

PHARMACOKINETICS AND PHARMACODYNAMICS OF HEROIN

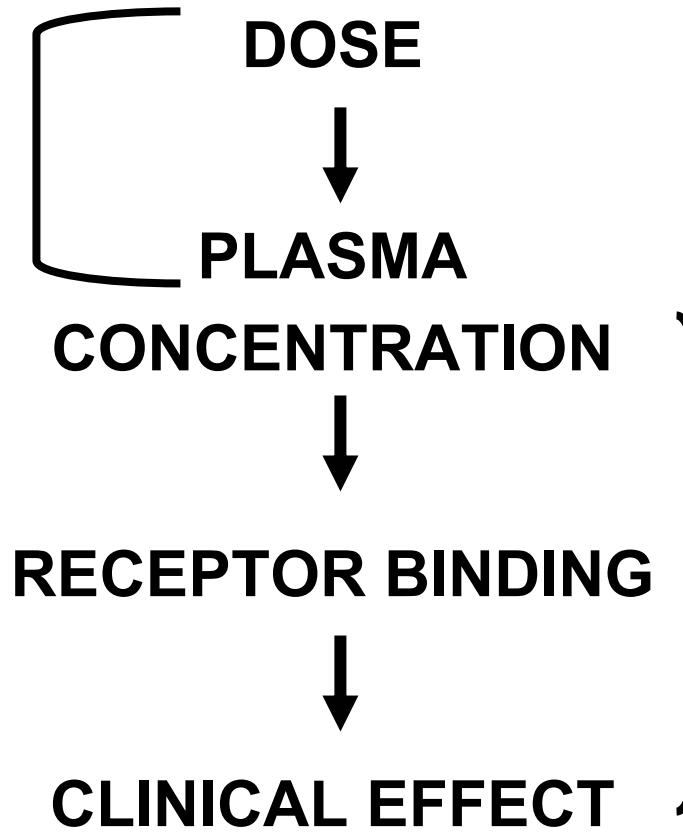
Third Network Meeting

Medical Prescription of Heroin

- Liesbeth Rook
- J.H. Beijnen
- W. van den Brink
- J.M. van Ree

- **Introduction**
 - Concept of pharmacokinetics and pharmacodynamics
 - Metabolism of heroin
 - Administration by inhalation
- **Results of a PK-PD study (KNL40058)**
- **Future prospective**

