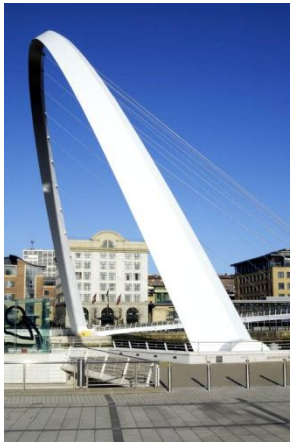





AN INTRODUCTION TO DRUG METABOLISM AND PHARMACOKINETICS: ROLE IN PAEDIATRIC DRUG DEVELOPMENT

ITCC Introductory Course in Paediatric Drug Development

Prof Gareth Veal

Newcastle University

The Newcastle upon Tyne Hospitals NHS
NHS Foundation Trust

NCCPG
Newcastle Cancer Centre Pharmacology Group

‘Perfect Drug’

‘Real Drug’

- Benefits all patients
- One dose fits all
- Responses in all patients
- No adverse effects

- Benefits some patients
- Variable doses for different patients
- Responses in some patients
- Adverse effects in some patients

- A key component of precision medicine strategies and treatment individualisation relates to the understanding of inter-patient variability in drug exposures

FACTORS DETERMINING DRUG ACTION

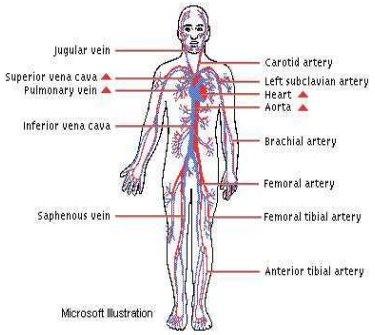
Drug

↓

Pharmacokinetics

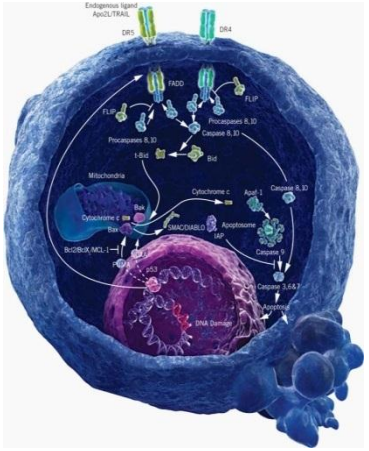
Protein binding

Cell uptake



↓

DNA damage

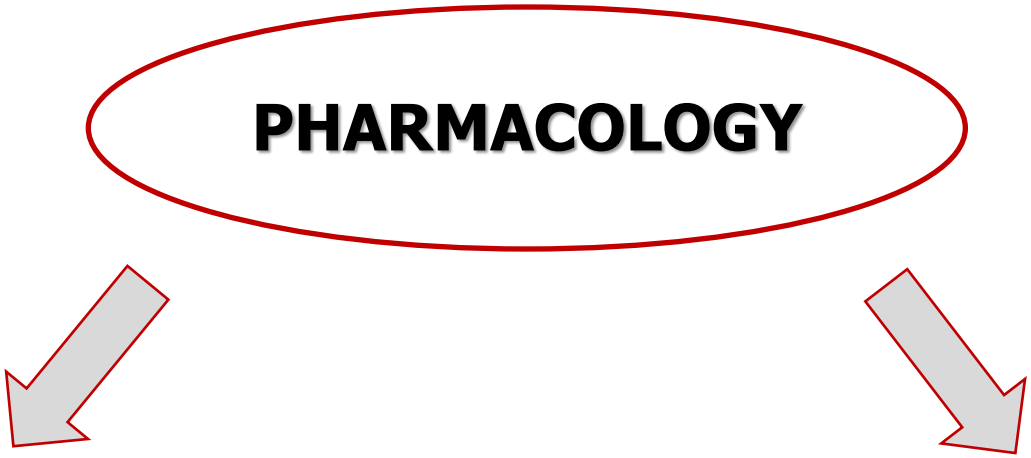


↓

Cell death

WHAT IS PHARMACOLOGY

- The study of how drugs affect a biological system



Pharmacokinetics

- what the body does to the drug

Pharmacodynamics

- what the drug does to the body

PHARMACOKINETICS AND PHARMACODYNAMICS

Key definitions:

- Pharmacokinetics (PK): "study of the bodily absorption, distribution, metabolism, and excretion of drugs"

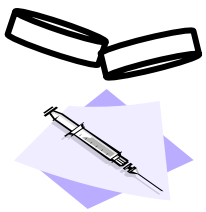
  - *describes relationship between the administered dose and the observed biological fluid/tissue concentrations of a drug with time.*

- Pharmacodynamics (PD): "study of the action or effect of drugs in the body"

  - *concerned with the magnitude and time course of an observed pharmacological effect*.

