was increased by 2 mg/m²/w at successive dose levels (DL). A total of 60 pts were included in the first 3 DLs of each sch. During each pt's first 3 infusions, 10 plasma samples were collected up to 6 hours post-infusion. We report on the first 50 pts evaluable for day 1 PK analysis. Doses were (mg/m²): 13.3 (6 pts); 15 (3 pts); 16 (9 pts) 18 (9 pts); 18.6 (6 pt); 20 (3 pts); 21 (7 pts); 24 (9 pts), 28 (8 pts). The PK parameters exhibited high inter-pt variability. The PK of irofulven was characterized by a short terminal half-life (3.7–6.6 min). Cmax and AUC increased dose proportionally; the coefficients of correlation (R) were 0.350 and 0.543. There were no dose-related effects on total body clearance (Clt) through the full dose range studied. Initial analysis fails to show any relationship between the AUC at D1 and T nadir. Fully updated PK analysis will be presented.

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Pharmacokinetics of single and multiple oral doses of zd1839 ('Iressa'), a specific epidermal growth factor receptor tyrosine kinase inhibitor (egfr-tki), in healthy male volunteers

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Aims: ZD1839 ('Iressa') is an orally active, selective EGFR-TKI which blocks signal transduction pathways involved in the proliferation and survival of cancer cells and has shown activity in Phase I trials. Two studies have been conducted to (1) assess the dose proportionality of ZD1839 and (2) evaluate multiple-dose pharmacokinetics.

Methods: In study 1, 15 male volunteers were randomised to receive single ZD1839 doses (50, 100 and 500 mg or 50, 250 and 500 mg) to assess ZD1839 linearity across a dose range that encompassed the doses being used in clinical efficacy trials. Doses of ZD1839 were administered orally in random order with a minimum 2-week washout period between each dose. In study 2, 12 male volunteers received a single oral dose of ZD1839 100 mg, followed by a washout period of at least 2 weeks, before receiving 100 mg twice at 12-hour intervals for 1 day, followed by 13 daily doses of 100 mg.

Results: In study 1, following a single oral dose of ZD1839 Cmax was reached in 3-5 hours and plasma concentrations declined in a biexponential manner. Dose proportionality was observed at 50, 100 and 250 mg dose levels with respective mean Cmax values of 11.8, 32.7 and 82.1 ng/ml and mean AUC(0-24) values of 143, 388 and 1088 ng.h/ml. Mean AUC and Cmax values for ZD1839 50, 250 and 500 mg were not dose-proportional as a greater than proportional increase in both parameters was observed for the 500 mg dose.

In study 2, Cmax, t1/2 and AUC(0-24) ranged from 23.6-57.8 ng/ml, 13.7-42.2 hours and 308-927 ng.h/ml, respectively, following a single 100 mg dose of ZD1839. Steady-state ZD1839 plasma concentrations were reached within 3-5 days of starting multiple dosing using a loading dose regimen. The multiple-dose pharmacokinetics of ZD1839 were generally not well predicted from the single-dose parameters. As expected from the ZD1839 t1/2, there was evidence of accumulation (approximately 3-fold) during the 14-day multiple-dosing period.

Conclusion: Overall, ZD1839 was well tolerated when administered as a single dose or a multiple-dose regimen to healthy male volunteers. Events that were considered possibly related to treatment with multiple doses of ZD1839 included mild rash, acne and dry skin, which have been reported previously. The good tolerability profile of ZD1839 confirms the feasibility of such studies in healthy volunteers.

'Iressa' is a trade mark of the AstraZeneca group of companies

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Pharmacokinetics of Irinotecan (CPT-11) in wildtype- and P-glycoprotein- (P-gp) knockout (mdr1a/1b (-/-)) mice

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Purpose: In vitro studies have demonstrated that CPT-11 is a substrate of the transmembrane efflux pump P-gp. Previously we have shown in a pharmacokinetic study in mice, that the co-administration of a P-gp inhibitor could be an approach to reduce CPT-11 induced diarrhoea by blocking biliary secretion of CPT-11 and its metabolite SN-38 into the intestinal lumen.. To further investigate the in vivo influence of P-gp on the pharmacokinetic behaviour of CPT-11 and SN-38, we have administered an i.v. bolus of CPT-11 to wildtype- and mdr1a/1b (-/-) mice, focussing on the drug distribution to the brain and the intestinal excretion of CPT-11.