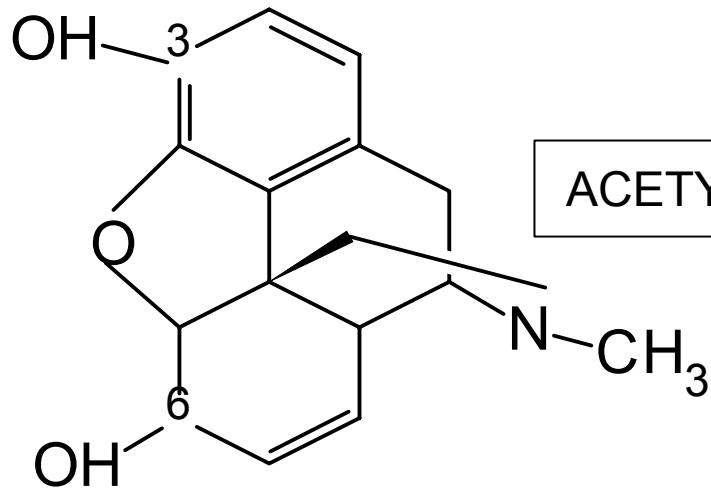
**PHARMACO
KINETICS**



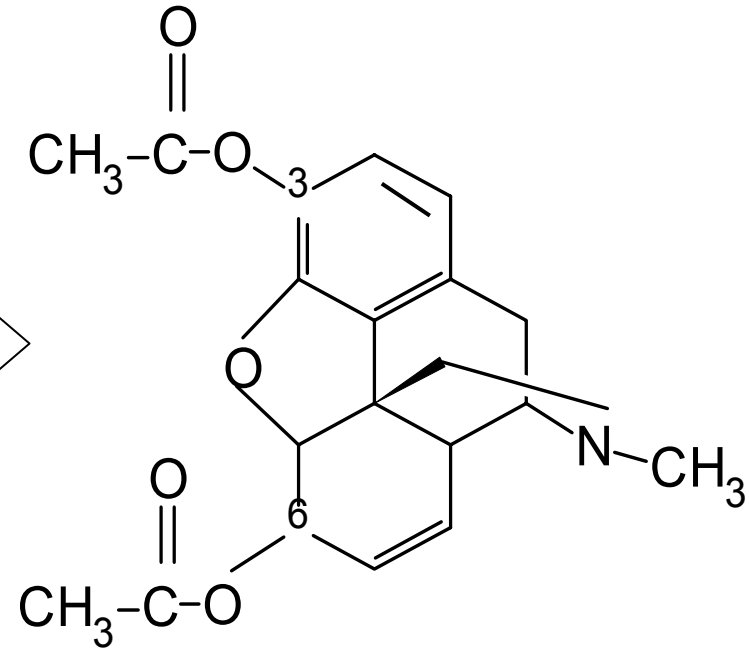
**PHARMACO
DYNAMICS**

MORPHINE & HEROIN

• MORPHINE



• HEROIN



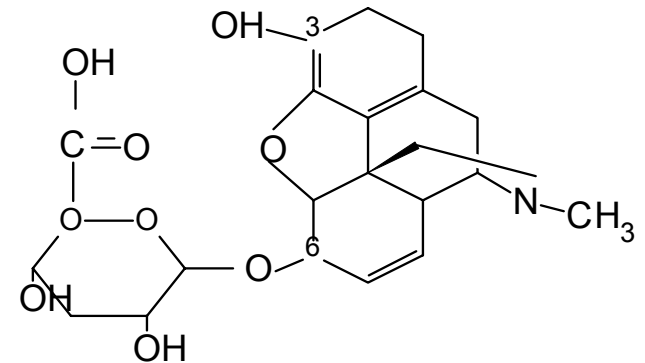
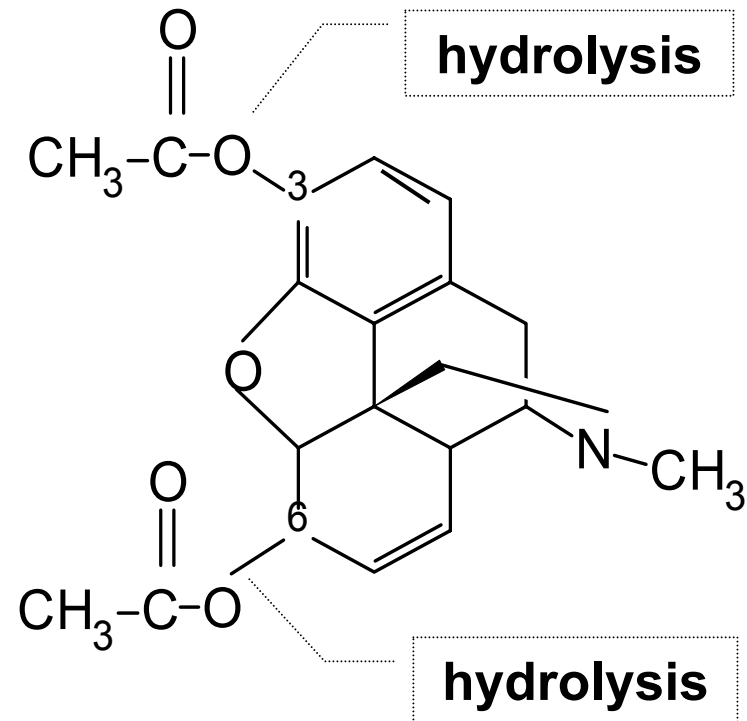
ACETYLATION

