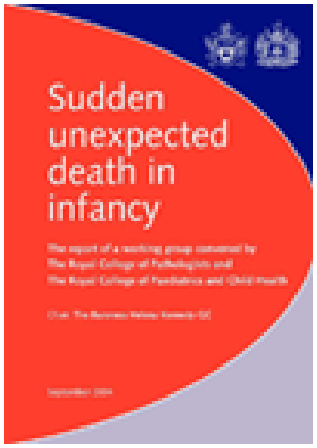
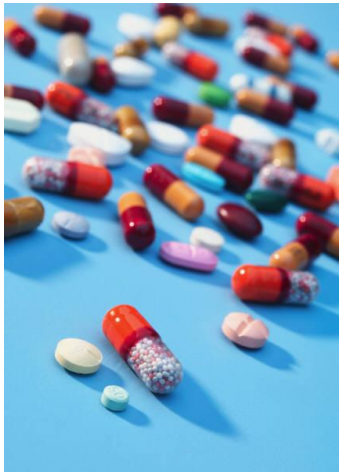


Toxicology aspects of SUDI

Dr Stephen Morley

STH



Epidemiology of SUDI toxicology

- Neonatal-placental transfer
- Breast milk
- 3rd person administration

- Association between illicit drug use in pregnancy and SUDIn

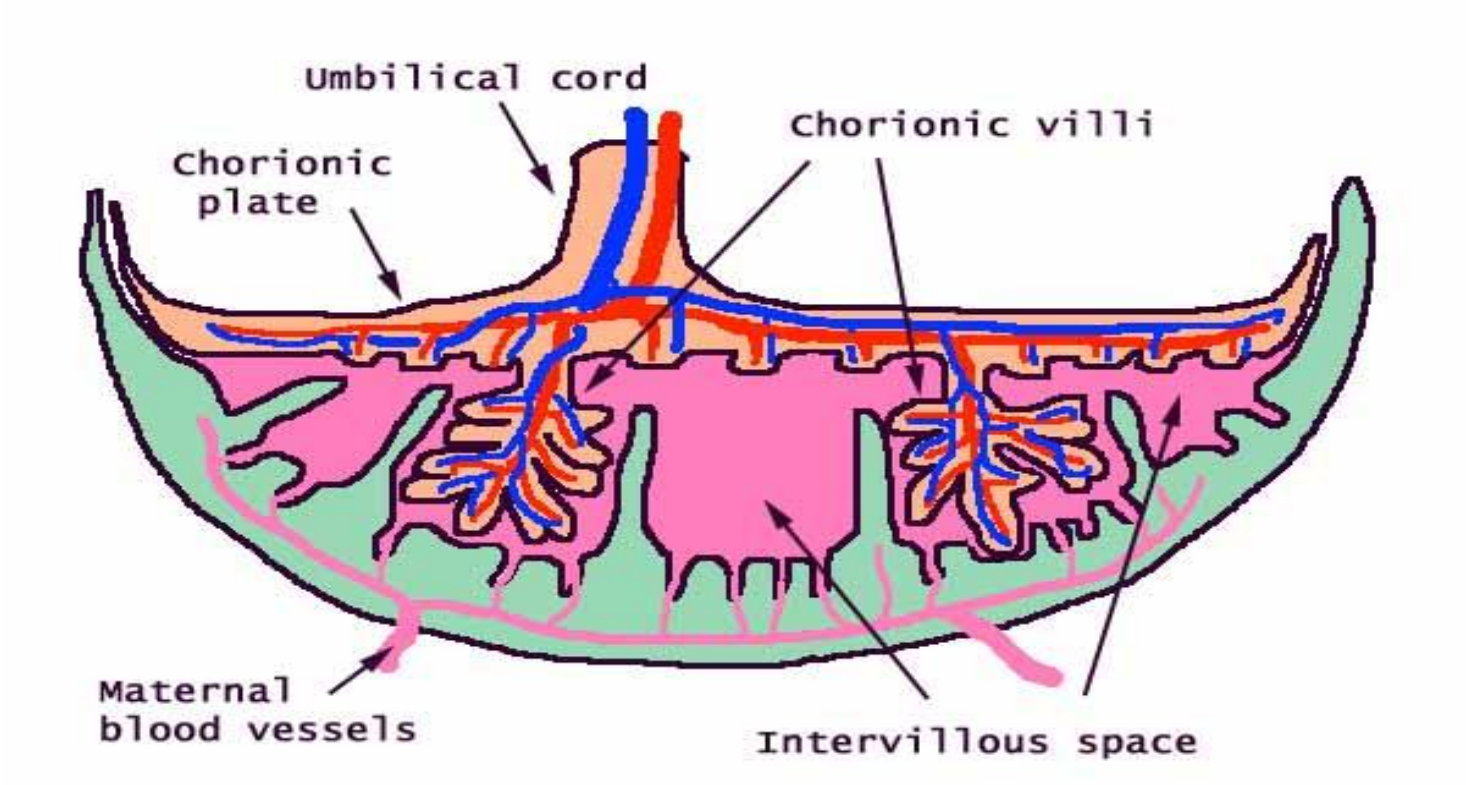
Children are not just small adults

- Body composition
- Gut absorption
- Liver enzymes/ metabolism
- Lack capacity
- Difficulty in swallowing tablet so
  (methadone) or rectal administration

Toxic Exposures → Death

- Analgesics
- Sedative-hypnotics
- Alcohols
- Gases & fumes
- Cleaning substances

Placental anatomy and circulation



Some drug metabolism as passes across placenta cf liver

Factors that affect entry into placenta

- Bioavailability
- Lipid solubility
- Water solubility
- Molecular Weight (MW = Daltons)
- Protein Binding
- Half-life of drug (t ½)
- Maternal health….ability to Metabolise and Excrete

DRUG TRANSFER

Total drug dose to infant = Maternal concentration X F: M ratio of drug

F:M Ratio = umbilical Vein Vs maternal venous concentration

BENZODIAZEPINES

AGENT	F:M	REMARKS
DIAZEPAM	**1**	Loss of baseline variability of FHR Dose dependent hypotonia (FLOPPY INFANT) Depression of temp. regulating system immature infants)
MIDAZOLAM	**0.76**	

OPIOIDS

DRUGS	F:M	REMARKS
MORPHINE	0.6	Resp.depression & acidosis Max: 2.5 -3hrs Loss of baseline variability of FHR Impaired acid-base balance Impaired neurobehavioral responses
