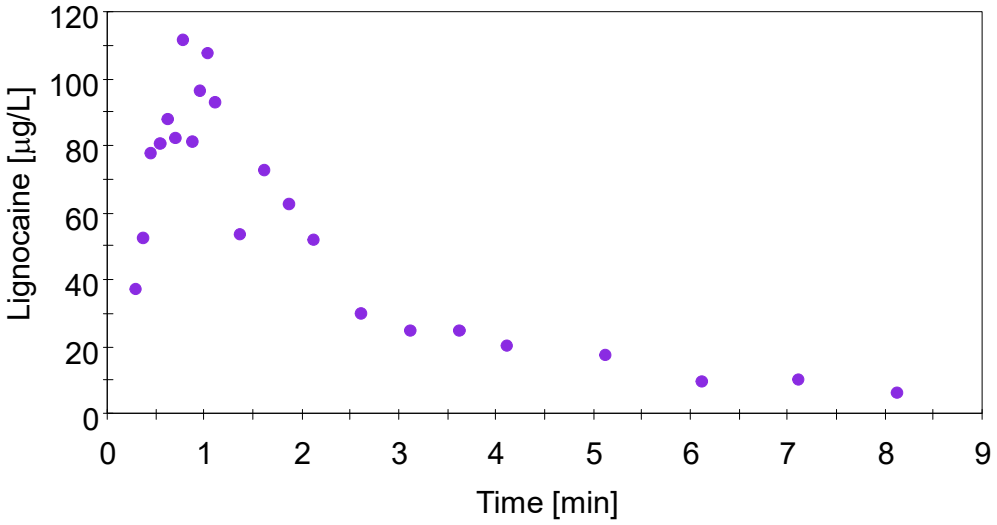
Lidocaine Disposition following A Subcutaneous Administration: A Typical Drug Study

Ray Boston and Glenys Noble

Background to Study of Lidocaine Disposition

Lidocaine, also known as **lignocaine**, is a medication used to numb tissue in a specific area (local anesthetic). It is also used to treat ventricular tachycardia and to perform nerve blocks. **Duration of action**: 10 min to 20 min(IV), 0.5 h to ... **AHFS/Drugs.com**: Local Monograph Injectable ... **Onset of action**: within 1.5 min (IV) **Trade names**: Xylocaine, others

Data from a Subq administration of Lidocaine into an Equine Model



800 µg/Kg of Lignocaine was administered to a horse subq over approximately 1 minute.
We are asked to create a model of the disposition of this antipain medication … the bioavailability of the dose was earlier estimated to be ≈ 50%

```
A SAAM31                                        H_1
2       10
H PAR
c Analysis of lignocaine
c BW =  kg
c Dose = 0.8 mg/kg lignocaine subcutaneous,
c Dose = 800 µg/kg 50% bioavailabity?
   p(1)=400
   L(3,2)    2.044213E-01  0.000000E+00   1.000000E+02
   L(2,3)=L(3,2)
   L(0,2)    4.202207E-01  0.000000E+00   1.000000E+02
   P(2)      3.033287E+00  0.000000E+00   1.000000E+04
 DT(22)      7.585208E-01  0.000000E+00   1.000000E+02
 dn(22)=20
 ic(22)=1
 l(0,22)=1
H DAT
c F(8) = F(2) is total lignocaine administered 400 µg/Kg
c [F2]= µg/kg
c [P2]= [L/kg]
x uf(2)=p(1)*f(22)/dt(22)
x uf(8)=p(1)*f(22)/dt(22)
x g(1)=f(2)/p(2)
```

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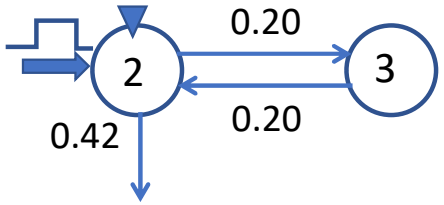
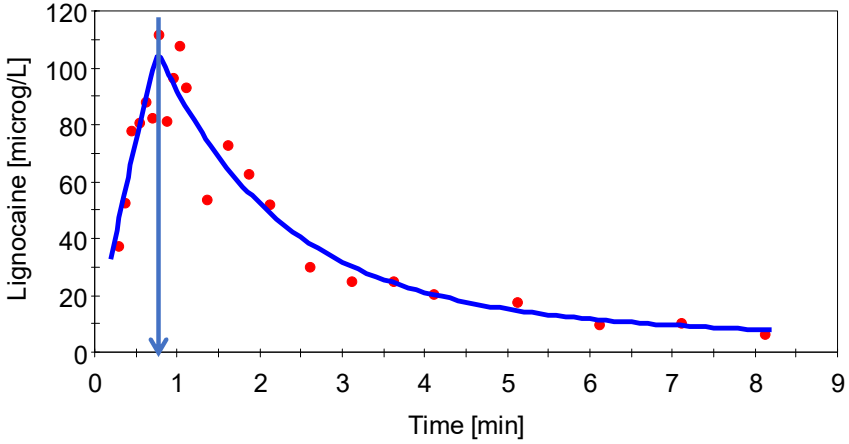