METABOLIC PATHWAY OF HEROIN

heroin → 6-MAM → morphine

morphine-3-glucuronide

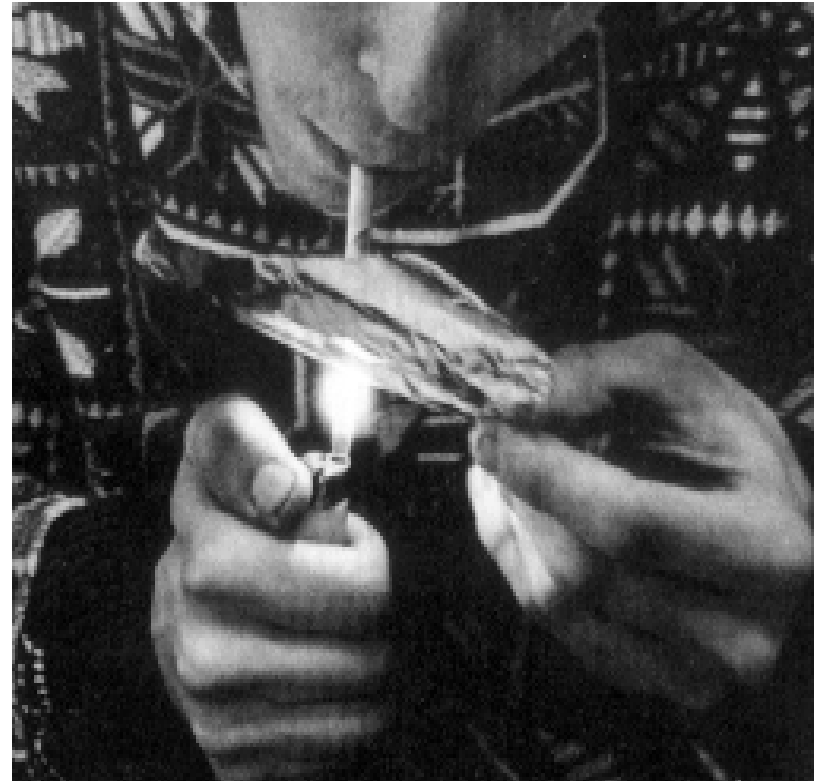
morphine-6-glucuronide



Administration of heroin

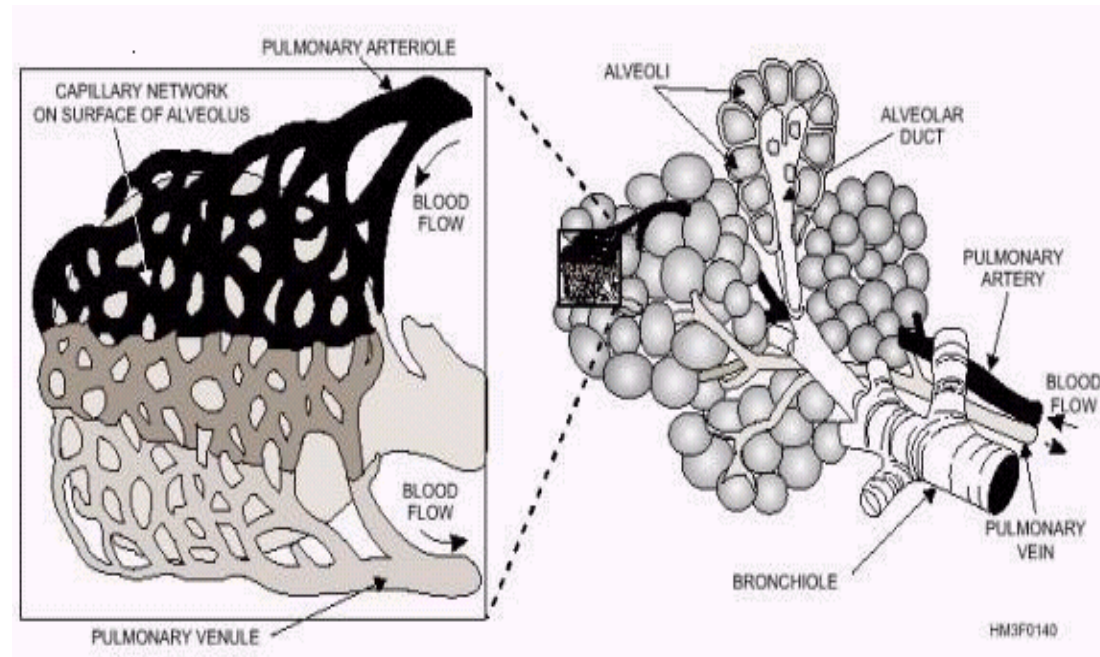
- **Intravenously;**
heroin hydrochloride
- **By inhalation**
heroin base

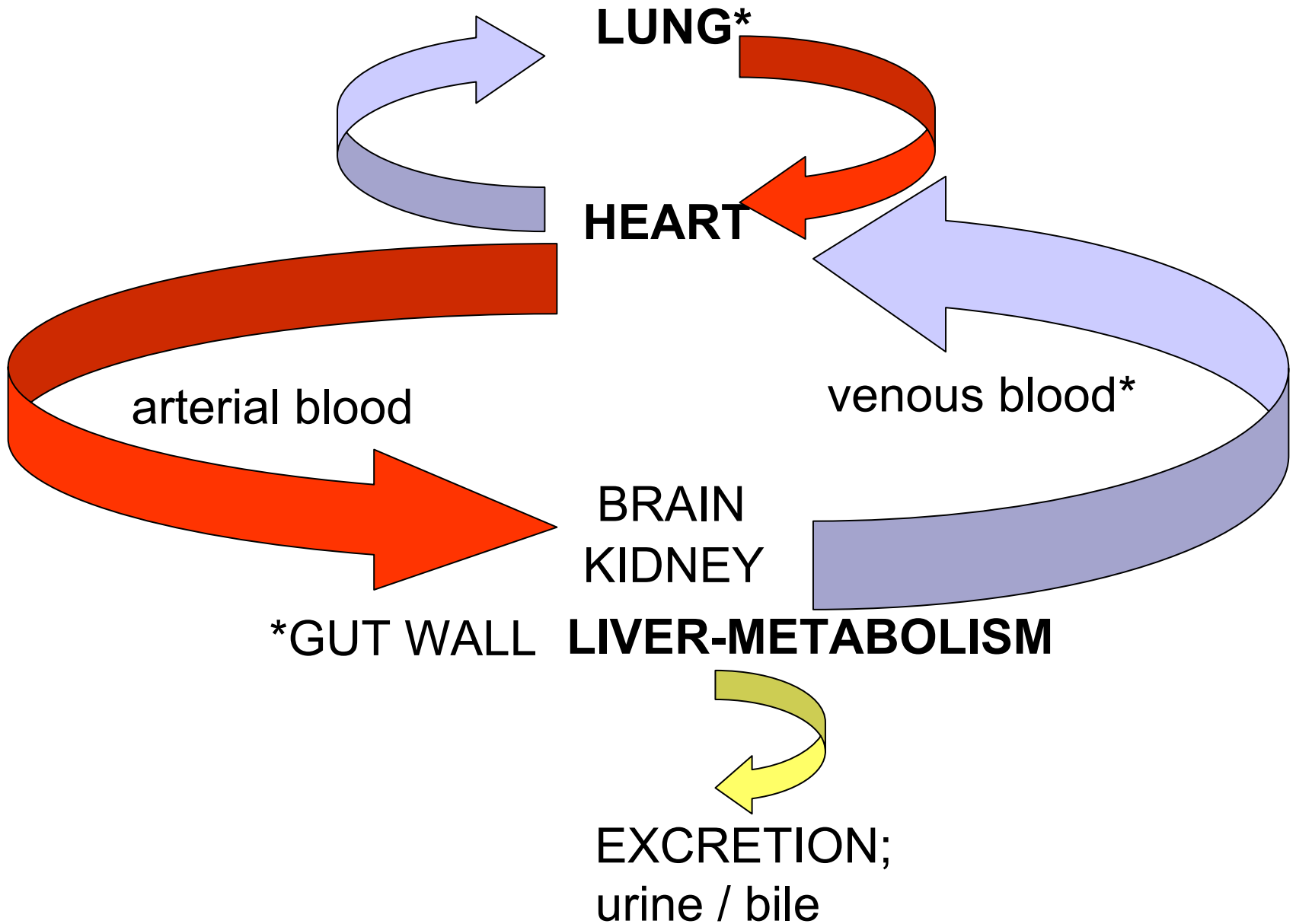
“chasing the dragon”



Administration in lung

- Good permeability for heroin
- Large alveolar surface area ($\pm 100\text{m}^2$)
- high perfusion rate; 5 L/minute