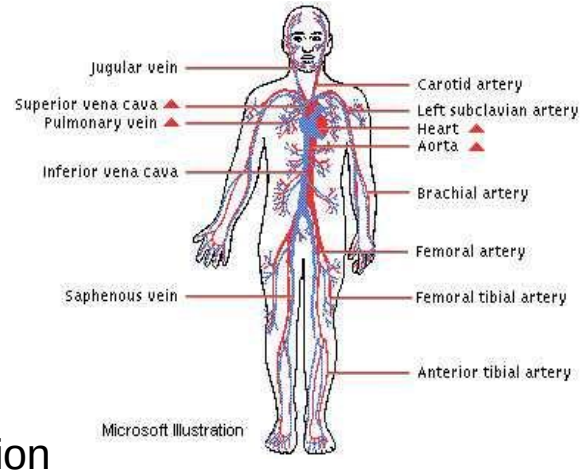
ADME

- the study of the fate of an externally administered compound

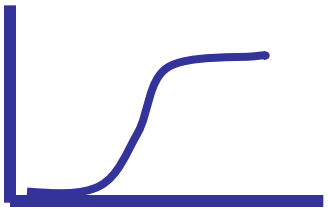


- Absorption
- Distribution
- Metabolism
- Excretion

Drug in



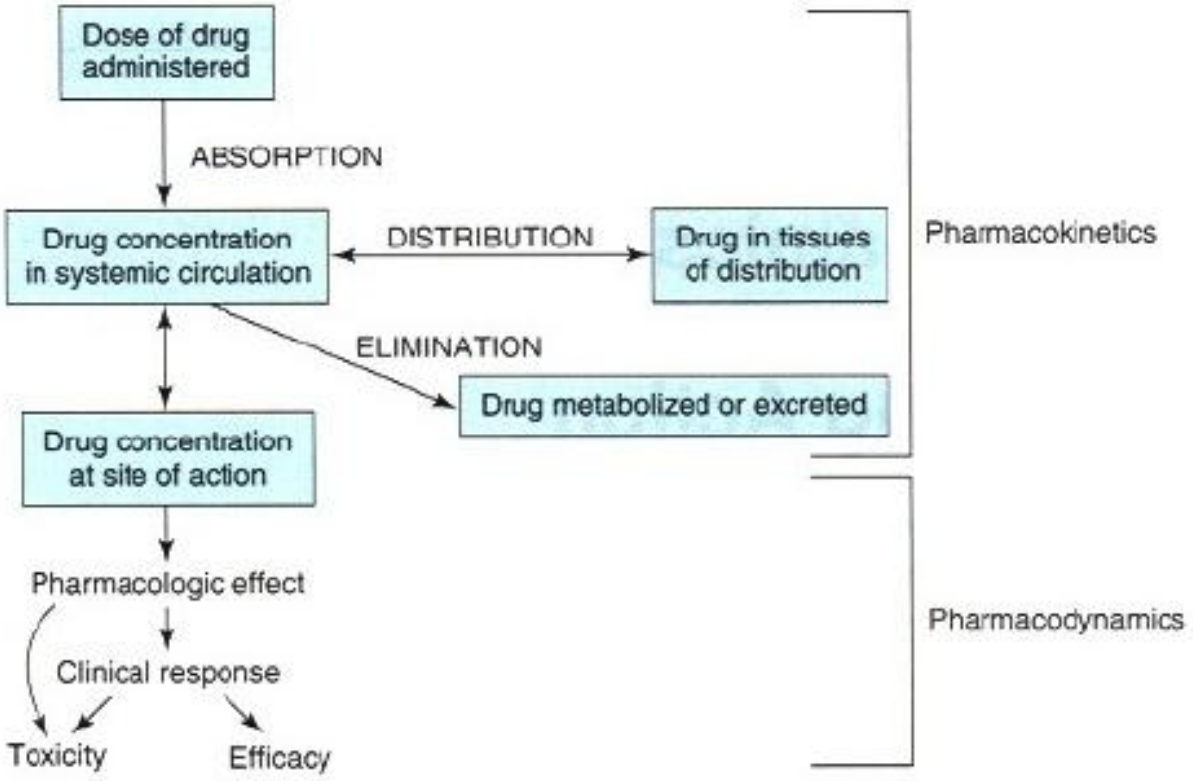
Response



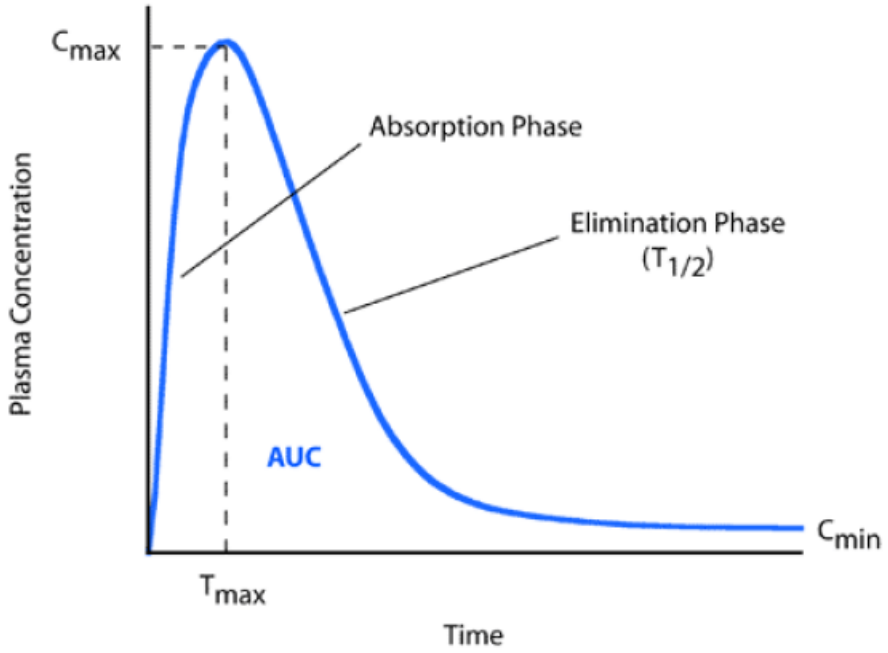
- Drug in plasma reflects:
  - active drug (concentration related to effect)
  - drug available for elimination
  - drug in equilibrium with rest of body

Drug out

RELATIONSHIP BETWEEN DOSE AND EFFECT

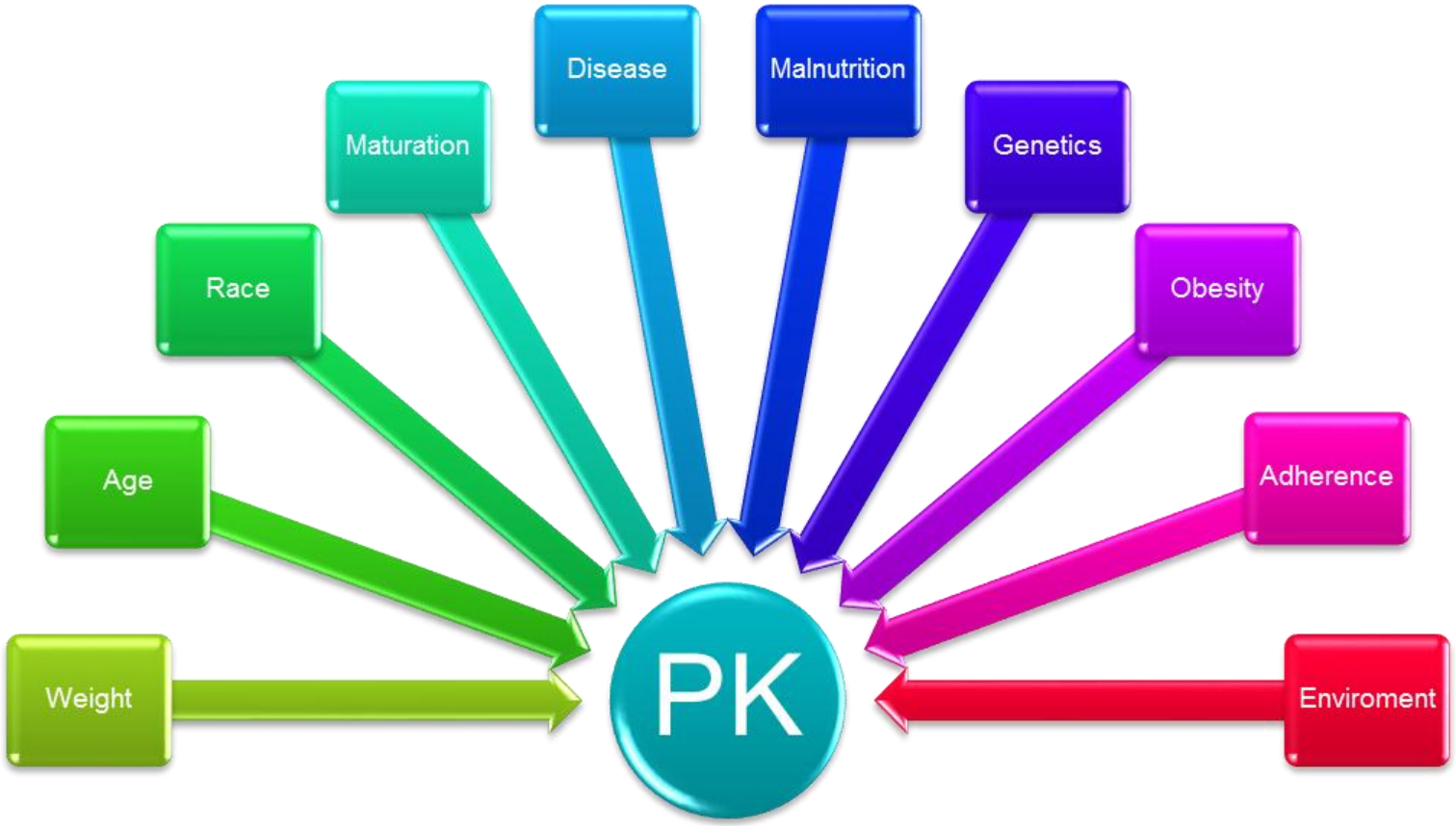


PHARMACOKINETICS: ADME

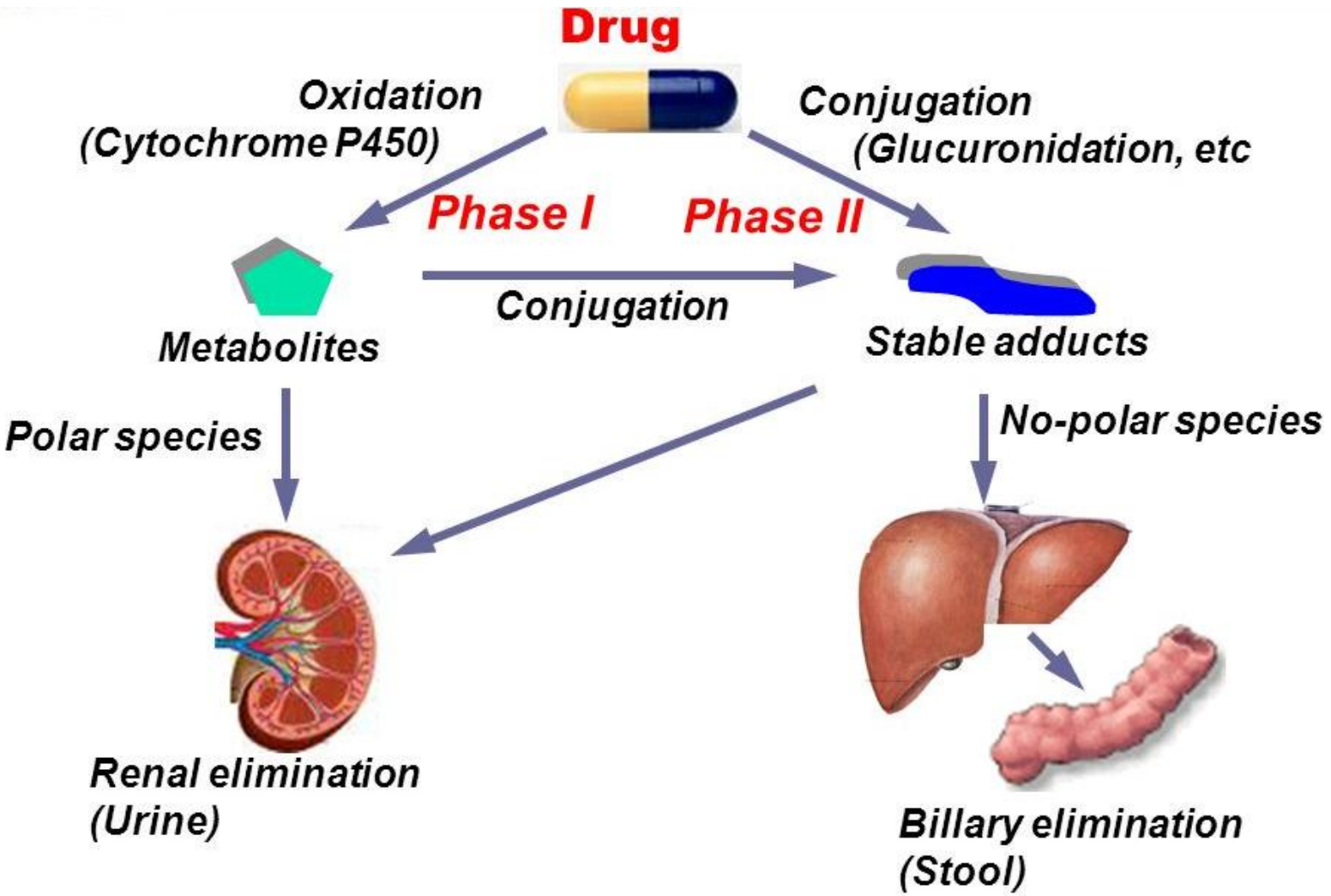


- Pharmacokinetics (PK) – the mathematics of the time course of Absorption, Distribution, Metabolism, and Excretion of drugs in the body.
- A favorable PK profile is vital to the therapeutic success of a drug
- Drug must be able to reach its intended target