The plot of our model for Lg disposition seems to peak at 0.75 mins which would suggest that the subq takes that much time at least to be fully administered




```
102 g(1)    +.1                                  SD=1
c           Time          Mean Lignocaine (ug/L)
c           0.0833        6.52
            0.1667        37.6
            0.25          52.9
            0.3333        78.2
            0.4167        80.9
            0.5           88.5
            0.5833        82.7
            0.6667        112
            0.75          81.8
            0.8333        97
            0.9167        108
            1             93.7
            1.25          54.1
            1.5           73.3
            1.75          63
            2             52.3
            2.5           30.7
            3             25.4
            3.5           25.5
            4             20.8
            5             18
            6             10.3
            7             10.9
            8             6.53
c           12            1.54
102 g(1)    +.2
            0
2           .1                                   80
108
            0
2           .1                                   10
```

```
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c BW =  kg
c Dose = 0.8 mg/kg lignocaine subcutaneously,
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   p(1)=400
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c F(8) = F(2) is total lignocaine administered 400 μg/Kg
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102 g(1)    +.1                          SD=1
c           Time          Mean Lignocaine (μg/L)
            0.1667        37.6
 …
            8             6.53
102 g(1)    +.2
            0
2           .1                           80
108
            0
2           .1                           10
```

Objects in the model and their names

Objects

P1
P2
L(I,J)
DN22
DT22
IC22
L(0,22)
F(22)
UF(2)
UF(8)
G(1)
QO(2)
QC(2)
QC(8)
SD=1

Object	Unit	Value	Purpose
P1	μg/Kg	400 (50% Bioavail.)	Dose Admin, Sub-cutaneous
P2	$L.Kg^{-1}$	Estimated	Unit management. Pools Size
L(I,J)	min^{-1}	Estimated	Micro Rates
DN(22)	number	20	Stiffens delay
DT(22)	min	Estimated	Admin duration
IC(22)	min	1	Needed for delay
L(0,22)	min^{-1}	1	Needed for delay
F(22)	min	Estimated	Admin control
UF(2)	$\mu g.Kg^{-1}.min^{-1}$	Equation	Dose input
F(8)	$\mu g.Kg^{-1}.min^{-1}$	Integral of UF(2)	Input validation
G(1)	$\mu g.L^{-1}$	Data	Fit objective
QO(2)	$\mu g.L^{-1}$	Data	Observations
QC(2)	$\mu g.L^{-1}$	Data	Fitted values
QC(8)	$\mu g.Kg^{-1}$	~400	Validation
SD=1	number	Based on observations	PK study warrants weighting big pts