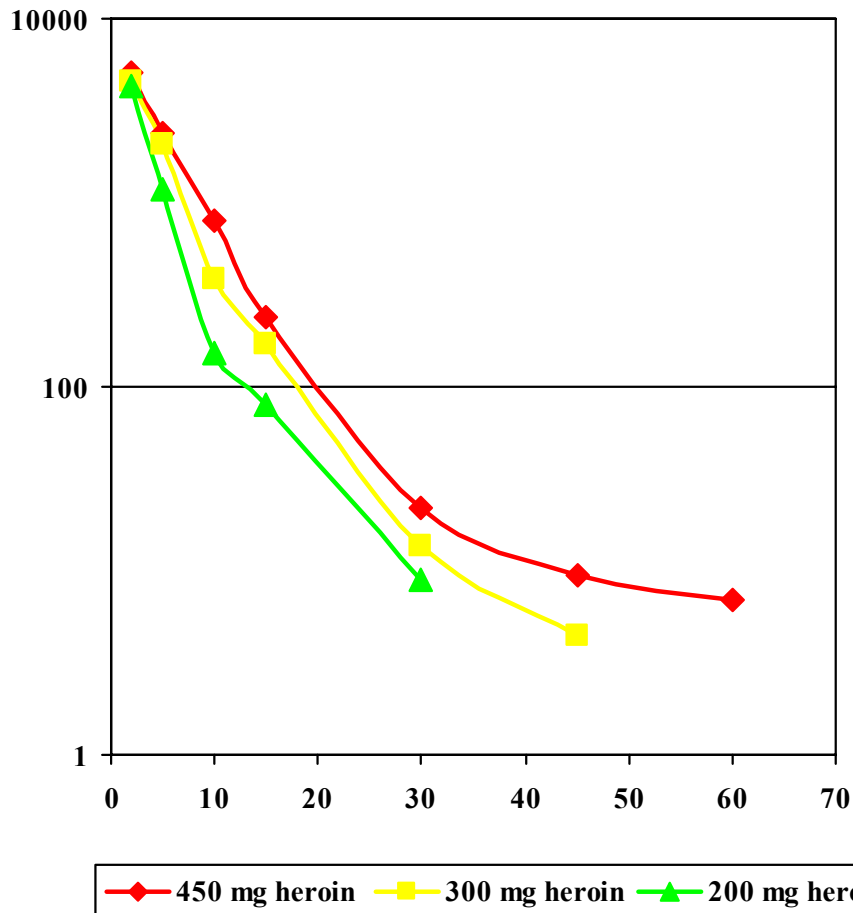




PK research project (KNL 40058)

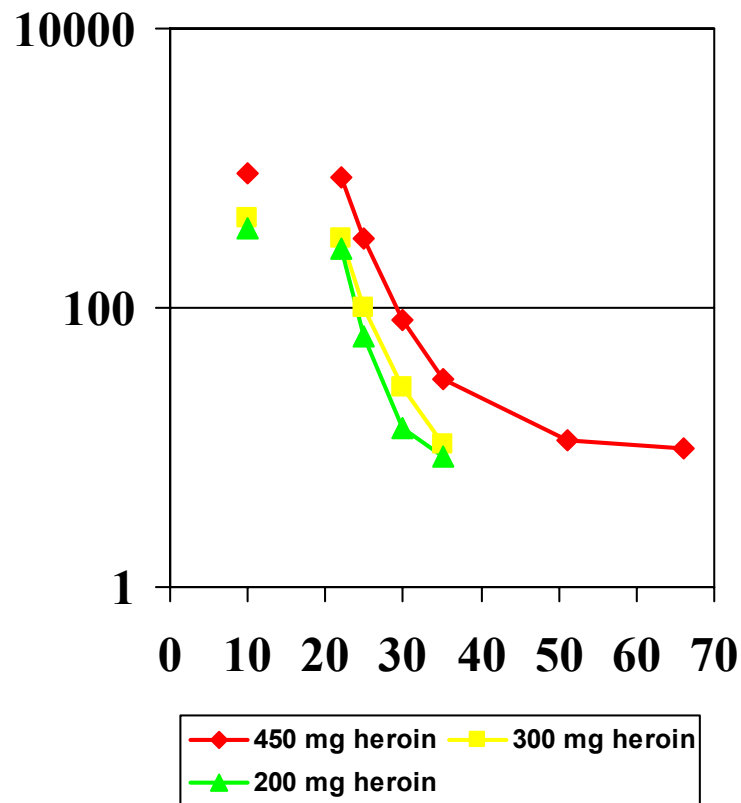
- 12 intravenous users
 - 10 heroin inhalers
-) Patients Dutch heroin trial
- double blinded heroin **dose variation**
66%-100%-150%
 - **sampling schedule:**
 - midway heroin inhalation session
 - after heroin administration2-5-10-15-30-45-60-115-240-480 minutes
 - **bio-analysis:** HPLC-MS-MS (LLQ 5 ng / mL)

Heroin concentration-time curve intravenous use (patient 502)