PETHIDINE	<1 (Neonatal depression longer than pentazocine)	
PENTAZOCINE	< pethidine	
FENTANYL	0.37 to 0.57	
SUFENTANIL	0.81	>maternal prot binding
ALFENTANIL	0.3	↓ 1 min apgar score
REMIFENTANIL	0.88	No adverse neonatal effects

Placental transfer not usually an acute problem

- Paediatric care in acute labour ward setting

Neonatal Abstinence Syndrome

A constellation of signs and symptoms which result from the abrupt cessation of a drug to which the fetus/neonate has become physiologically dependent

NAS

W - wakefulness
I - irritability
T -tremors, twitching, tachypnea
H - hyperventilation, hypertonia, hyperpyrexia, hyperaccusis, hiccups
D - diarrhea, diaphoresis,
R - rub marks
A - alkalosis
W - weight loss
A - apnea
L - lacrimation,
S - seizures (myoclonic), sneezing, skin mottling

History of NAS

- Illicit drugs (Heroin) / Methadone
- Iatrogenic withdrawal:
  - ECMO - Fentanyl infusions
  - Around 50% of neonates & older children requiring ICU support experience WD

Drugs Causing NAS

Opiates

- Heroin
- Methadone
- Morphine
- Other
  - Oxycodone

Non-opiates

- Alcohol
- Barbiturates
- Benzodiazepines
- SSRIs
- Other (caffeine, tricyclics, valproate, antihistamines)
- Cocaine

Mechanism of NAS ?

- Neurochemical reaction due to depletion of drug from receptors in the brain.

The neonate is NOT addicted/ psychologically dependent.