Methods: CPT-11 was given as an i.v. bolus at a dose of 10 mg/g bodyweight. At fixed time points mice were sacrificed and organs were prepared for analysis. Intestinal contents have been collected in specific metabolic cages. Standard High Pressure Liquid Chromatography (HPLC) was used for the detection of CPT-11 and metabolites.

Results: 4h after an i.v. bolus 3-4 fold higher levels of CPT-11 have been found in brain tissue of mdr1a/1b (-/-) mice compared to wildtype mice. In contrast significantly more CPT-11 was detected in the intestinal contents of wildtype mice. For the pharmacodynamic active metabolite SN-38 no differences have been found both in brain tissue (negligible levels of SN-38) and intestinal contents between wildtype and mdr1a/1b (-/-) mice.

Conclusions: A lack of functional P-gp increases the penetration of CPT-11 into the brain in vivo. By co-administering certain P-gp inhibitors (e.g. PSC833) + CPT-11 an increased CNS-toxicity should be taken into account.

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Pharmacokinetics of amifostine after subcutaneous administration in head and neck cancer patient during postoperative radiotherapy

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Purpose: Amifostine (Ethyol®) is the prodrug for the dephosphorylated metabolite WR-1065, which is formed intracellular dependent on alkaline phosphatase. The drug serves as a protector against chemotherapy- and radiation-induced toxicities. Determination of amifostine and WR-1065 as well as the resulting disulfid-metabolites in plasma and urine was done after subcutaneous (s.c.) or intravenous (i.v.) application of 500 mg amifostine in patients with head and neck cancer receiving radiotherapy.

Methods: Blood and urine samples (n= 752) of 5 patients were enrolled into this study. Amifostine was given 30 min prior to daily fractionated irradiation, five days a week during post-operative radiotherapy. Plasma and urine analysis was performed on day 1, 4, and 5 of week one, and for the first days of the following weeks of treatment. For the quantification of amifostine, WR-1065 and the disulfides a RP-HPLC method was performed. The detection was done electrochemically with a Pt-working electrode and an Ag/AgCl counter electrode. Amifostine was converted to WR-1065 by acidic hydrolysis, the disulfides were reduced to WR-1065 by the use of DTT. Calculation of amifostine and the disulfides was performed after conversion, by substracting the measured concentrations of the active metabolite WR-1065.

Results: The limit of quantification was 10 ng/ml WR-1065. The within- and between-day accuracy of the assay for WR-1065 varied from 5% to 15% (from 100 μg/ml to 10 ng/ml, respectively), the precision was in the range of 8%. The s.c. administration led to comparable AUCs as was obtained after i.v. dosage. There is evidence for an accumulation of the disulfides and the active metabolite WR-1065 in plasma, leading to an increase of cmax as well as AUC after repeated s.c. administrations. The mean terminal half life for the parent compound was calculated in a one compartmental analysis to 60 min, for WR-1065 to 30 min. Tmax for amifostine and WR-1065 was in the range of 30 min after s.c. application, and in the range of 5 min after i.v. administration. The peak plasma level for the dithiols after s.c. formulation was observed after 75 min. The disulfides were cleared much slower from the plasma than amifostine and WR-1065, leading to an increase of the peak plasma levels of WR-1065.

Conclusion: The subcutaneous route of administration seems to be an attractive choice and offers a more practical route of administration for cancer patients during radiotherapy.

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Pharmacokinetics (P) of Tamoxifen (T) and related biological variables during long-term adjuvant T therapy in M_0 primary breast cancer (M_0PBC)

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The antiestrogen T is currently used for breast cancer but TP is very seldom studied and the induced biological variables (ibv) by the estrogen-like T activity have not sufficiently related to the TP. Moreover, the ibv were studied regardless the presence of cancer, inherited or acquired lipid disorders, chemotherapy and the T day dose. No relation is clear between TP, vaginal epithelial maturation and endometrial behaviour.

