinoline ring. SCID mice were inoculated with K562/MDR cell lines and the tumor was permitted to grow to about 10% body weight. After the tumor achieved the desired size, the mouse was injected via tail vein with one of the GF120918 isotopes. Mice were sacrificed at 4 and 24 h post-injection and whole body autoradiography was subsequently performed. This study design used both the ^{14}C and ^{3}H isotopes, in separate studies. Both isotopes showed a wide whole-body distribution at 4 h post-injection with greatest activity seen in the liver, kidney, tumor and feces. Whole-body autoradiography indicates a homogeneous distribution of radioactivity within the tumor. At 24 h post-dose the brain, muscle, liver and kidney showed reductions in radioactivity ranging from 84% to 96% for ^{14}C and 74% to 93% for ^{3}H. In contrast, the tumor and skin were reduced by only 68% and 52%, respectively, for ^{14}C and 74% and 66% respectively for ^{3}H. Measurements based on total radioactivity suggest that the residence time in the tumor is longer than other well perfused tissues and similar to the residence time in the skin. Retention in the skin may be associated with the melanin binding observed with this compound. Actual amounts of radioactivity (at 24 h) were similar in the skin and tumor.

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Experimental assessment on enhancing cytotoxicity of doxorubicin by verapamil in the hepatic artery infusion for liver tumors and preliminary clinical studies

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The effect of the calcium channel blocker verapamil (VER) on cytotoxicity of anti-cancer agents was assessed in hepatic artery infusion (HAI) for liver tumors in rats. Furthermore its clinical significance was studied in patients with hepatic metastases. Doxorubicin (DOX) was infused with HAI for liver tumors of Walker 256 carcinosarcoma in rats; VER and DOX increased 90% and 66%, respectively, in tumor tissue following HAI of VER ($p = 0.05$). The HAI of VER with DOX inhibited the tumor growth by 73% in comparison with DOX only ($p = 0.05$). DOX levels in tumor tissues were measured in six patients with hepatic metastases after HAI of DOX. One of six patients demonstrated an increase of DOX levels in tumor tissues by combined HAI of VER; the tumor demonstrated P-glycoprotein (P-gp) expression. The other five patients without the expression of P-gp showed no influence on DOX levels from VER administration. The HAI of VER remarkably enhanced the cytotoxicity of HAI of DOX for the treatment of hepatic tumors in rats. Clinical studies suggested that DOX levels in tumor tissues might be increased by the combined HAI of VER only in patients with hepatic metastases revealing the expression of P-gp in the tumor.

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Competition between verapamil and doxorubicin for binding to anionic phospholipids: consequences for internal doxorubicin concentration

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It is well documented that the Ca^{2+} channel antagonist verapamil can reverse multidrug resistance by decreasing the P-glycoprotein (P-gp) mediated drug efflux. Several explanations focus on binding of verapamil at and/or competition for export by the P-gp. However, little or no information is available about the effect of verapamil on drug–phospholipid interactions and passive drug diffusion across the membrane. The present experiment studies the binding of verapamil to model membranes (large unilamellar vesicles prepared by extrusion) composed of various phospholipids. Increasing the amount of anionic phospholipids resulted in an enhanced binding of verapamil. Since the anti-cancer drug and P-gp substrate doxorubicin also strongly interacts with anionic phospholipids,[1] a competition between doxorubicin and verapamil for membrane binding was expected. This competition was indeed observed, and not only in model membranes, but also in membranes composed of native *Eschericia coli* phospholipid mixtures and in cytoplasmic membrane vesicles of this organism, which have been used as a model for the plasma membranes of cancer cells.[1] Passive diffusion of the neutral form of doxorubicin across the membrane is thought to be the route of entry into a cancer cell. The rate of import is