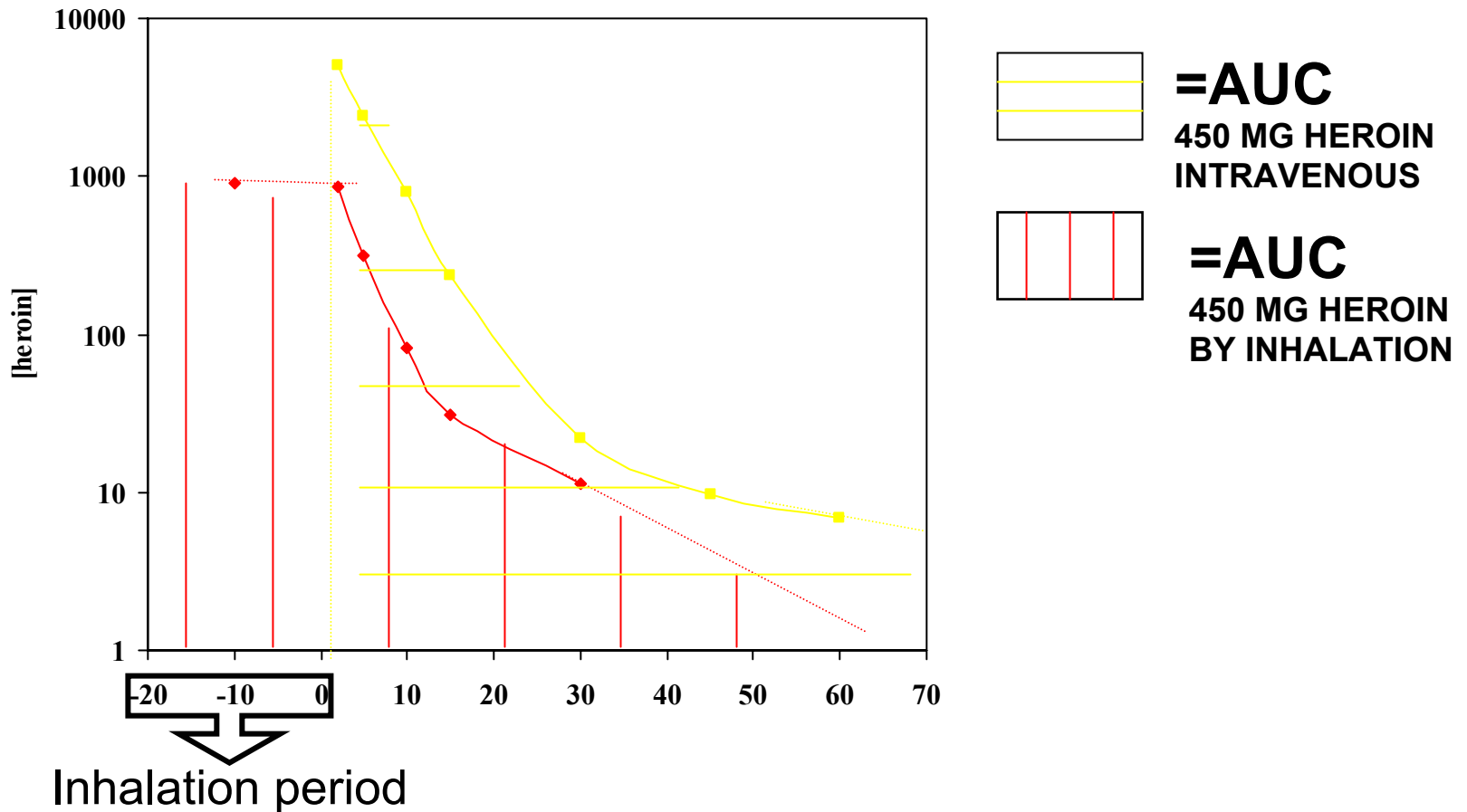
- High peak concentration
- Rapid decline
- two phase;
1.;ultra-rapid:
elimination &
distribution 2.;rapid:
elimination

Heroin plasma concentration -time curve at inhalation (patient 603)



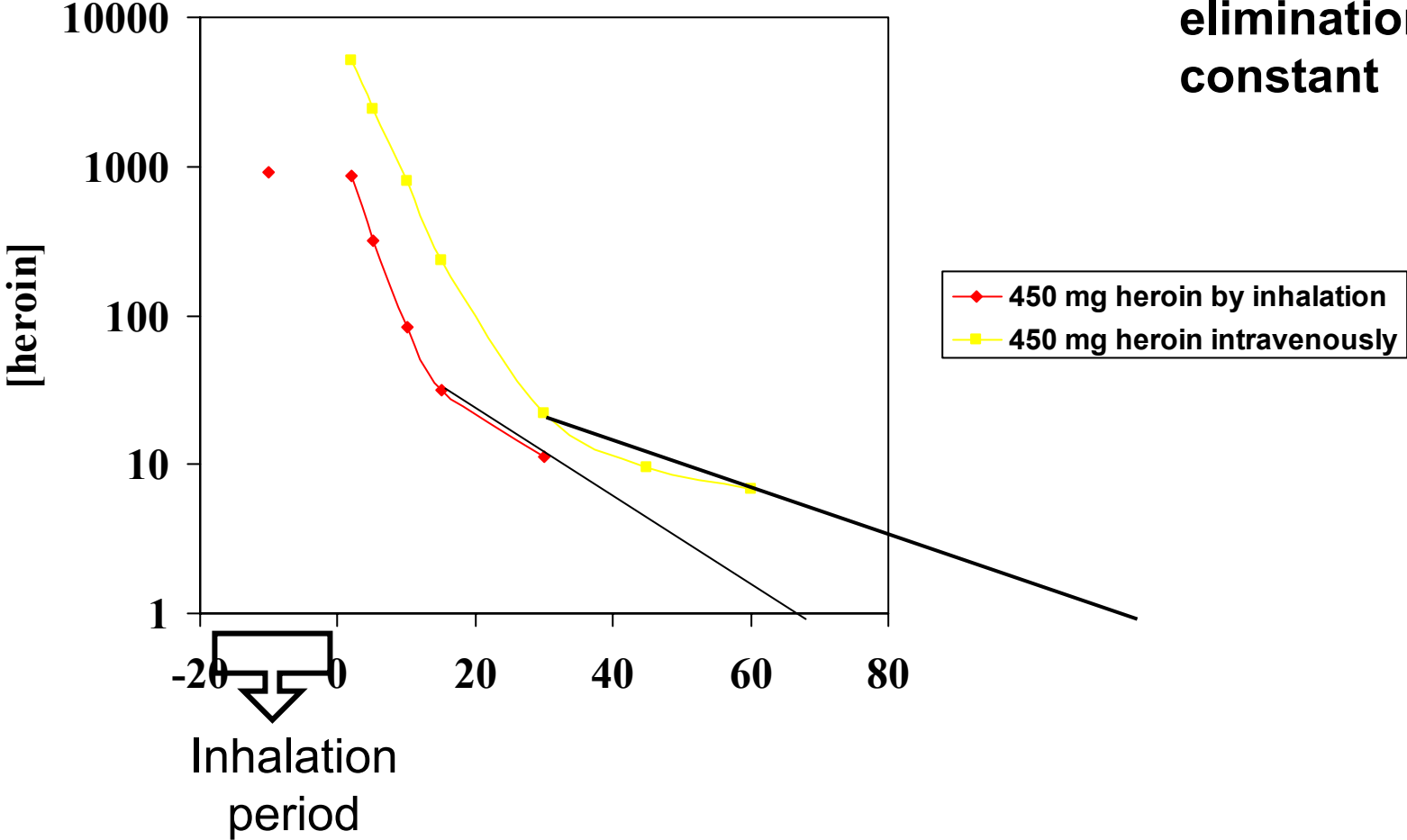
- Peak concentration **midway** inhalation as high as **end-inhalation** peak
- elimination similar to intravenous use