Onset & Frequency of NAS

	Onset	Frequency
Heroin: (1-6 days)	24-48 hr	50-80%
Methadone: (2-28 days)	48 – 72 hr	60-90%
Phenobarbitol: days	10 –14	

Maternal Methadone & NAS

- **Dose –**
  - No consistent correlation with incidence and severity of NAS

- **Onset**: (T/2 = 24 hrs)
  - **48-52 hrs after the last maternal dose**
  - Serum methadone ≤ 0.06 ug/ml

Factors that affect entry into milk

- Method of delivery
  - Bioavailability
  - Lipid solubility
  - Water solubility
  - Molecular Weight (MW = Daltons)
  - Protein Binding
  - Half-life of drug (t ½)
  - Maternal health…ability to Metabolise and Excrete

Factors that affect entry into milk

- Bioavailability
  - For a drug to carry risk to a baby, it must be orally bioavailable, because this is the route of transmission for the baby.
  - IV drugs are 100% bioavailable
  - Oral drugs are always <100% bioavailable

Factors that affect entry into milk

- Lipid solubility
  - Drugs that are lipid soluble will enter milk more readily
  - Drugs that are polar to lipids, water soluble drugs, will not enter into milk as easily

Methadone in breast milk

TABLE 3 Concentrations of Methadone in Breast Milk, Mean Ingestible Infant Doses, and Median Breast Milk/Plasma Methadone Concentration Ratios

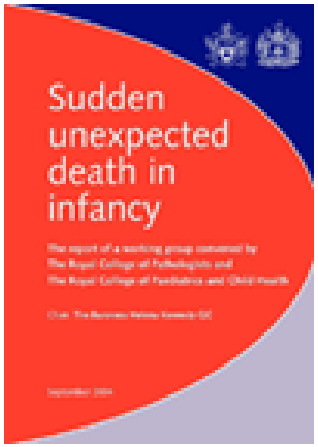
Sampling Period	*n*	Breast Milk Methadone Concentration, ng/mL		Ingestible Infant Dose, Mean, mg/d	Median Breast Milk/Plasma Methadone Concentration Ratio
		Median (Interquartile Range)	Range		
Day 1				0.004	
Trough					
Prefeeding	4	67.0 (77.5)	40.0–179.0		0.92
Postfeeding	2	48.5 (23.0)	37.1–60.3		0.34
Peak					
Prefeeding	2	98.0 (68.0)	63.6–132.2		0.47
Postfeeding	2	115.0 (10.0)	109.5–120.0		0.46
Day 2				0.012	
Trough					
Prefeeding	6	35.0 (27.0)	21.0–121.0		0.38
Postfeeding	5	41.0 (16.0)	20.6–175.4		0.47
Peak					
Prefeeding	5	64.0 (5.0)	27.4–135.7		0.22
Postfeeding	5	103.0 (31.0)	31.6–112.9		0.23

Standard adult starting dose is 10-40mg/d

Pediatrics 2008;121;106-114

Post mortem
Kennedy report

The examination of an infant found suddenly and unexpectedly dead has to be conducted even more thoroughly and carefully perhaps than any other type of post mortem. The cost of paediatric post mortems must be met by the coroner and adequate resources should be made available. A full range of tests, including neuropathology, microbiology, biochemistry, toxicology, as well as investigations for genetic metabolic disorders, will all add to the expense of these post mortems and the cost must be met.



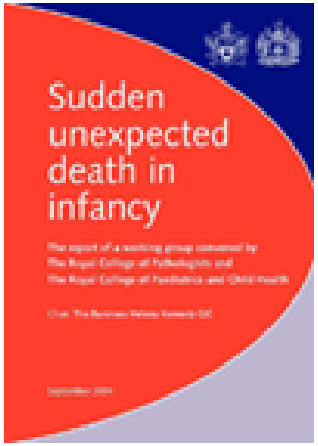
Kennedy report

Blood samples should be taken from a venous or arterial site (e.g. femoral vein)*. Cardiac puncture should be avoided as this may cause damage to intrathoracic structures and make post-mortem findings difficult to interpret.

