1185 PUBLICATION

Pharmacokinetics (PK) of Aromasin® (exemestane, EXE) after single and repeated doses in healthy postmenopausal volunteers (HPV)

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EXE is a new steroidal irreversible aromatase inactivator under development for palliative and adjuvant therapy of breast cancer. The drug was given orally to eight HPV to evaluate the PK after single and repeated administration at the therapeutic dose of 25 mg/day. The possible effect of repeated doses of EXE on the activity of cytochrome P-450 3A subfamily (CYP3A) was also examined.

EXE plasma levels were determined using HPLC-RIA. The urinary amounts of 6-β-hydroxycortisol (6βOH) and cortisol, markers of CYP3A activity, were determined using ELISA and radioimmunological assays, respectively.

After a single dose, EXE achieved peak levels (on average 17 ng/mL) at 2 h post dosing and then declined polyexponentially with a terminal half-life of 27 $\pm$ 19 h (mean $\pm$ SD). The oral plasma clearance (CL/F) was 517 $\pm$ 226 L/h. Plasma levels of EXE after repeated dosing were essentially similar to those measured after single administration. CL/F (715 $\pm$ 296 L/h) was higher than after single dose. The urinary 6βOH to cortisol ratio was not significantly different after single and repeated dosing (5.7 $\pm$ 1.4 vs. 5.0 $\pm$ 1.5 (n = 6), respectively).

The increase of CL/F after repeated treatment, although suggestive of induction/activation of some metabolism, did not involve the CYP3A activity, based on 6βOH/cortisol data. This possible induction, although statistically significant, did not influence the pharmacological effect of EXE. EXE was well tolerated.

1186 PUBLICATION

Clinical pharmacokinetics (PHK) and red blood cell partitioning (k_{RBC}) of topotecan (TOPO) during consecutive chemotherapy

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Purpose: PHK of TOPO (Hycamtin®; 30 min i.v. infusion for 5 consecutive days) in serum and erythrocytes on day 1 and day 5 was investigated. Additionally the RBC-uptake and partitioning of TOPO was evaluated in regard to haematotoxicity (40% of patients treated with TOPO suffer from grade 3 and 4 anemia).

Methods: Serum and RBC concentrations of TOPO were measured on day 1 and day 5 using reversed phase HPLC with fluorimetric detection.

Results: TOPO rapidly distributes into RBCs during infusion proving that RBCs represent a concrete target for the drug and may act as an intravasal depot:

PHK noncompartimental analysis of TOPO (lacton plus carboxylate form) in RBCs:

Parameter	Dimension	d 1 mean	% of serum	d 5 mean	% of serum
C_{max}	[ng/ml]	7.7	(16.3)	7.9	(15.1)
AUC_{last}	[ng/ml*min]	575.6	(10.6)	385.2	(6.7)
MRT_{last}	[min]	67		56	
kRBC		d1: 0.12 (SD 0.04)		d5: 0.09 (SD 0.04)	
p-level	d1 <> d5: 0.0589				

Conclusion: The present data indicate that distribution, elimination and/or biotransformation of TOPO is not affected by repeated doses (accumulation can be excluded). The evaluation of RBC partitioning gives evidence that the percentage of TOPO in RBC is rather low and it is unlikely that anemia is caused by TOPO partitioning in RBCs. Nevertheless a slight tend is apparent: repeated doses of TOPO reduce binding-capacity of RBCs for carboxylate form (p level d1 <> d5 0.0043), for lacton form it is equal (p level d1 <> d5 0.153).

1187 PUBLICATION

Study of antitumor activity of phenolic complex of agrimonia asiatica

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Purpose: The aim of this work is to study the phenolic compound of Agrimonia asiatica Juz. (Rosaceae family) and to investigate antitumor activity of the agent obtained from it.

Methods: Toxicity and antitumor activity of the obtained preparations were studied. Mice of mass 18–20 g of line F1 (CBA $\times$ C57Bl6) and rats of mass 100–130 g with inoculated tumors: adenocarcinoma of mammary gland 755, sarcoma 37, sarcoma 180, Ehrlich tumors, lymphosarcoma of Plyss, carcinosarcoma of Walker were used for experiments. The agent was given i.p. for 8–10 days to rats and for 5 days to mice.

Results: Multiple intraperitoneal injections showed maximal tolerance dose (MTD) of 200–250 mg/kg. The agent possessed antitumor activity in cases of Walker carcinoma (60%). Such treatment effect was not followed by a significant increase of body weight and change of spleen coefficient of animals under study in comparison with untreated ones. The significant tumor growth inhibition was seen in cases of the treated animals with Ehrlich solid tumor (68%), sarcoma 180 (52%), carcinoma 755 (71%), lymphosarcoma of Plyss (78%).

Conclusion: Thus, it was stated, that phenolic complex of Agrimonia asiatica includes a group of flavanoid compounds (flavanols, flavan-3-ols) and coumarins, agents, obtained from this plant possesses a moderate antitumor activity in cases of Plyss lymphosarcoma and Ehrlich tumor.

1188 PUBLICATION

Drug monitoring and pharmacokinetics of a methotrexate-albumin conjugate (MTX-HSA) in cancer patients with long term remission

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Purpose: Methotrexate covalently bound to human serum albumin (MTX-HSA) has shown significantly enhanced cytostatic effects in the preclinical setting. Properties of the drug were investigated in responding patients receiving MTX-HSA for more than 14 months.

Methods and Results: Out of 11 patients being treated within a first Phase I trial or as compassionate use at a dose level of 50–60 mg/kg MTX-HSA 4 patients had long term remission of their disease: PR in one patient with renal cell carcinoma (response duration: 33 months, ongoing), MR in a patient with pleural mesothelioma (34 months, ongoing), in a patient with desmoid tumor (20 months, ongoing) and in a patient with renal cell carcinoma (14 months until progression). Treatment in these patients was continued at extended i.v. administration intervals every 2–4 weeks, without signs of toxicity. Monitoring of plasma MTX-HSA levels revealed a continous plasma presence of the drug during the whole treatment period with baseline concentrations ranging between 5–15 μmol/L and a terminal half-life up to 19 days.

Conclusion: Altered properties of this conjugate in terms of plasma half-life, tumor targeting, and intracellular metabolism might have contributed to the responses. Early data indicates favorable long-term tolerance in patients.