Area under the curve



Elimination constant

$T_{1/2} = \underline{0.693}$
elimination
constant



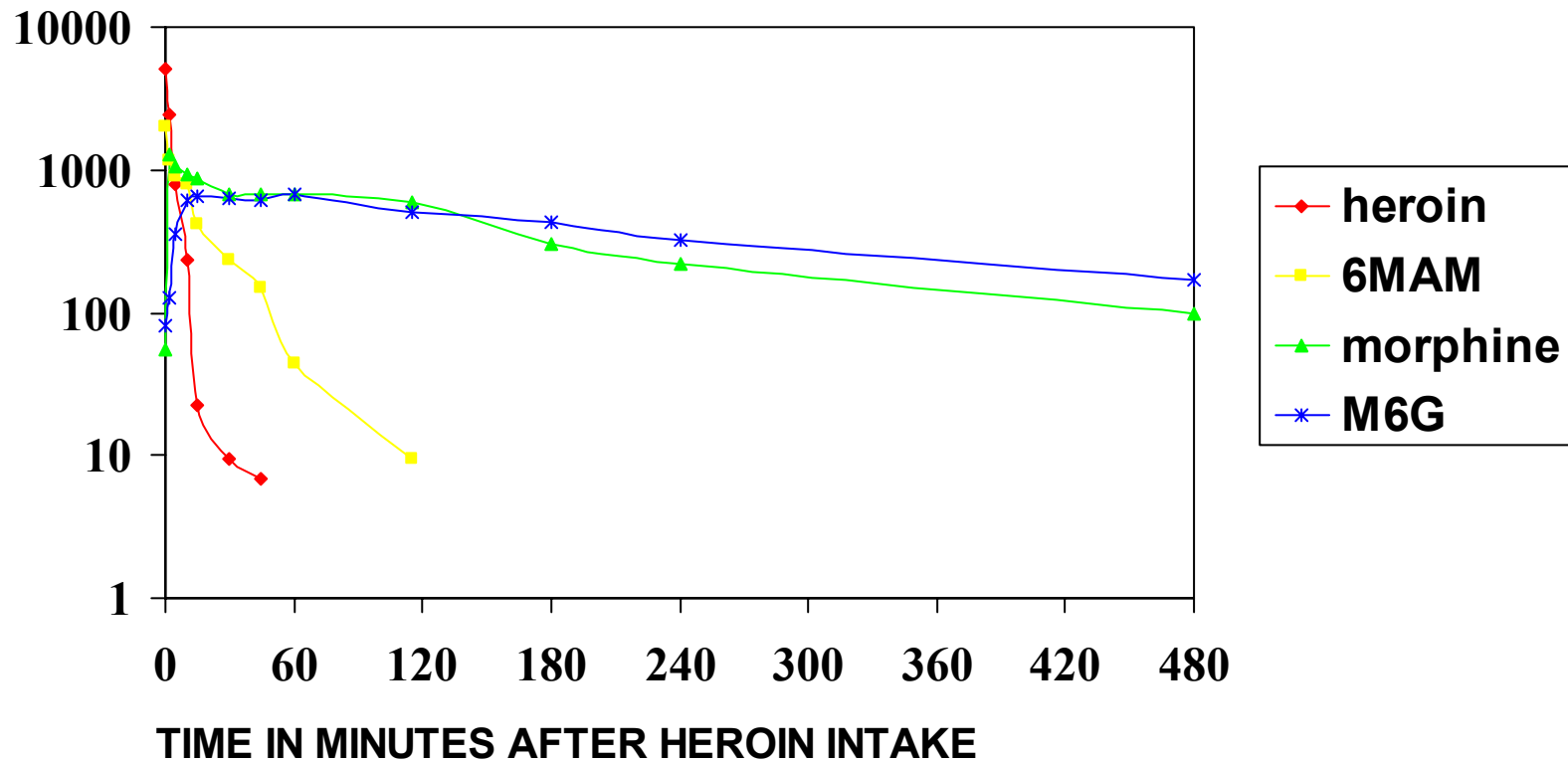
Pharmacokinetic parameters

Non-compartmental analysis

	AUC/Dose	Half life	observed peak concentration
by inhalation (16 curves)	630 ± 55	4.6 minutes (±1.6)	651 ng/mL ±189
intra- venous (12 curves)	1254 ± 53	5.0 minutes (±1.1)	3051ng/mL ±758

