## PII-75

COMPARISON OF DAILY (5 MG/DAY AND 15 MG/DAY) ORAL DOSING REGIMENS OF RISEDRONATE TO HEALTHY MALE AND FEMALE VOLUNTEERS. D. E. Burgio, PhD, L. A. Sun, MD, PhD, D. A. Russell, BS, D. J. Whitham, BS, R. Eusebio, MS, G. A. Thompson, PhD, P&GP, Mason, OH.

**Purpose.** To compare the pharmacokinetics of risedronate administered as multiple daily oral doses of 5 and 15 mg in healthy male and female volunteers. **Methods.** This was a 20 week (2 groups; 24-28 subjects per group, age range 43-75 yr), multiple-dose, randomized, parallel group design study. Serum samples were obtained on Days 1, 85, and 112-115. Urine samples were obtained on Days 1, 8, 29, 57, 78, 85, 105, 112-140. Risedronate concentrations were determined by ELISA. Serum and urine data were simultaneously analyzed using nonlinear regression.

**Results.** Results are given as LS/Geometric Mean.

| Parameter | 5 mg/day | 15 mg/day | Ratio/Diff (95% Conf. Interval) |
|---|---|---|---|
| Dose-norm $C_{max}$ (ng/mL/mg) | 0.303 | 0.290 | 0.958 (0.766,1.199) |
| Dose-norm $C_{avg}$ (ng/mL/mg) | 0.068 | 0.061 | 0.892 (0.710,1.120) |
| Dose-norm $C_{min}$ (ng/mL/mg) | 0.030 | 0.029 | 0.950 (0.677,1.333) |
| Dose-norm $AUC_{tau}$ (ng*h/mL/mg) | 1.665 | 1.467 | 0.882 (0.706,1.100) |
| $A'_e$ (%) | 0.432 | 0.364 | 0.843 (0.660,1.077) |
| $t_{max}$ (h) | 0.736 | 0.667 | -0.069 (-0.210,0.072) |
| $CL_o$ (L/h/kg) | 8.06 | 9.25 | 1.149 (0.909,1.452) |
| $CL_R$ (L/h/kg) | 0.035 | 0.034 | 0.969 (0.810,1.159) |
| $t_{1/2,Z}$ (h) | 420 | 377 | 0.899 (0.657,1.231) |

**Conclusions.** Analysis of predicted $C_{min}$ indicated that risedronate pharmacokinetics achieved steady-state by Day 57. As indicated by the pharmacokinetic parameters, the steady-state pharmacokinetics were shown to be dose proportional between 5 and 15 mg/day. Both risedronate dosing regimens were well tolerated by the study population.

## PII-76

PHARMACOKINETICS OF CAPECITABINE GIVEN IN COMBINATION WITH OXALIPLATIN: A PILOT STUDY OF ADULT CANCER PATIENTS. X. Guo, MD, PhD, A. Ernst, J. Grem, MD, NCI/NIH, Bethesda, MD.

Capecitabine (cape), an oral pro-drug of 5-fluorouracil (5FU), & oxaliplatin are both active chemotherapeutic agents in the treatment of adult advanced colorectal cancer. The aims of this study are to determine the pharmacokinetic (PK) profile of cape & its metabolites, & to define any possible PK interaction between the drugs. Patients received a single dose of cape to permit PK sampling. The next week, oxaliplatin 130mg/m2 IV/2 hr was given on day 1, followed by cape twice daily on days 2-5 & 8-12. After 9-day rest, cape was given twice daily starting after the oxaliplatin on days 1-5 & 8-12 every 3 weeks in cycle 2. Blood samples were taken from 14 patients, 6 at 1650mg and 8 at 2300mg half-daily dose, were subjected to PK analysis by non-compartmental methods. Plasma levels of cape & its nucleoside metabolites were measured by high-performance liquid chromatography-mass spectroscopy; 5-FU & fluoro-beta alanine were measured by gas chromatography-mass spectroscopy. Cape is rapidly absorbed from gastrointestinal tract with Tmax of 1.5 hour for both dosing groups. The elimination half-life is 0.62 hr (0.3-1.5 hr). For cape, the Cmax is 7.4 mg/L & 11.68 mg/L (1650 & 2300 mg); the AUC (0-t) is 9.2 & 10.03 mg*hr/L (1650 & 2300 mg). For 5-FU, the Tmax is 1.9 hr & 1.6 hr for 1600 & 2300 mg; the terminal half-life is 0.60 hr for both groups of patients; the Cmax is 0.14 & 0.23 ug/L for 1650 & 2300 mg; the AUC(0-t) was calculated as 0.22 & 0.845 mg*hr/L (1650 & 2300 mg).

