unteers. Pharmacokinetics was linear at the investigated doses with maximum plasma concentrations (Cmax) seen at the end of the 30 min. infusion. Within 4-6 h thereafter concentrations declined rapidly and the mean terminal phase half-lives were in the range of 10-12 h. Renal excretion of the parent compound is less than one percent of the dose. The systemic safety profile of WX-UK1 was highly acceptable at all dose levels. No changes in vital signs, ECG parameters, general safety laboratory parameters and adverse event profiles were observed which could be attributed to the administration of the study drug. Evaluation of regular inspections of the infusion site during and after infusion gave no indication of substance related local intolerance reactions. For the coagulation parameters PT, aPTT and TT minor increases were observed at doses of 0.05 mg/kg and higher (mean increases of 6-13% after WX-UK1 compared to 0-5% with placebo) at the end of infusion. Except for aPTT and PT (2.6% and 4.6% above the upper limit of normal) at Cmax all parameters remained within normal limits. All values returned to baseline within 15 min. and were regarded not clinically relevant. Bleeding times remained unchanged and there was no indication of a drug-induced hemolysis. The promising results of this phase I healthy volunteer study warrants further development of WX-UK1 as an anti-metastatic compound for the treatment of solid, malignant tumors. A phase I/II trial in gastric, pancreatic, ovarian and head & neck cancer patients will be launched in Q3 2002.

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Non-clinical assessments of safety profiles of S-3304, a matrix metalloproteinase inhibitor

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To assess safety profiles of S-3304 in non-clinical settings, we conducted single and multiple dose toxicity studies in rats and dogs, reproductive toxicity studies in rats and rabbits (seg I, seg II), and genotoxicity studies in three systems (reverse mutation, chromosomal aberration and micronucleus tests). Safety pharmacology was also investigated. All these studies were conducted in accordance with Good Laboratory Practice and were approved by Animal Care and Use Committee. Oral single-dose toxicity studies with doses of 2000 mg/kg showed that S-3304 was well-tolerated and exerted no apparent abnormalities in rats and dogs. Oral one-month, three-month and six-month repeated-dose toxicity studies in rats showed no toxicologically significant findings with the doses up to 1000 mg/kg/day. The no-observed-adverse-effect level (NOAEL) in each rat study was estimated to be 1000 mg/kg/day. In oral one-, three- and twelve-month repeated-dose toxicity studies in dogs, reversible increases in plasma ALAT and ALP concentrations were observed at doses of 600 mg/kg/day, 200 mg/kg/day and 300 mg/kg/day, respectively. The NOAELs in these studies were 200 mg/kg/day, 70 mg/kg/day and 70 mg/kg/day in the one-, three-, and twelve-month studies, respectively. Several tests showed that S-3304 has no genotoxic potential *in vivo* as well as *in vitro*. In fertility and early embryonic development study in rats, the NOAELs were estimated to be 1000 mg/kg/day for fertility, development of embryos and general toxicity in males, and 100 mg/kg/day for general toxicity in females due to a decrease in the body weight gains. In teratogenicity study in rats, the NOAELs were estimated to be 1000 mg/kg/day for reproduction and development of embryos or fetuses, and 300 mg/kg/day for general toxicity in dams due to a decrease in food consumption. In the rabbit teratogenicity study, the NOAELs were estimated to be 1000 mg/kg/day for general toxicity in dams and developmental toxicity in embryos or fetuses, and 300 mg/kg/day for reproduction due to abortions in 2 dams. In the safety pharmacology, S-3304 antagonized drug-induced contractions of isolated gastrointestinal tissues at 10 and 100 μM, and inhibited gastric emptying in rats at 300 mg/kg p.o. However, S-3304 did not show any significant effects in general activity, central/autonomic nervous, respiratory/cardiovascular, digestive and renal systems. The data supported the initiation of clinical studies of S-3304.