HEROIN & METABOLITES

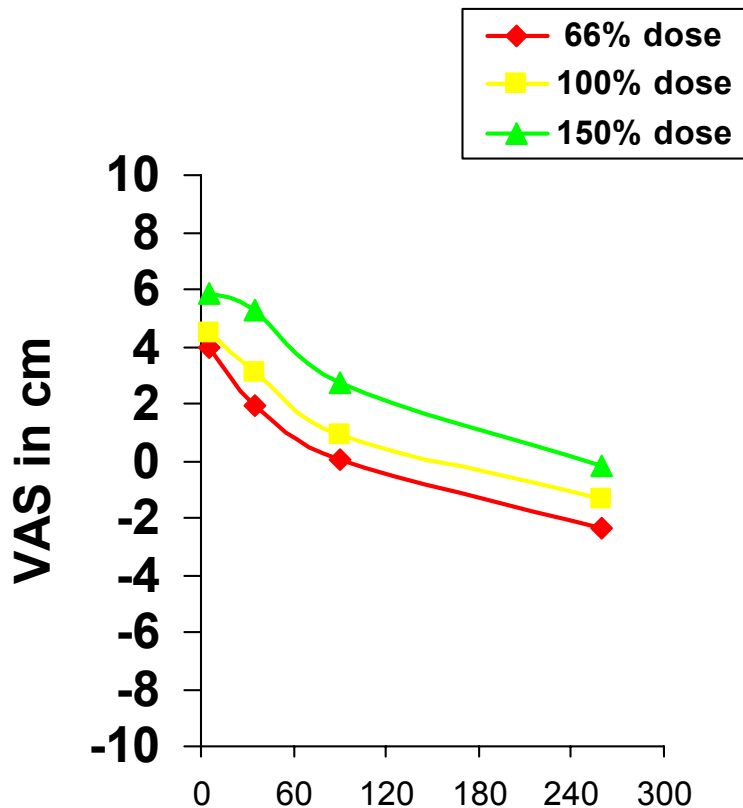
DOSE: 450 MG HEROIN I.V.



PHARMACODYNAMIC RESEARCH (KNL 40058)

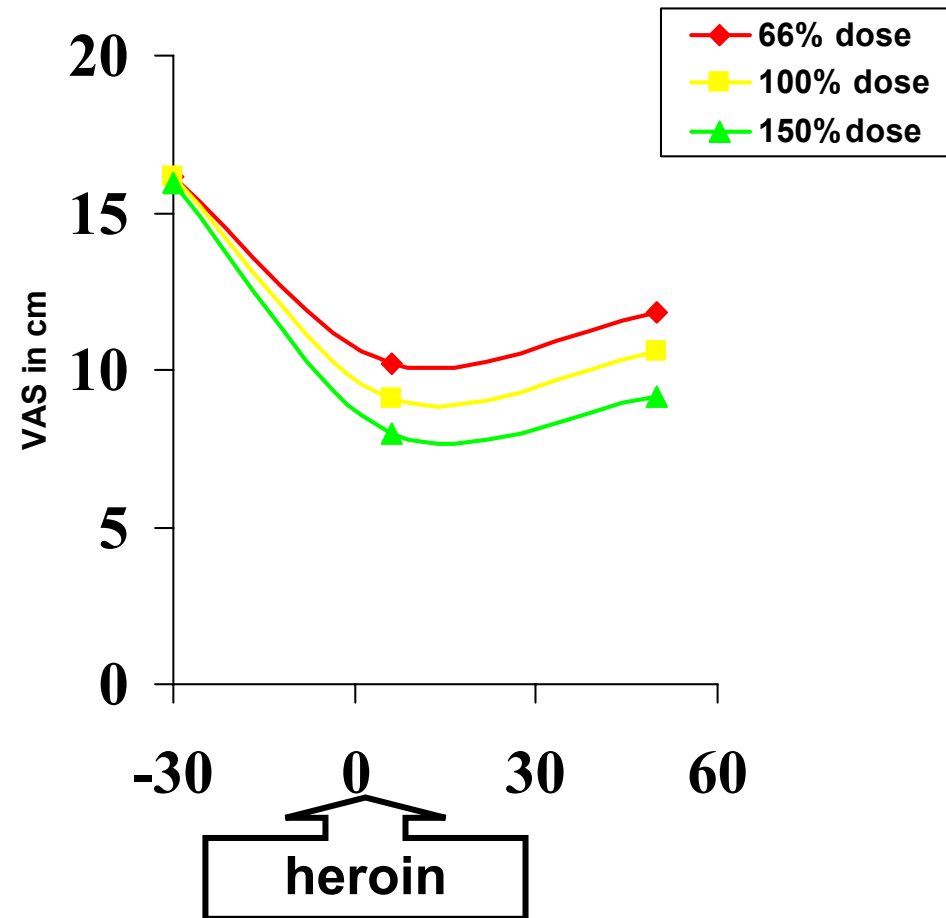
- N=22 (12 intravenous users & 10 heroin inhalers)
- double blinded heroin dose variation
66%-100%-150%
- Psychological;
Rating / Craving (VAS-scales)
- Physiological features

Visual Analogue Scale Rating Heroin Effect (subjective)



- VAS Scale Rating; from -10 cm (negative) to +10cm (effect highly approved)
- Appreciation of heroin dose-dependent (dose blinding)