## PII-77

PLASMA CONCENTRATIONS OF DESETHYLOXYBUTYNIN (DEO), THE PRIMARY ACTIVE METABOLITE OF OXYBUTYNIN (OXY), ARE INVERSELY RELATED TO SALIVARY PRODUCTION. D. R. Guay, PharmD, University of Minnesota, Minneapolis, MN.

**Purpose.** Oral OXY is subject to presystemic metabolism, resulting in high plasma levels of the active metabolite DEO. Oral OXY extended-release (OXY-ER) attempts to reduce the peak-trough excursions in plasma concentrations of OXY and reduce plasma DEO. This study compared the pharmacokinetics (PK) of a new OXY transdermal delivery system (OXY-TDS) with OXY-ER and correlated PK parameters with salivary gland output.

**Methods.** In a randomized, open-label, 2-way crossover trial, healthy subjects were assigned to either two OXY-TDS applications (3.9 mg/d for 7.5 days) or OXY-ER (10 mg/d for 6 days), then the alternate treatment after a 5-7 day washout. Blood was collected serially over the last 96 hours of drug administration and analyzed for OXY and DEO content. Saliva weight was measured at regular intervals by chewing Parafilm® for 2 minutes and determining the weight of the expectorant minus the premeasured weight of the film.

**Results.** Significantly more saliva production ($P = 0.0167$) occurred during OXY-TDS compared with OXY-ER treatment. There was also a significant inverse correlation ($r = -0.5865$; $P = 0.0351$) between plasma DEO concentration and saliva production.

**Conclusions.** These results demonstrate a significant association between increased plasma DEO concentrations and decreased saliva output in healthy volunteers. Clinically, OXY-TDS therapy would be expected to produce a lower incidence of dry mouth due to the reduced DEO concentrations associated with its use.

## PII-78

PHYSICOCHEMICAL FACTORS ON THE HYDROLYSIS OF DIPYRONE. H. Ergun, MD, M. Aravind, BSc, D. A. Frattarelli, MD, J. V. Aranda, MD, PhD, Wayne State Uni. Children's Hospital of Michigan, Wayne State University, Children's Hospital of Michigan, Detroit, MI.

Dipyrone is a prodrug, which is used mainly for its analgesic and antipyretic effects. Several other beneficial effects (vascular smooth muscle relaxant, antiapoptotic, and anticonvulsant) have been reported. After oral intake, dipyrone is rapidly hydrolyzed to its main metabolite 4-methylaminoantipyrine (4-MAA). The active metabolite(s) of dipyrone are not well known. It has been found that only 4-MAA and 4-AA saliva concentrations correlate with the analgesic effect of dipyrone. However in most of the studies in which dipyrone is used, the prodrug form is tested using *in vitro* methodologies, which do not represent or predict the actual *in vivo* activity of dipyrone. In this study we have characterized the hydrolysis kinetics of dipyrone as a function of pH, concentration, and temperature. Dipyrone and 4-MAA were measured by HPLC.

Acid-catalyzed hydrolysis is the major reaction at lower concentration (10uM) of dipyrone. At higher concentrations (1mM) other factor(s) are involved in the reaction. Ionic strength is an important factor in the hydrolysis. Low concentrations of dipyrone are hydrolyzed more rapidly than concentrated solutions. Temperature catalyzes the hydrolysis reaction, significantly. These physicochemical factors must be considered in *in vitro and in vivo* studies, as well as in designing clinical trials of dipyrone.