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Inhibition of VEGF binding to HUVEC receptors and of heparanase by the nonanticoagulant and antiangiogenic heparin derivatives ST1514 and ST2184

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Heparin, in addition to its anticoagulant effect, displays many other biological properties including modulation of growth factor activity and inhibition of the heparanase. However, heparin-based therapy in cancer is limited due to its anticoagulant activity. We have synthesized novel heparin derivatives with the aim to abolish the anticoagulant effects of heparin and to inhibit the heparin-binding growth factor activity. Several *in vitro* and *in vivo* tests were carried out for the identification and characterization of the most active compounds. The anticoagulant properties of the heparin were completely abolished in ST1514 and the corresponding low-molecular weight derivative ST2184. However, the compounds retained the ability to bind FGF-2 as the original heparin, but had significantly reduced capacity to induce FGF-2 dimerization. Receptor binding studies showed that both ST1514 and ST2184 were able to prevent the binding of VEGF165 to cell surface receptors in human umbilical vein endothelial cells (HUVEC) with an IC_{50} equal to 14 μM and 22.4 μM, respectively. Scatchard analysis of binding studies showed that ST2184 decreased three times the number of VEGF apparent receptors (KDR) but did not alter the receptor ligand affinity. The heparanase-inhibiting effect of compounds ST1514 and ST2184 was tested using recombinant human heparanase (Hpa1) and sulfate labeled, naturally produced extracellular matrix substrate. Both compounds were highly effective, yielding 95-100% and 70-80% inhibition of heparanase activity (i.e., release of labeled heparan sulfate degradation fragments) at 1 and 0.2 ug/ml, respectively. In the mouse Matrigel plug implanted subcutaneously, ST1514 and ST2184 treatment (25mg/kg s.c. twice daily for 7 days) caused a significant ($p<0.01$) reduction of the hemoglobin content in FGF-2-containing pellets. In conclusion, ST1514 and ST2184 represent heparin derivatives, devoid of anticoagulant effects, with potential antiangiogenic and antimetastatic properties.

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The effect of nitric oxide on cyclooxygenase-2 expression is mediated through the activation of guanylate cyclase in head and neck cancer cell lines

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The over-expression of cyclooxygenase-2 (COX-2) in head and neck squamous cell carcinoma (HNSCC) was previously reported. Nitric oxide (NO) was also known to be simultaneously produced by inducible nitric oxide synthase (NOS) when COX-2 was over-expressed in many cancer cells. Since up-regulation of COX-2 by NO was reported in inflammatory responses, we hypothesized that NO may increase the expression of COX-2 in cancer cells. We investigated the cross-talk between nitric oxide and prostaglandins (PGs) pathway in HNSCC cell lines (SNU-1041, SNU-1066, and SNU-1076). When adding a NO donor, 50-500 μM SNAP, PGE2 level was increased 2-20 times through the increase of COX-2 expression. This increase of COX-2 expression by a NO donor or PMA was blocked in various degrees by NO-scavengers (PTIO, C-PTIO), NOS inhibitors, L-NAME and 1400W. Also, the increased expression of COX-2 in basal level was inhibited by NOS inhibitors. When treating with dibutyryl-cGMP, its effect on COX-2 expression was similar to one by SNAP in SNU-1041. COX-2 expression induced by SNAP was inhibited by ODQ, a guanylate cyclase (GC) inhibitor. These results imply that endogenous or exogenous NO activates GC and the increase of cGMP induces new sigaling to up-regulate the expression of COX-2 in HNSCC cell lines. We observed that there was this interaction between NO and COX-2 in three additional HNSCC cell lines (PCI-1, PCI-13, and PCI-50) and other types of cancer cells with the detectable expression of COX-2. We suggest that blocking NO production will be able to be a potent strategy for inhibition of COX-2 expression itself in some cancers. (This study was supported in part by 2001-2002 BK21 project for Medicine, Dentistry and Pharmacy)