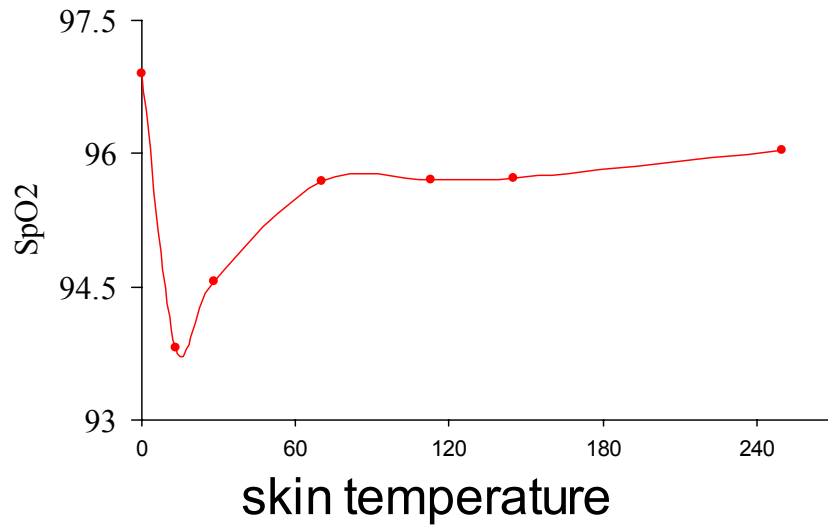
Visual Analogue Scale Craving Feelings (means)



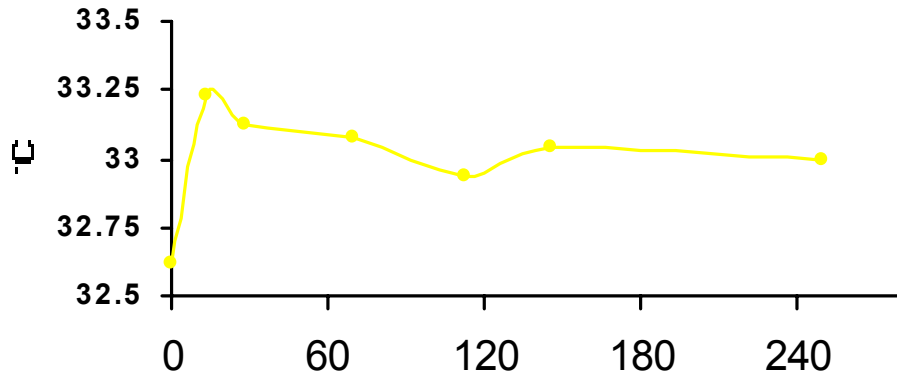
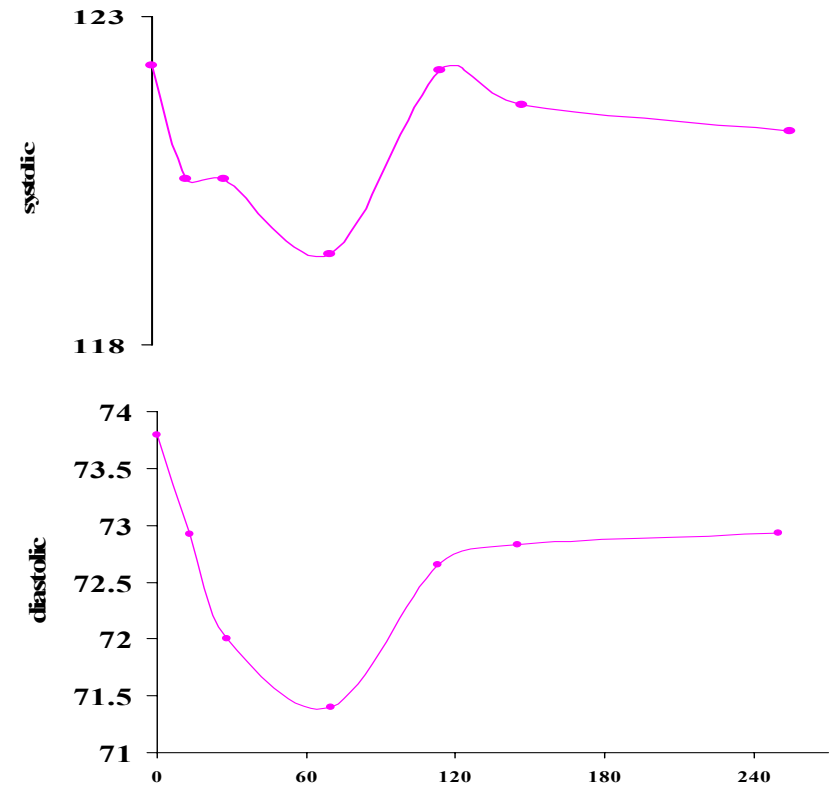
- VAS Craving;
Continuous scale
from 0 to 20 cm
(no craving feelings
at all → severe
craving)
- Decline in craving scale
heroin dose dependent

Changes in physiological functioning (means)

OXYGEN SATURATION



BLOOD PRESSURE




Changes in physiological functioning

- **Marginal changes after heroin administration**
- **none heroin dose relationships**
- **no differences between intravenous using group and heroin inhalation group**

conclusions

- About 50% of the heroin dose is absorbed at “chasing the dragon”
- Heroin half-life of 5 minutes
-95% of the dose eliminated within 30 minutes
- Highest heroin doses best appreciated
- heroin dose increase of 50% caused no severe side-effects

HEROIN PK-PD STUDY FUTURE PROSPECTIVES

- **RELATIONSHIP BETWEEN PHARMACODYNAMIC EFFECTS AND PLASMA CONCENTRATION**
- **DEVELOPMENT OF ONE INTEGRATED POPULATION PK MODEL (NONMEM)**

- **COVARIATE ANALYSIS:**
 - WEIGHT, SEXE, RACE**
 - LIVER / KIDNEY FUNCTIONING**
 - INTERACTION WITH COCAINE, ALCOHOL**
- **POPULATION PK STUDY: 100 PARTICIPANTS, SPARSE SAMPLING (3)**