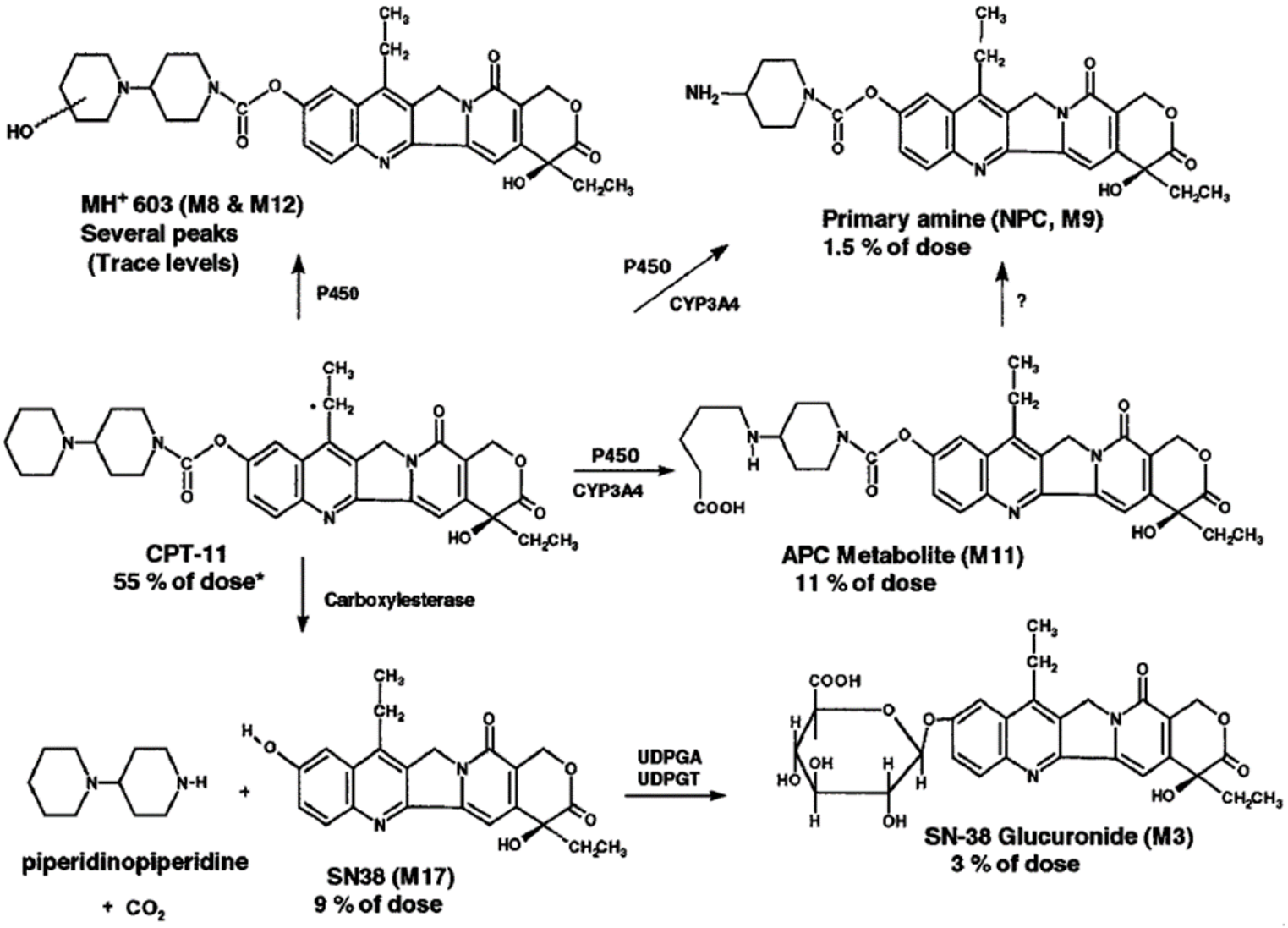
PHARMACOKINETIC VARIATION



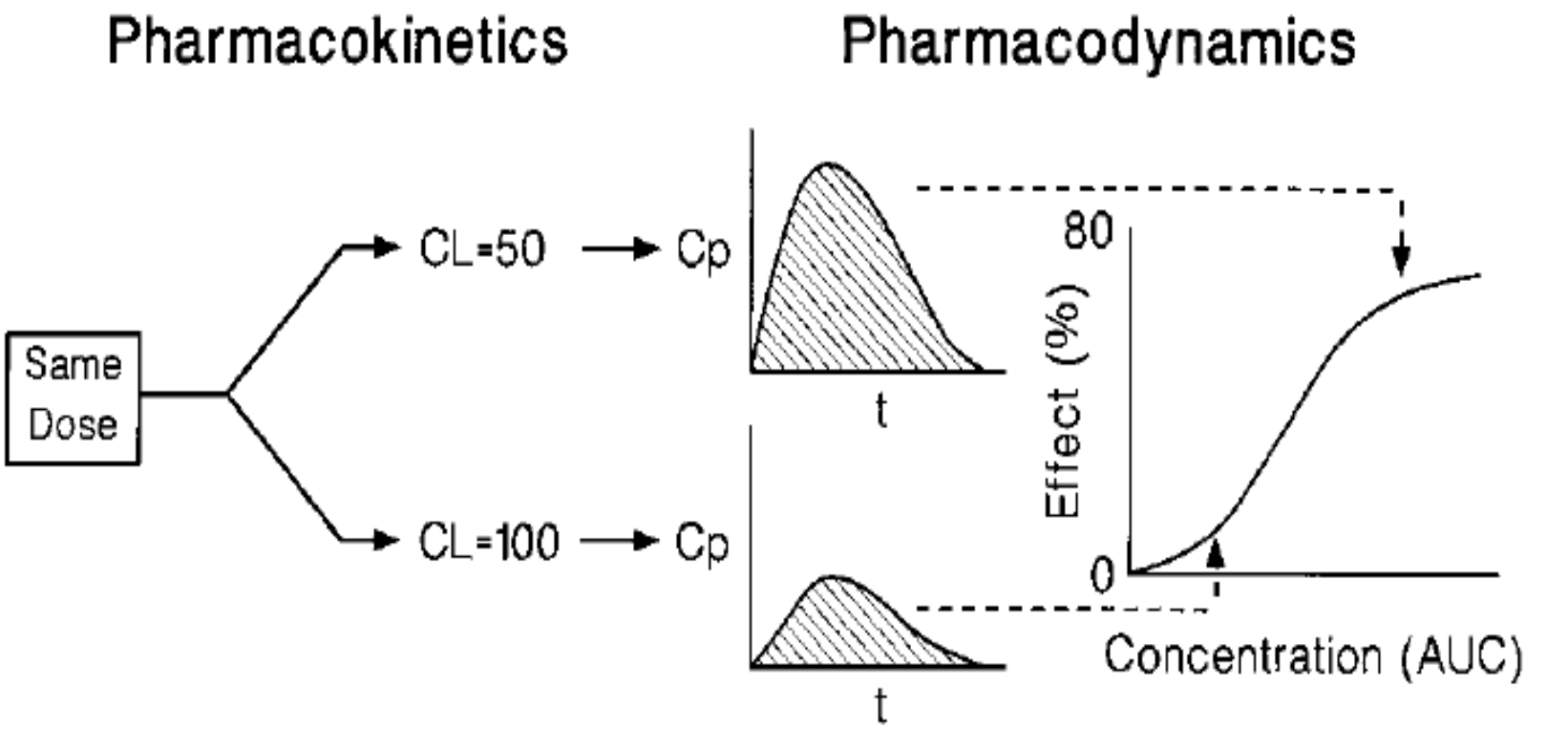
DRUG METABOLISM



DRUG METABOLISM – IRINOTECAN (CPT-11)