Objects

P1
P2
L(I,J)
DN22
DT22
IC22
L(0,22)
F(22)
UF(2)
UF(8)
G(1)
QO(2)
QC(2)
QC(8)
SD=1

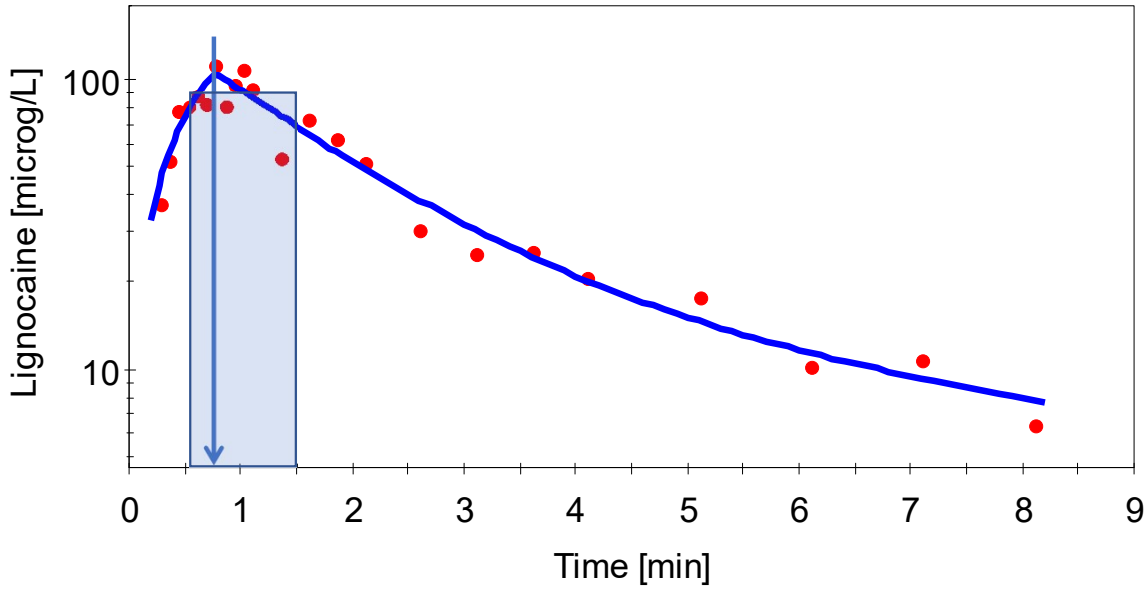
PARAMETER	VALUE	ERROR	FSD
DT(22, 0)	7.585E-01	5.437E-03	7.168E-03
P (2, 0)	3.033E+00	2.990E-02	9.859E-03
L (3, 2)	2.044E-01	1.499E-02	7.332E-02
L (0, 2)	4.202E-01	6.952E-03	1.654E-02

CORRELATION MATRIX

COLUMN	1	2	3	4
ROW 1	1.00	-0.73	0.61	0.40
ROW 2	-0.73	1.00	-0.81	-0.44
ROW 3	0.61	-0.81	1.00	-0.05
ROW 4	0.40	-0.44	-0.05	1.00

Estimated values and errors of the adjustable parameters

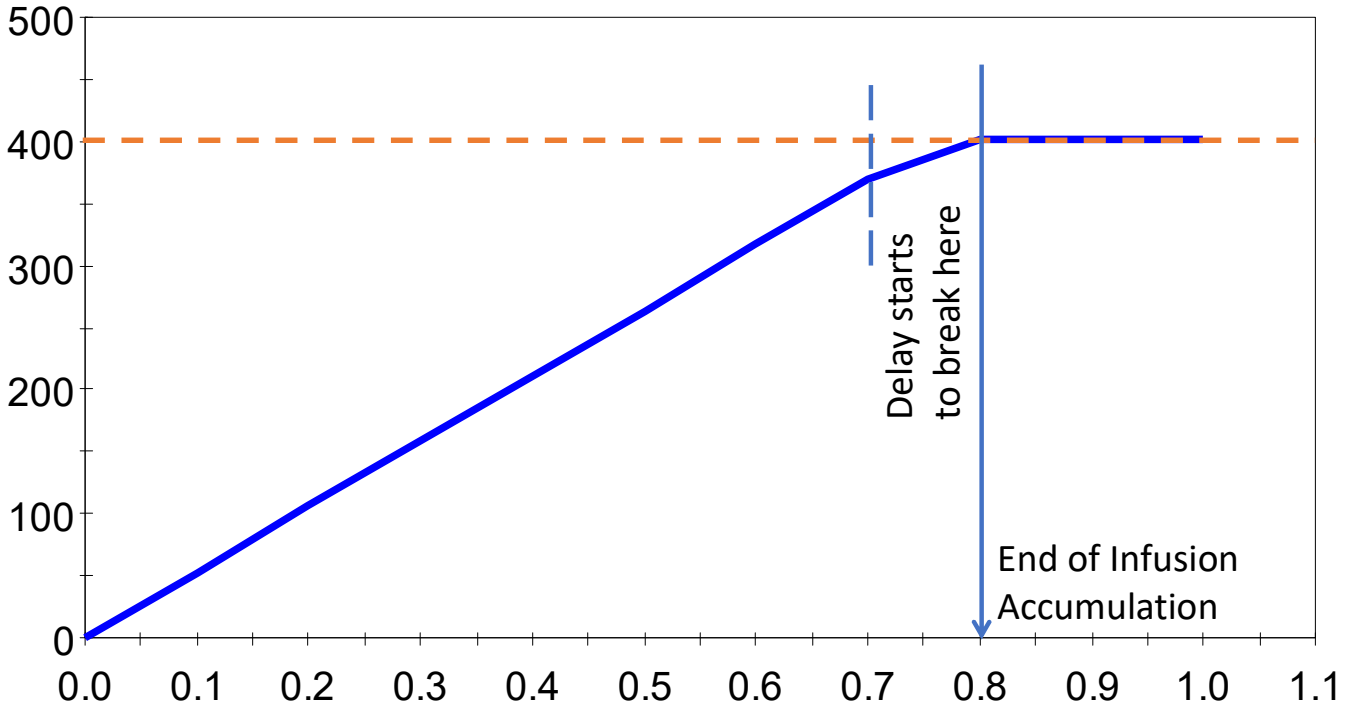
What gives the response in the model its shape around the $C_{max\_}$ point?
How could we confirm the assumption re the fractional exchange rates between compts. 2 and 3 being identical?
Does the fit look consistent with the observations?
Are the parameters all resolved?
What are the units of DT(22), DN(22), P(2) and L(3,2)?