Aim of the Study: We prospectively studied circulating T, N-demethyl T, N-dedimethyl T and 4-hydroxy T (D-T, DD-T and 4-OH-T) that to be matched with lipids, coagulation, blood counts, steroid hormone binding globulin (SHBG), various hormones, vaginal karyopyknotic index (KPI) (our previous studies BMJ ii: 1351–2, 1977; Cytopatol 9: 263–270, 1998) and transvaginal ecosonography endometrial morphology.

Patients were 85, consecutively enrollrd after radical surgery for M_0PBC, and given adjuvant T 20 mg/day for 5 years.

Results: T induces most of its agonist estrogen-like effects within 2 w.s therapy. A steady state of the biological events is reached in about 4 w.s and persists up to 60 mo.s. Cholesterol, LDL-C, HDL-C, LDL-C/HDL-C ratio, apolipoprotein B/apolipoprotein A ratio, fibrinogen and antithrombin III activity dropped from 2 w.s to 60 mo.s. HDL-C was unchanged, SHBG and KPI increased early, while FSH, LH and prolactin decreased. A late rise of Hb, PCV occurred from the 18th mo. Platelets were lower from the 4th w (all quoted results: $p \leq 0.005$). Plasma concentration of T and its metabolites shows interpersonal variations; the steady state was reached at the 4th w. Positive relations ($p \leq 0.005$) existed between 4-OH-T and fibrinogen and KPI, inverse relation between 4-OH-T and antithrombin III, D-T and fibrinogen, DD-T and fibrinogen. Agonistic properties are mainly exerted by the three metabolites. Further analyses is ongoing.

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Pharmacokinetics (PK) of irofulven using two different intermittent dosing schedules as a 30 minute (MIN) infusion in advanced solid tumors (AST): Preliminary data

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Purpose: Irofulven, an acylfulvene analog of illudin S, has shown promising anti-tumor activity during preclinical/clinical development, with delayed thrombocytopenia, severe asthenia and nausea/vomiting as treatment-limiting toxicities (tox). PK analysis of the 5 min daily × 5 or intermittent weekly dosing q3 or 4w schedules (sch) has shown a short mean plasma half-life ($t_{1/2}$) range: 4–6 min, with a large interpatient (pt) variability. A 30 min administration corresponds to approximately 5 $t_{1/2}$. Therefore, by the end of a 30 min infusion, a steady state will be reached. Within the ongoing Phase I study, we decided to use the 30 min infusion to improve the PK and pharmacodynamic (PD) analyses and to investigate a possible correlation between observed tox and Cmax.

Methods: Pts with AST were treated with the same schedules (sch) previously explored with the 5 min infusion duration (B: D1, 8, q3w and C: D1, 15 q4w) using the following dosing levels (DL in [*mg/m²/d*]). Sch B: DL2 [*18*], DL3 [*21*]; Sch C: DL2 [*24*], DL3 [*28*]. During each pt's first 3 infusions, 10 plasma samples were collected up to 5 hours post-infusion. As of 04/2001, 24 pts were included in DL2 and DL3 of both sch.

Results: PK analysis has been performed for day 1 in the first 17 pts. Total body clearance appeared stable up to 28 mg/m².

Dose mg/m²	Sch (DL)	N eval. pts	Cmax ng/ml	AUC ng/mlxh	Clearance l/h/m²	$T_{1/2}$ beta min
18	B (DL2)	7	112 ± 58	38.8 ± 18.1	568 ± 279	7.1 ± 3.6
21	B (DL3)	2	115 ± 4	35.9 ± 1.4	586 ± 23	1.9 ± 0.1
24	C (DL2)	7	202 ± 181	68.7 ± 61.6	532 ± 293	8.5 ± 6.8
28	C (DL3)	1	214	70.3	398	4.7

Conclusions: Preliminary results show that AUCs and total body clearances are similar when irofulven is administered as a 5 or a 30 minute infusion, despite its short terminal half-life. Fully updated PK analysis and the PK/PD relationships will be presented.