RATIONALE FOR CLINICAL PHARMACOLOGY STUDIES

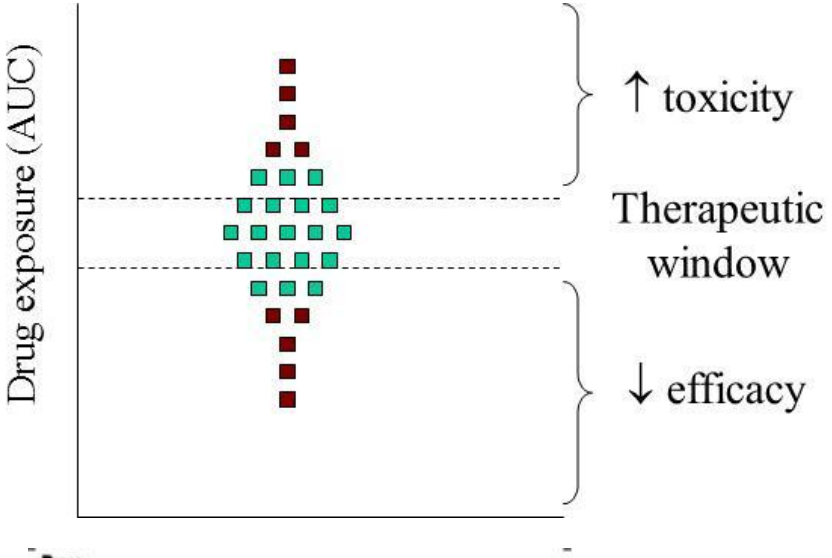


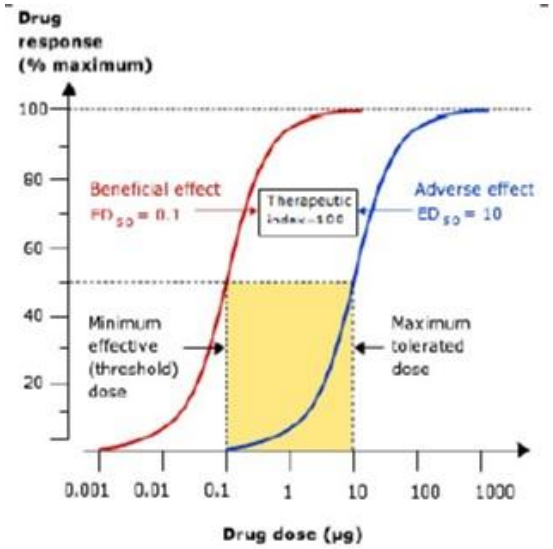
Dose --------→ Clearance - - -→ Systemic Exposure - - -→ Clinical Response

CLINICAL PHARMACOLOGY STUDIES

"optimization of the therapeutic use of a drug to prevent exposure to toxic or sub-therapeutic concentrations, and/or achieve the Biologically Effective Dose in individual patients through dosage adjustments based on plasma concentrations in individual patients"

Increased importance of both PK and PD endpoints in demonstrating the biological effect on target/ downstream molecules



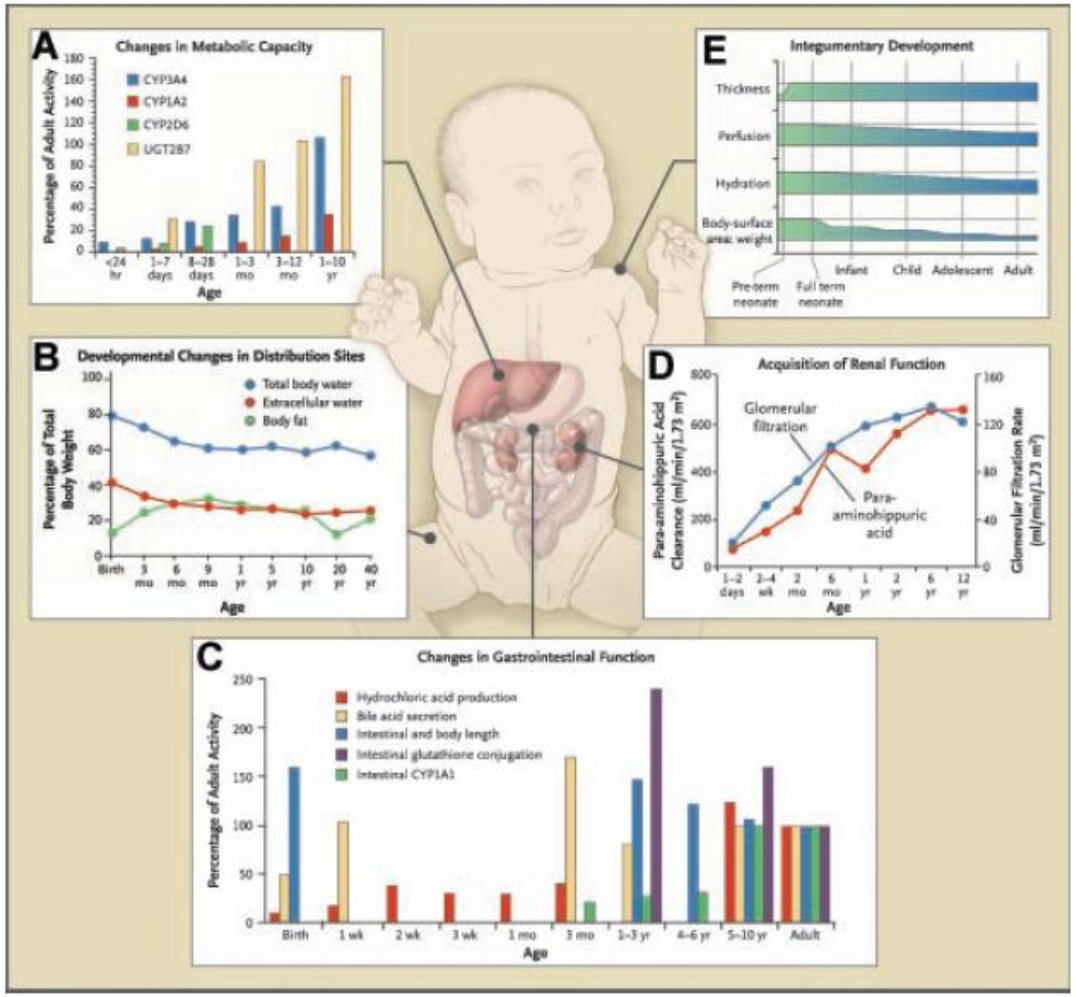


NEED FOR CLINICAL PHARMACOLOGY STUDIES IN CHILDHOOD CANCER

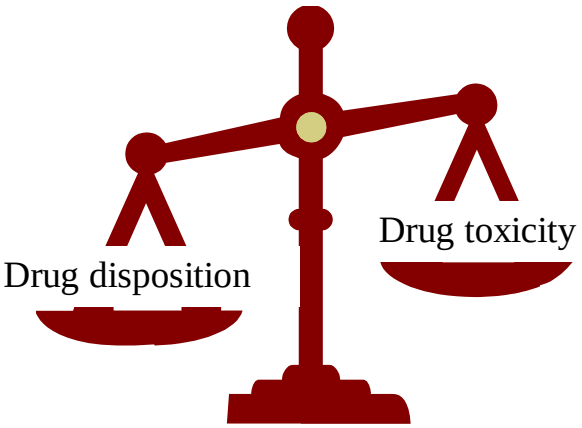
Paediatrics

Adults

DEVELOPMENTAL CHANGES AND CLINICAL PHARMACOLOGY IN THE INFANT ONCOLOGY PATIENT



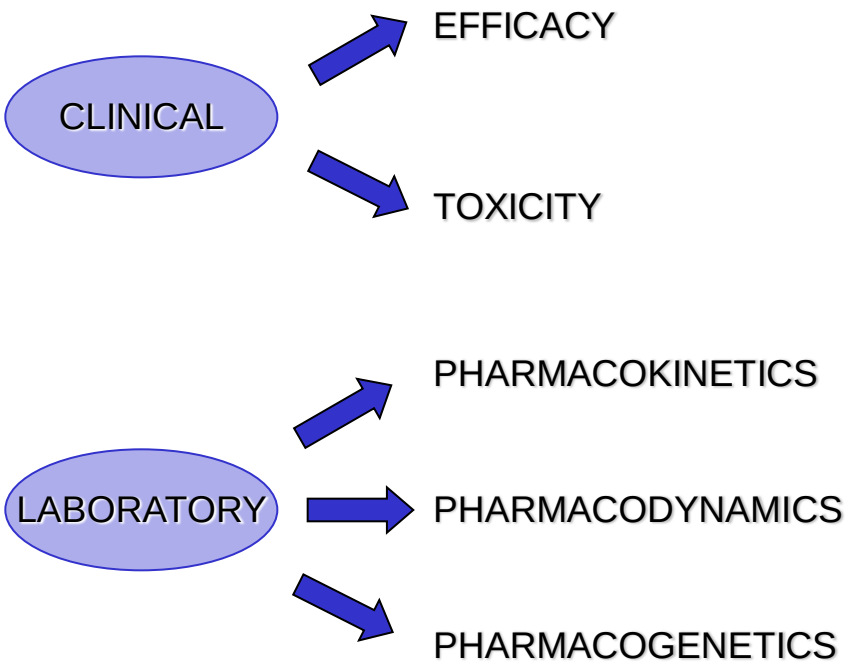
- Rationale for dose reductions in infant patients?