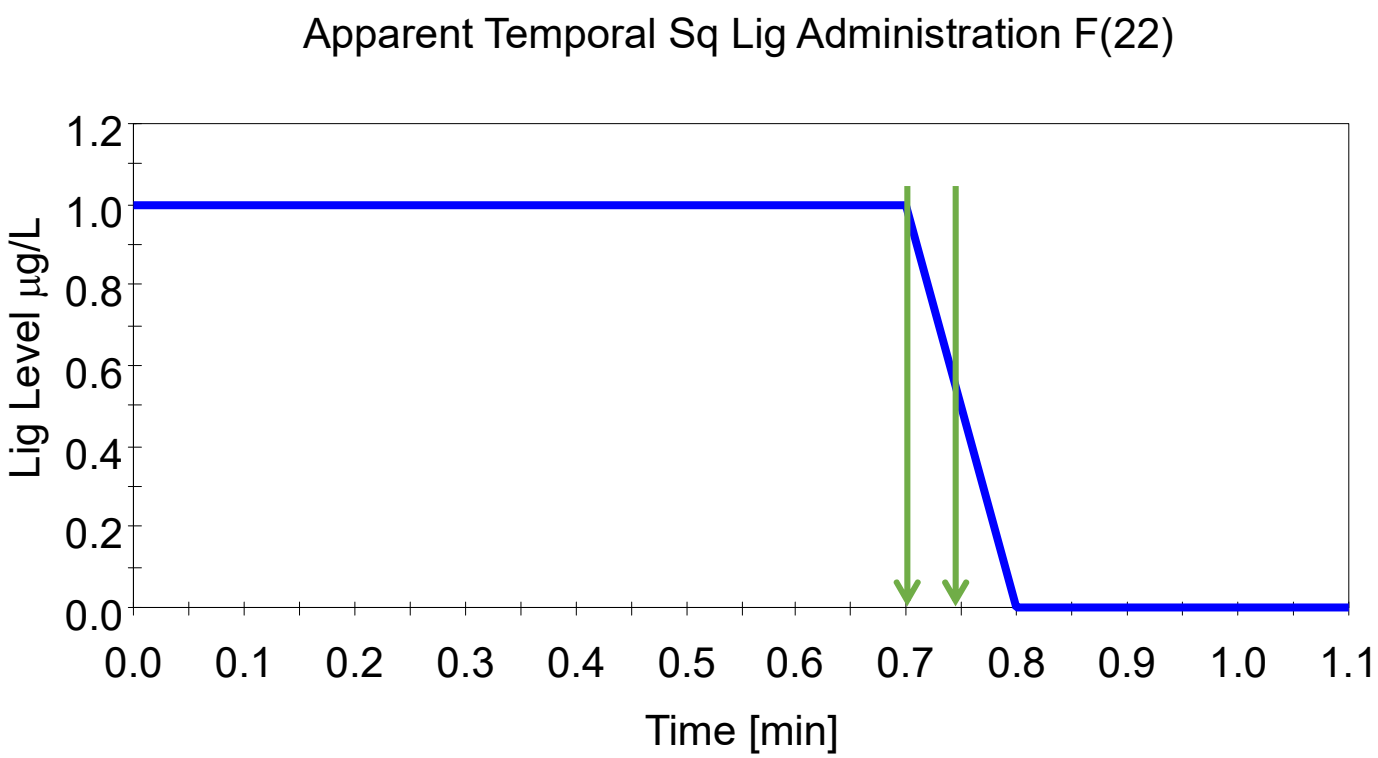
Validation of our intermediate steps
is always a smart thing to do

Plot qc(8) … where x uf(8)=p(1)*f(22)/dt(22)

f(8,t)= $\int_0^1$ [p(1)∗f(22)/dt(22)] dt ... p(1) ≈ 400



Sq Administration Control (F22) .. Slow down from t=0.7 [min] on



Thank You