If the post mortem is to be conducted within 24 hours of the death, it may be best for the samples to be taken by the pathologist.

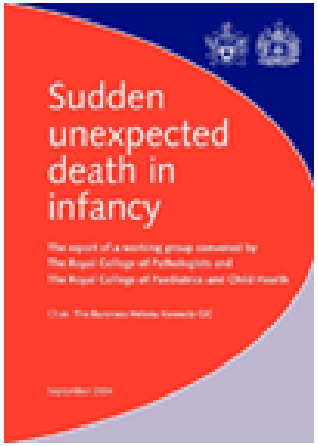
- *This refers to the peri-mortem taking of samples

- Have you ever tried taking a femoral sample from an infant!!!!!!



Forensic considerations

- Ensure you have the permission of the coroner to take samples.
- Document all samples taken, label and ensure an unbroken ‘chain of evidence’.
- This may mean handing samples to a police office directly, or having the laboratory technician sign on receiving them in the laboratory.
- Samples given to police or coroner’s officer must be signed for.
- Record the site from which all samples were taken.



SUDI investigation in Sheffield

- The investigations undertaken in all these cases include
- virology and bacteriology,
- metabolic investigations,
- full skeletal X- ray,
- toxicology
- neuropathology.

Illustrative cases

- Baby born to heroin addict
- Not “used” for several weeks
- On methadone 65ml per day

- Born and took 10 breaths

- PM tox methadone = 64µg/L

Neonatal methadone

- Guthrie card methadones (day 5-7) <20µg/L
- No good studies looking at newborns
- Breast feeding
- Placental transfer affecting tolerance

Sheffield pathology data 2004-2010

- 1669 paediatric pms (up to age 16)
- 10 cases toxic post mortem levels of drugs
- 3 in SUDI age range

Age	Drug involved
2 h	Methadone
	Promethazine
3m	Methadone
12d	Diazepam Nordiazepam Temazepam
2 y	Dothiepin Nordothiepin

Serial Blood GHB on a potential IEM patient

- 05/6 187 mg/L
- 06/6 52 mg/L
- 07/6 <5mg/L
- 08/6 <5mg/L

- So probably not!
- GHB administration far more likely

Gamma hydroxybutyrate

- Anaesthetic
- Body building
- Drug of abuse
- DFSA

- Therapeutically useful in narcolepsy/ alcohol withdrawal

- Colourless
- Soluble in water
- Salty taste

PM tox (coroners case) SUDI case

	Blood	**Urine**
Ethanol	Not detected	Not detected
Paracetamol	32mg/l	-
Salicylate	Not detected	-
Opiates	-	Present*
Benzodiazepines	-	Not detected
Barbiturates	-	Not detected
Cannabinoids	-	Not detected
Methadone	-	Not detected
Cocaine metabolites	-	Not detected
Phenethylamine group	-	Not detected
Dihydrocodeine	261μg/l	-

- *** Insufficient urine to identify**

- There were no additional toxicological findings in blood or urine by gas chromatography/mass spectrometry.

Considerations

- How did DHC and paracetamol got into pm blood in a 2 month old child?

- Must have been 3rd party
- ? Crushed tablets
- ? rectal

How to detect the unknown?

- Immunoassay – poor
- GCMS- chemical basic screen for toxicology but need “full” screen and library
- LCMS- targeted/ “full” screen so need to ensure in library
- HRMS- definable from accurate mass and fragmentation patterns again need library

Samples

- Urine- detect drugs for ~ week – quants difficult
- Blood- detect for 1-2 days good for quants
- Gastric content- 2-4 hours after ingestion
- Liver/muscle if inadequate blood can do quants
- Hair- chronic exposure- littleork on hair growth rates in infants

Samples

- Vitreous-
  - best for alcohol-
  - renal function salt poisoning

- For blood/vitreous- Fluoride oxalate
  - Cocaine
  - Benzos
  - Alcohol
  - Rubbish for biochemistry

Who gets the samples?

- virology and bacteriology,
- metabolic investigations,
- Toxicology
  - Urine
  - Blood
  - Gastric
  - (Hair)