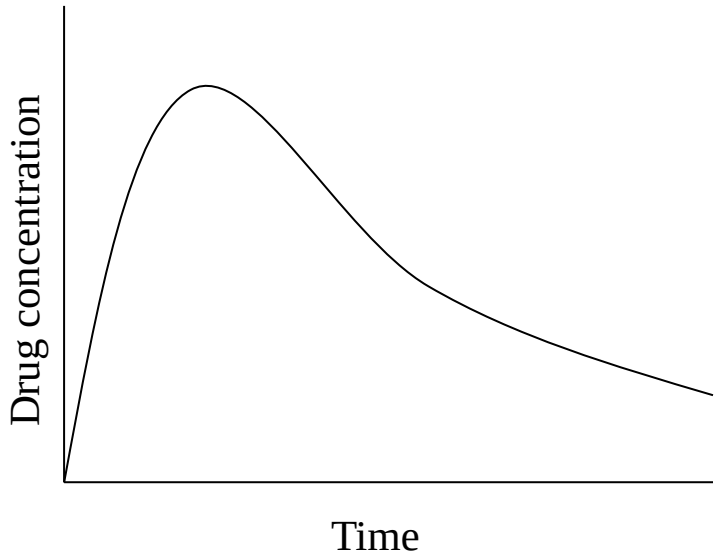
Taken from Kearns GL*: New Engl J Med, 2003;349:1157-1167*

DRUG PHARMACOKINETICS / CLINICAL PHARMACOLOGY

- Clinical pharmacology studies



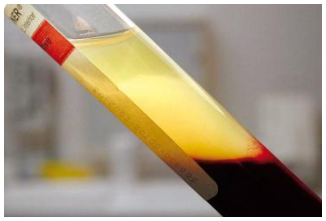
- Relationship between drug concentration and time



PHARMACOKINETIC STUDIES – WHAT'S INVOLVED?

- Drug administered
  - *Oral*
  - *IV*
  - *Other*

- Blood sample taken
  - *Whole blood sample*
  - *Separation of plasma*
  - *Ultrafiltration*



- Analysis
  - *HPLC with UV detection (μg/ml)*
  - *HPLC with fluorescence detection (ng/ml)*
  - *LC-MS (mass specific detection – pg/ml)*
  - *AAS (Atomic Absorption Spectrometry)*

PK VARIABILITY OF TARGETED AGENTS

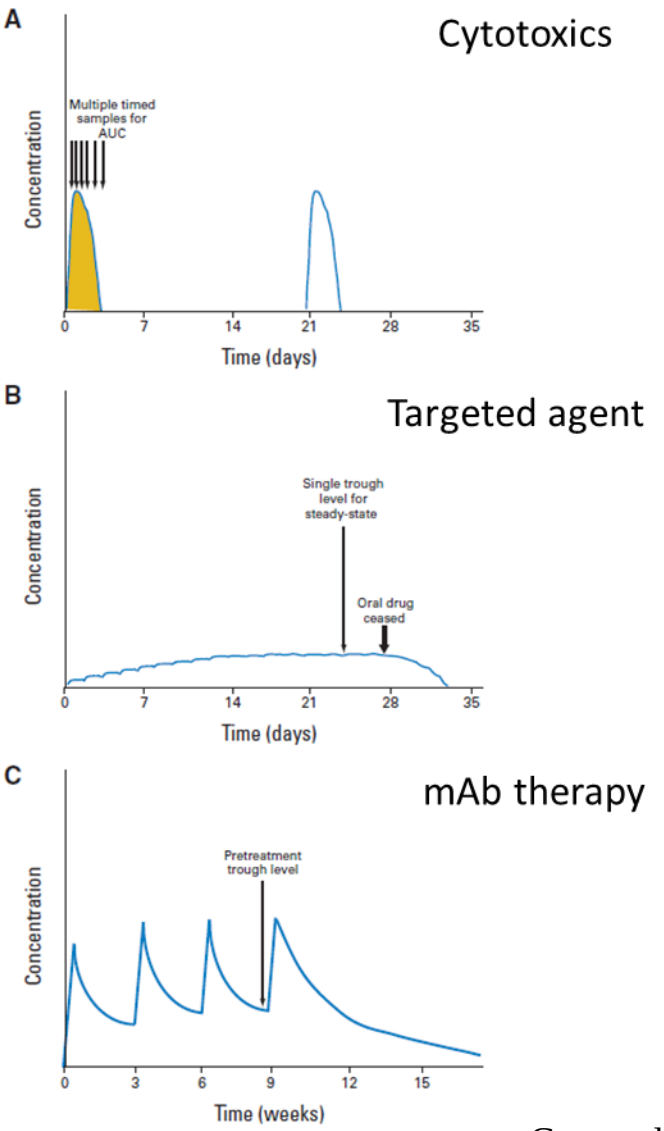
Table 2. Pharmacokinetic Variations of Selected Targeted Anticancer Therapies

Drug	Dosage per Day	Interpatient Variations (fold or CV*) AUC	Trough Level
Hormones			
Tamoxifen†	20 mg		26-fold[28]
Letrozole	2.5 mg	40%[29]	12-fold[30]
Anastrozole	1 mg	25%[31]	11-fold[32]
Bicalutamide	50 mg	25%[33]	
Abiraterone	1,000 mg	58%[34]	
Tyrosine kinase inhibitors			
Imatinib	400 mg	25%[35]	16-fold[36]
Nilotinib	400 mg bd	51.9%[37]	51.3%[37]
Gefitinib	250 mg	15-fold[38]	23-fold[39]
Erlotinib	150 mg	64%[40]	51%[40]
Sunitinib	50 mg	41%[41]	54%[41]
Sorafenib	400 mg bd	39-82%[42]	11-fold[43]
Temsirolimus	25 mg	26%[44]	
Monoclonal antibodies			
Cetuximab	400 mg/m^2	39%[45]	6-fold[46]
Trastuzumab	6 mg/kg	10-35%[47]	>10-fold[48]
Rituximab	375 mg/m^2	6.2-fold[49]	23-fold[50]
Bevacizumab	10 mg/kg	2.4-fold[18]	

Abbreviations: AUC, area under the concentration-time curve; CV, coefficient of variation.

*A CV of 30% to 50% represents an approximately 10-fold variation between maximum and minimum drug concentrations for most drugs.[51,52]

†Pharmacokinetic variation of endoxifen, the main active metabolite of tamoxifen, was used.



Gao et al., *JCO* 2012

HOW CAN WE UTILISE CLINICAL PHARMACOLOGY STUDIES IN THE TREATMENT OF CHILDREN WITH CANCER?

- Drug development / early phase trials
- Definition of most appropriate doses and schedules in different patient populations
- *Therapeutic* drug monitoring approaches

DEVELOPMENT OF 'FIT FOR PURPOSE' PK/PD ASSAYS

- Selectivity
- Matrix effect
- Recovery
- Limit of Detection (LOD)
- Low limit of quantification (LLOQ)
- Linearity and Range
- Dilution integrity
- Carry-over
- Intra/Inter-assay Precision and Accuracy
- Stability:
  - Freeze an thaw cycles
  - Short term
  - Long term
  - Autosampler

EARLY PHASE PK/PD BIOMARKER STUDIES

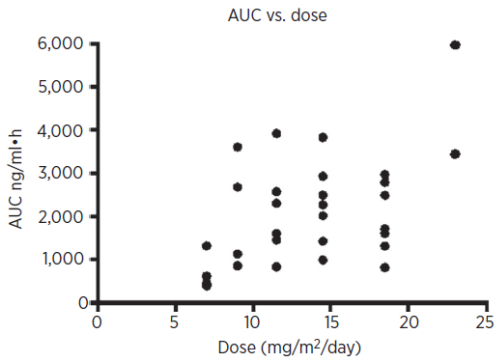


Figure 2.
Summary of pharmacokinetics: AUC versus dose of AT9283.

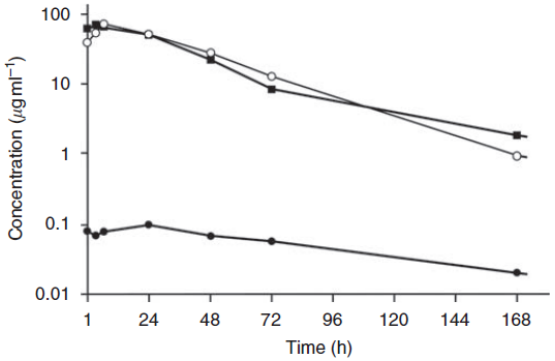


Figure 3 Plasma Pt concentration–time curve from a patient treated at 90 mg m^{-2} of NC-6004. ■, total Pt, ○, gel-filterable Pt, ●, ultrafilterable Pt.

