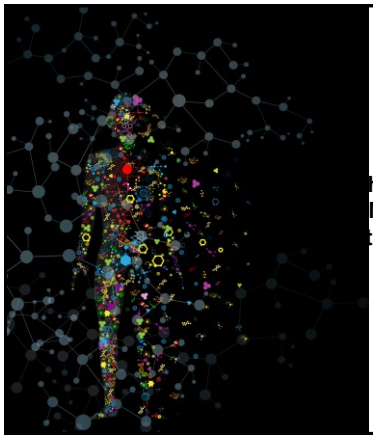


hool:
Multiple
tion Routes

PK43: Protocol

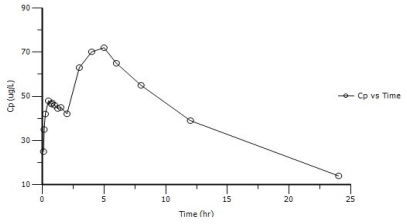
- 1 subject received a 2mg (2000 µg) sublingual dose of a new analgesic compound X.
- Compound X is absorbed rapidly via the buccal route, and delayed absorption also occurs in the GI tract.
- Plasma concentration samples were collected
- Compound X has 1 compartment elimination

PK43: Objective

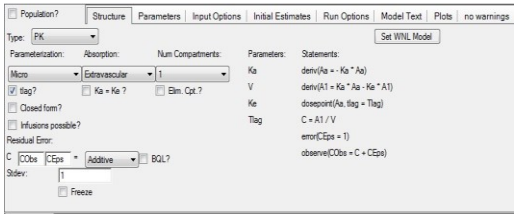
- Characterize absorption of Compound X by both the buccal and GI routes, with different ka for each
- Model one-compartment elimination
- Find estimates for:
  - ka1 = rapid absorption in buccal cavity
  - ka2 = delayed absorption via GI tract
  - V = volume of distribution
  - K = elimination rate for compound X
  - Frapid = fraction absorbed via the rapid buccal route
  - 1 - frapid = fraction absorbed via GI route
  - Tlag = lag time to reach the GI absorption site

PK43: Exploratory Data Analysis

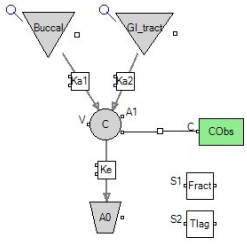
- Plasma Concentrations vs Time



PK43: Built-in 1-compartment PK model with Tlag



PK43: Graphical Model with Multiple Absorption Routes



PK43: Textual Model: PML Code

```
test(){
    # differential eqs to describe PK
    deriv(Al = - (Al * Ke) + (Buccal * Ka1) + (GI_tract * Ka2))
    deriv(Buccal = - (Buccal * Ka1))
    deriv(GI_tract = - (GI_tract * Ka2))
    urinecpt(A0 = (Al * Ke))
    # initial concentration of central compartment
    C = Al / V
    # fractional dosing by the buccal route
    dosepoint(Buccal, bioavail = (Fract), idosevar = BuccalDose, infdosevar = BuccalInfDose, infratevar = BuccalInfRate)
    # fractional dosing by the GI route
    dosepoint(GI_tract, tlag = (Tlag), bioavail = (1-Fract), idosevar = GI_tractDose, infdosevar = GI_tractInfDose,
  infratevar = GI_tractInfRate)
    # observed concentrations and error model
    error(CEps = 1)
    observe(CObs = C + CEps)
    # PK parameters as fixed effects with initial estimates
    fixef(V = c(, 20, ))
    fixef(Ke = c(, 0.1, ))
    fixef(Ka1 = c(, 1, ))
    fixef(Ka2 = c(, 0.5, ))
    fixef(Fract = c(, 0.7, ))
    fixef(Tlag = c(, 2, ))
}
```

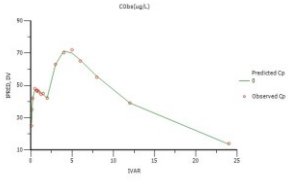

PK43: Initial Estimates

- K = 0.09 L/hr, obtained from NCA terminal phase regression
- V = 20 L/kg, obtained from NCA analysis
- ka1 = 7 1/hr, obtained graphically (slope of 1st pass ascending limb)
- ka2 = 0.5 1/hr, obtained graphically (slope of 2nd pass ascending limb)
- Frapid = 0.55, obtained from NCA (AUCinf_rapid/AUCinf_total)
- Fslow = 1-frapid = 0.45
- Tlag = obtained graphically, start of 2nd pass absorption

Demo

PK43: Results

- Fit



- PK Parameter Estimates

	Parameter	Estimate	Units	Stderr	CV%	2.5% CI	97.5% CI	Var. Inf. factor
1	tvV	20.6274		0.38978199	1.8896322	19.758911	21.495889	0.23353
2	tvKe	0.0886931		0.0031341346	3.5336849	0.081709807	0.095676393	1.4226E-05
3	tvKa1	7.62369	1/hr	0.25433246	3.3360808	7.0570015	8.1903785	0.08969
4	tvKa2	1.0751	1/hr	0.15653754	14.560277	0.72631233	1.4238877	0.041617
5	tvFract	0.515023		0.0089912735	1.7458004	0.49498918	0.53505682	0.00012285
6	tvTlag	2.29614	hr	0.10182338	4.4345457	2.0692632	2.5230168	0.016987
7	stdev0	0.861457		0.14773964	17.149972	0.53227229	1.1906417	

PK43: Summary

- Fit 1-comp PK with multiple absorption routes + lag time
- Build model graphically
- Derive initial estimates
- Fit the model to the data
- Review results

PML School: Materials

- Each model will be made available in Certara Forum
  - Link to live webinar and presentation slides
    - https://support.certara.com/forums/forum/34-pml-school/
  - Model text as file download
    - Can be imported into Phoenix model object to be run on a new dataset
  - Questions and comments can be exchanged in the Forum
    - Topic 4: Multiple Absorption Routes using the Phoenix Graphical Model

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