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Pharmacokinetic interactions between gemcitabine (GEM) and vinorelbine (VNR) in patients with advanced stage solid tumors

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Purpose: GEM and VNR are both active as single agents in patients with advanced stage of solid tumors. Because of their different mechanism of action, good tolerability and feasible administration on an outpatient basis they should be an interesting combination for palliative chemotherapy. The aim of this study is to determine possible pharmacokinetic interactions between GEM and VNR.

Methods: A total of 11 patients with advanced non small cell lung cancer or metastatic breast cancer were treated with GEM (1h i.v. infusion, 1000 mg/m2) followed by VNR (10 min i.v. slow bolus, 25 mg/m2) on days 1, 8, every 3 weeks; 5 patients received single-agent GEM (1h i.v. infusion, 1000 mg/m2) as a control group. GEM and VNR were measured in blood samples taken at several time points after the starting of treatment and immediately added with enzymatic inhibitor of deaminase THU. Plasma levels were quantified by liquid extraction followed by HPLC analysis and pharmacokinetic data were processed by KineticaTM 1.1 computer program

Results: In the schedule GEM+VNR average Cmax of GEM was 26278±4671 ng/ml, AUC=20305±3111 ng/ml/h, Cltot=75,48±14,56 l/h, t1/2alfa=5,1±5,3 min;t1/2beta=18,2±3,4 min. The steady state was reached about 30 min after the beginning of administration; Cmax of VNR was 813±387 ng/ml, AUC=224±75 ng/ml/h, Cltot=192,74±72,51 l/h; Cmax of single-agent GEM was 29295±5681 ng/ml, AUC=24327±7346 ng/ml/h, Cltot=75,20±17,78 l/h, t1/2alfa=3,0±5,1 min, t1/2beta=20,0±5,2 min.

Conclusions: Cmax, AUC and Cl values of GEM followed by VNR agreed with the values shown in monotherapy; Cp/t curve for GEM in combination was best described by a biphasical model with a rapid distribution and elimination. Cp/t curve for VNR showed rapid distribution; moreover, interpatient variability was important for all parameters in accordance to the literature data; these preliminary data have shown that treatment with GEM+VNR do not alter the pharmacokinetic behaviour of both drugs compared with single agent therapy. Further investigation is needed to relate pharmacokinetic data to toxicity of the treatment.

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Pharmacokinetics of escalating doses of CCI-779 in combination with 5-fluorouracil and leucovorin in patients with advanced solid tumors

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Purpose: To evaluate the pharmacokinetics of 5-fluorouracil (5-FU) and CCI-779, administered in combination to patients with advanced solid tumors.

Methods: Weekly treatment spanned 6 weeks of a 7-week cycle. During day 1 of each treatment cycle, a 1 hour intravenous (IV) infusion of 200 mg/m2 leucovorin (LV) was followed by a 24 hour continuous infusion of 2600 mg/m2 5-FU. Starting on cycle1/day 8, 15 to 75 mg/m2 of IV CCI-779 preceded LV/5-FU treatment. Concentrations of 5-FU were measured throughout the 24 hour infusion period in cycle 1/weeks 1, 2 and 4; CCI-779 and its primary metabolite sirolimus (rapamycin) were followed for 8 days during cycle 1/weeks 2 and 4. Parameters were derived using noncompartmental methods.

Results: For 15 patients, mean±SD steady-state 5-FU plasma concentration was 667±202 ng/mL (Week 1 without CCI-779) and 666±248 ng/mL (Week 2 with CCI-779); mean clearance (CL) was 325±113 L/h (Week 2). For 13 patients, mean CCI-779 CL increased with increasing dose (13 L/h [low dose] to 41 L/h [highest dose] (CV ~ 30%). Mean half-life was 17±4 hours. The mean ratio of sirolimus-to-CCI-779 AUC was 2.4 to 3.8. No period effects were observed.

Conclusion: Inclusion of CCI-779 in the standard 5-FU/LV regimen did not affect 5-FU pharmacokinetic disposition, nor did 5-FU change CCI-779 pharmacokinetic parameters.