- Many years of experience in running Phase I trials in adults and paediatrics
- Development of novel PK and PD biomarker assays
- 20-50 patients per study
- Need to identify PK and PD endpoints specific to the new agent to guide incorporation into existing dosing regimens

Cancer Therapy: Clinical

Clinical Cancer Research

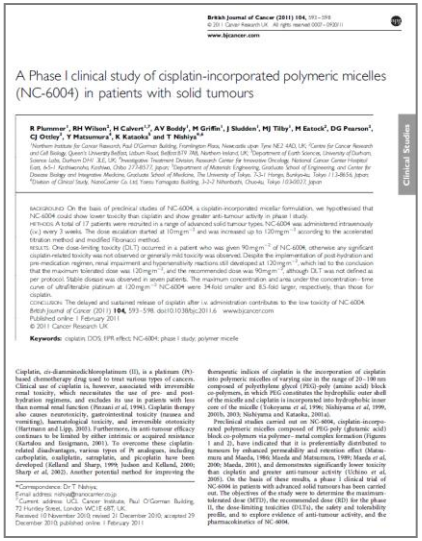
A Phase I Trial of AT9283 (a Selective Inhibitor of Aurora Kinases) in Children and Adolescents with Solid Tumors: A Cancer Research UK Study

Lucas Moreno[1,2], Lynley V. Marshall[1,2], Andrew D.J. Pearson[1,2], Bruce Morland[3], Martin Elliott[4], Quentin Campbell-Hewson[5], Guy Makin[6], Sarah E.R. Holland[7], Gary Acton[8], Philip Rose[9], Shamim Kazmi-Stokes[10], Victoria Loyd[10], Ana Rodriguez[10], John F. Lyons[11], Alan V. Boddy[12], Melanie J. Griffin[10], Murray Yule[10], and Darren Hargrave[13]

Abstract

Introduction

AACR



British Journal of Cancer (2011) 104, 593 – 598

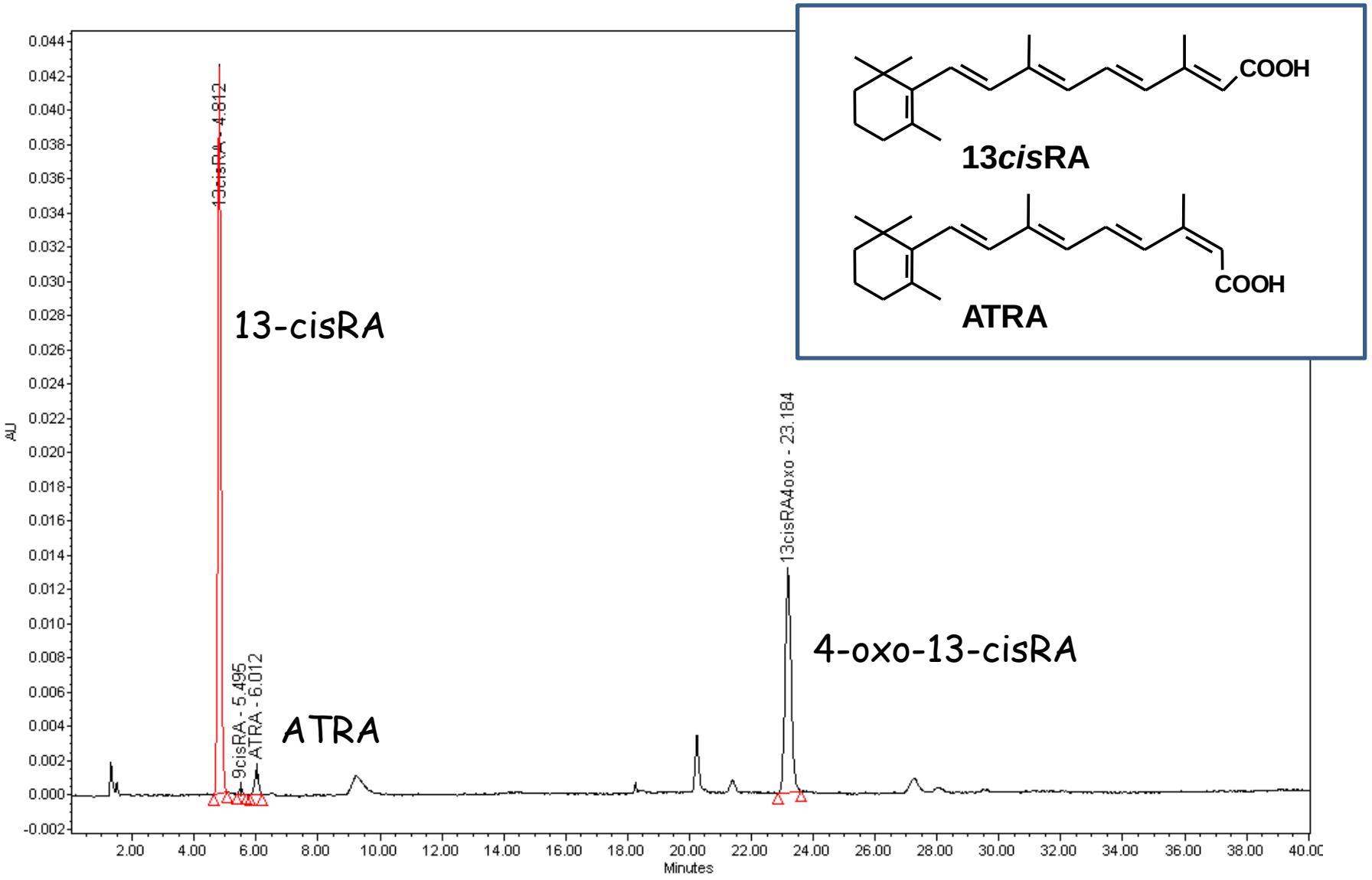
www.bjcancer.com

A Phase I clinical study of cisplatin-incorporated polymeric micelles (NC-6004) in patients with solid tumours

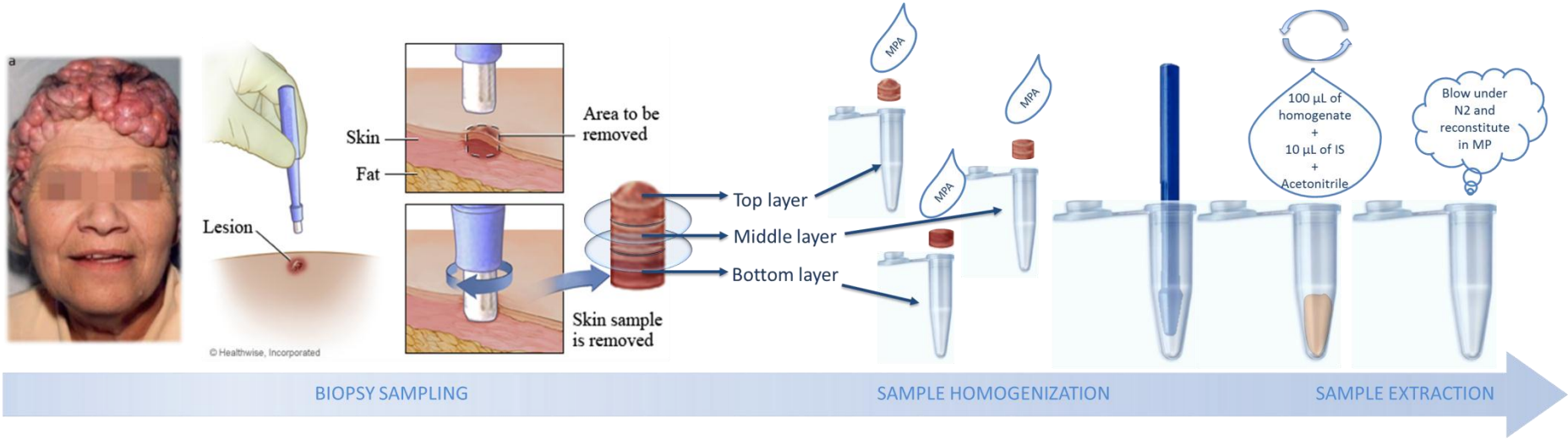
R Plummer[1], RH Wilson[2], H Calvert[1,2], AV Boddy[3], M Griffin[4], J Shudoin[4], MJ Tilby[3], M Eatock[5], DG Pearson[5], CJ Ottley[1], Y Matsumura[6], K Kataoka[7] and T Nishiya[7,8]

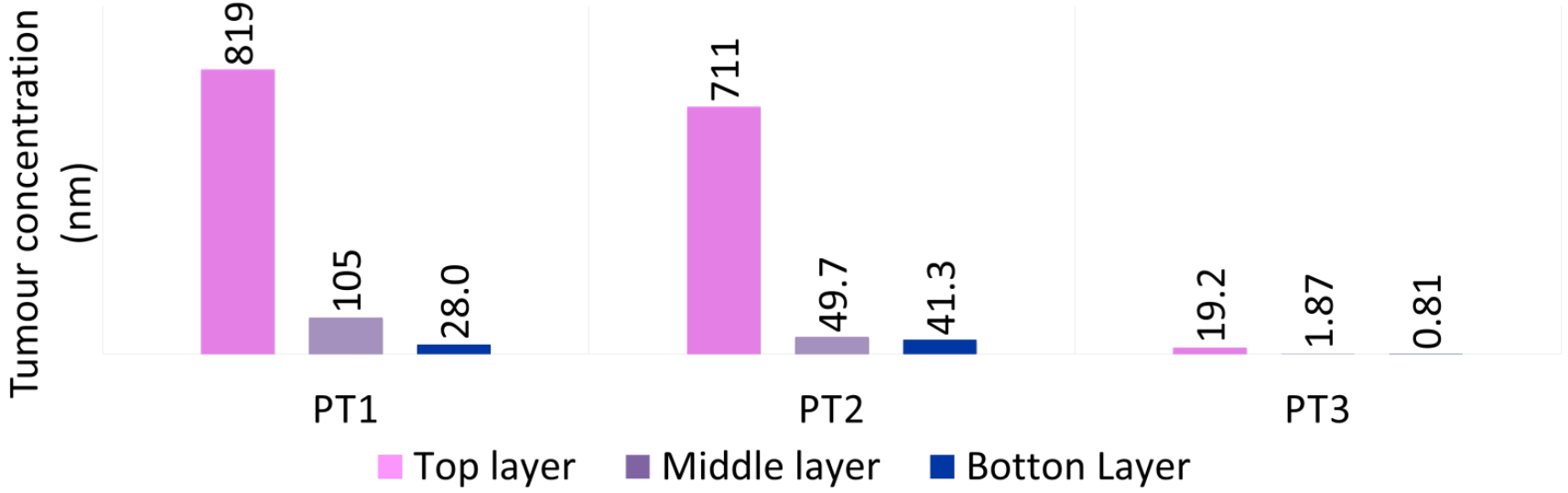
Clinical Studies

ANALYSIS OF DRUGS – RETINOIC ACID



Tropomyosin receptor kinase (Trk) inhibitor Pegcantratinib in human skin tumours

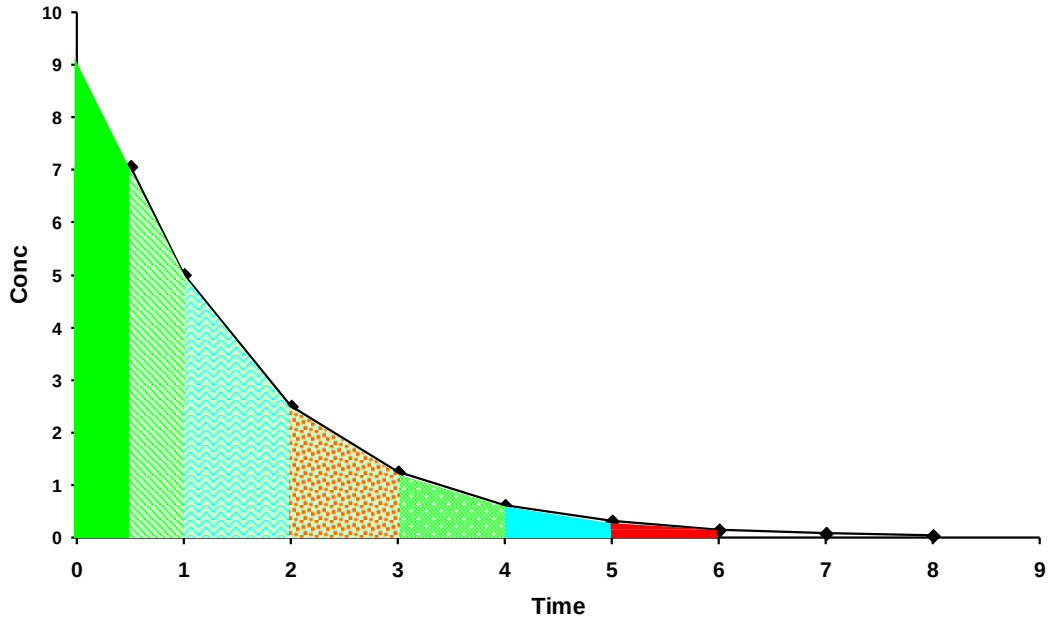




DRUG CLEARANCE AND AUC

$$AUC = Dose / Clearance$$

- Calculation of AUC by Trapezoidal rule
- Area of trapezoid =



INTERPATIENT VARIATION IN PHARMACOKINETICS – EARLY PHASE CLINICAL TRIAL DATA

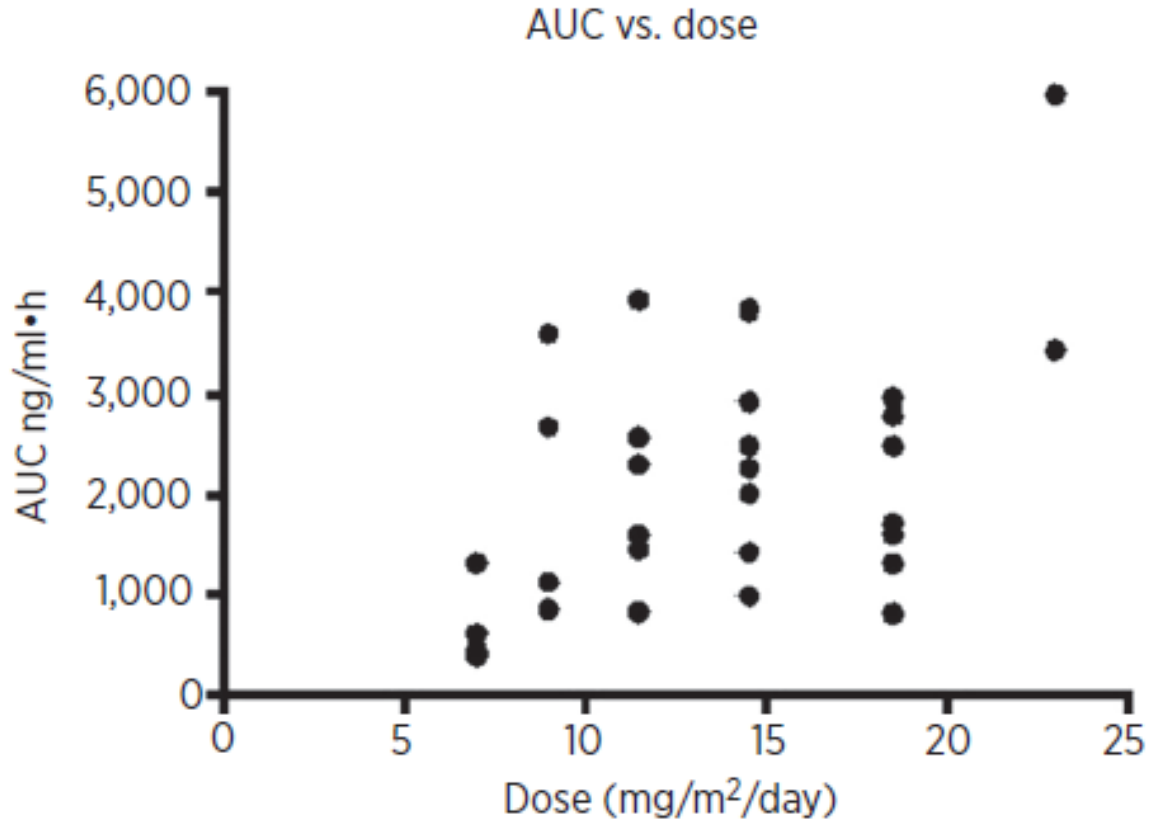


Figure 2.
Summary of pharmacokinetics: AUC versus dose of AT9283.

PHARMACOKINETICS OF TARGETED DRUGS

- Molecularly targeted drugs and immunotherapies have distinct toxicities from chemotherapies that are often not dose-dependent and can lead to chronic and sometimes unpredictable side-effects
- Utilisation of a dose escalation method with toxicity-based endpoints may be less appropriate for determination of RP2D
- PK and/or PD outcomes provide potentially appealing options
- Importance of informative and detailed PK/PD data from preclinical studies

Table 1 — Similarities and differences in phase I trials for different drug classes.

Trial elements	Cytotoxics	MTAs and immunotherapies
Primary end point	RP2D	RP2D
Secondary end points	Toxicity (MTD, DLT), response rate	PK or PD (molecular) parameter, toxicity, response rate
Dose escalation decisions	Toxicity based	Escalate based on toxicity or to a desired on-target effect
PK parameters	C_{max} may correlate with toxicity $t_{1/2}$ may predict recovery from toxicity	PK parameter (e.g. C_{max}, C_{min}, AUC) that correlates with desired target stimulation or suppression
Reasons for selecting RP2D	Toxicity RP2D must have tolerable toxicities and may demonstrate anti-tumor activity	Combination of toxicity and PD/PK parameters RP2D may demonstrate desired target effects with anti-tumor activity and tolerable toxicity

MTA, molecular targeted agent; RP2D, recommended phase II dose; MTD, maximum tolerated dose; DLT, dose limiting toxicity; PK, pharmacokinetic; PD, pharmacodynamic; AUC, area under the curve; SD, stable disease.

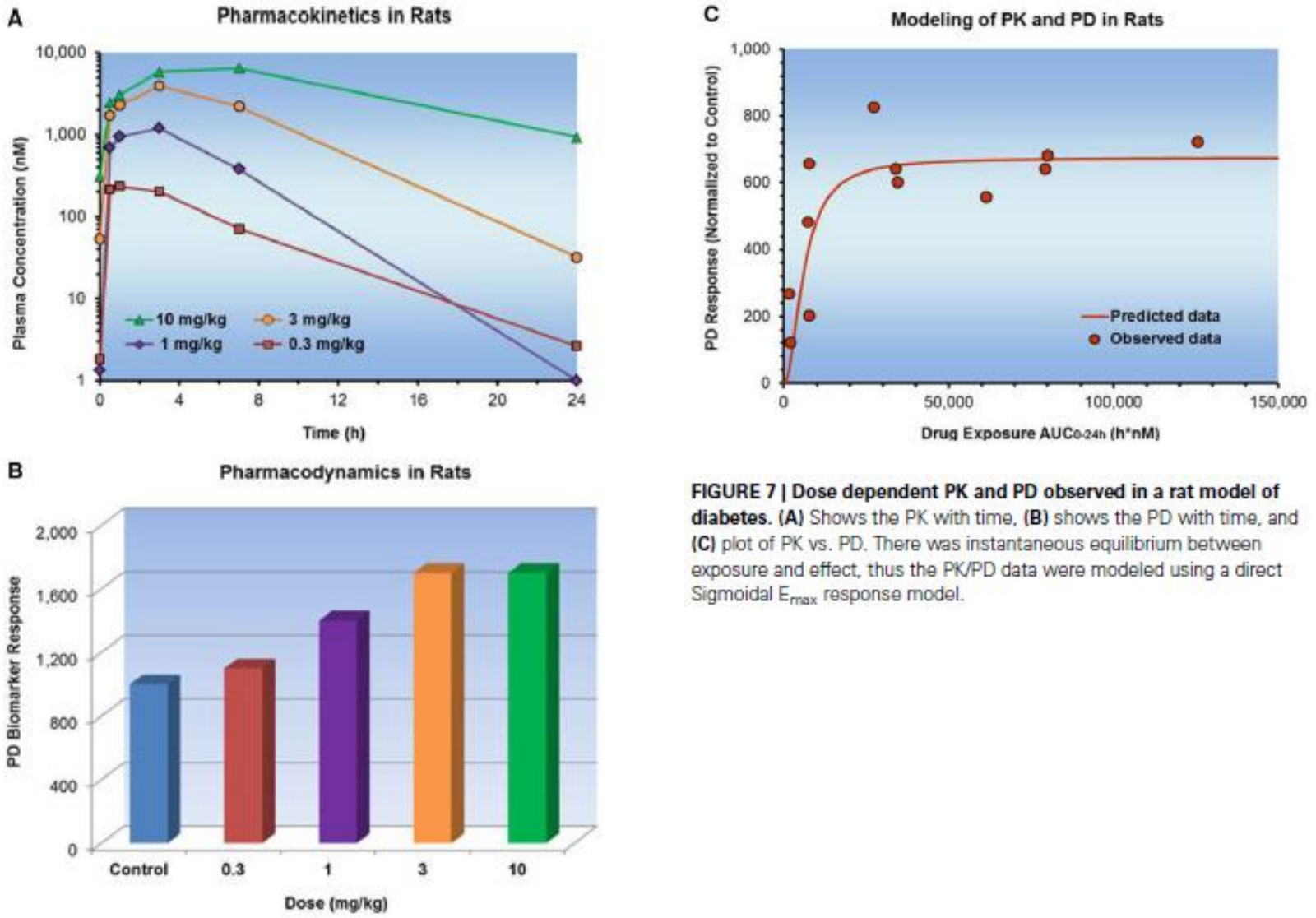


FIGURE 7 | Dose dependent PK and PD observed in a rat model of diabetes. (A) Shows the PK with time, **(B)** shows the PD with time, and **(C)** plot of PK vs. PD. There was instantaneous equilibrium between exposure and effect, thus the PK/PD data were modeled using a direct Sigmoidal E_{max} response model.

DETERMINATION OF BIOLOGICALLY ACTIVE DOSE

- Several FDA-approved agents, including imatinib, did not have MTD established in the Phase I setting, with PK/PD endpoints used to determine the RP2D

- Determination of the optimal biologically active dose (OBD) is increasingly becoming an attractive alternative

- Challenges to this approach include the requirement for serial collection of blood and tumour tissue or imaging approaches

- PK-guided dose escalation may be an appealing approach for molecules where MTD cannot be determined

Table 3 – Basis for RP2D and important toxicities of FDA approved MTAs in solid tumors.

Drug	Basis for RP2D	Select adverse events
Imatinib	PK/PD	Rash, edema, decreased LVEF, myelosuppression, myalgias and arthralgias
Trastuzumab	PK	Cardiomyopathy, asthenia, fever, chills
Pertuzumab	PK	Diarrhea, fatigue, nausea, anemia
Lapatinib	Toxicity + efficacy	Decreased LVEF, rash, hand-foot syndrome, diarrhea, elevated LFTs.
Erlotinib	Toxicity	Acneiform rash, diarrhea, interstitial lung disease
Gefitinib	PK + efficacy	Acneiform rash, diarrhea, interstitial lung disease
Cetuximab	PK	Acneiform rash, nail changes, diarrhea, hypomagnesemia, interstitial lung disease
Panitumumab	PK/PD	Acneiform rash, diarrhea, hypomagnesemia, hypocalcaemia, interstitial lung disease
Temsirolimus	Efficacy	Emesis, myelosuppression, dyslipidemia, diarrhea, rash and nephrotoxicity
Everolimus	PK/PD	Mucositis, rash, electrolyte abnormalities, dyslipidemia, diarrhea, pneumonitis, peripheral edema
Vemurafenib	Toxicity	Arthralgias, rash, squamous cell ca, keratocanthomas
Crizotinib	Toxicity	Nausea, vomiting, diarrhea, hepatotoxicity
Aflibercept	Toxicity + PK	Neutropenia, diarrhea, hypertension, eye irritation or visual disturbance
Bevacizumab	PK	Hypertension, thromboembolism, gastrointestinal perforation, poor wound healing
Sorafenib	Toxicity	Hypertension, rash, hand-foot syndrome, diarrhea, emesis, myelosuppression, delayed wound healing, hypophosphatemia
Sunitinib	Toxicity	Hypertension, emesis, myelosuppression, hypothyroidism, adrenal dysfunction, decreased LVEF, yellow skin discolouration and mucositis
Pazopanib	PK/PD + efficacy	Fatigue, increased LFTs, diarrhea, hypothyroidism
Regorafenib	Toxicity + PK/PD	Hypertension, hand foot syndrome and diarrhea
Cabazantinib	Toxicity + efficacy	Hand foot syndrome and mucositis
Vandetanib	Toxicity and PK	QTc prolongation, diarrhea, asthenia and fatigue
Ipilimumab	Efficacy	Autoimmune colitis, dermatitis and hepatitis. Various endocrinopathies.
Enzalutamide	Toxicity	Fatigue, diarrhea, flushing, edema
Axitinib	Toxicity	Diarrhea, hypertension, weight decrease, anorexia
Vismodegib	PK	Muscle spasms, alopecia, dysgeusia, weight loss, fatigue

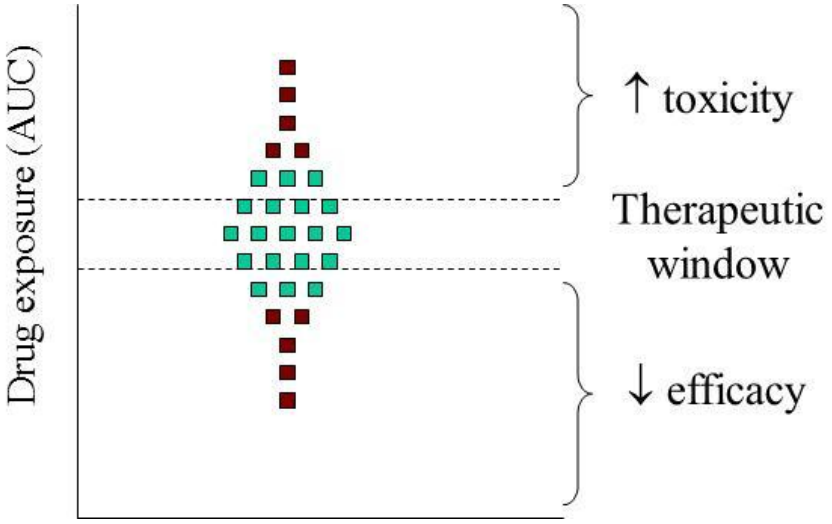
LFTs, liver function tests; LVEF, left ventricular ejection fraction; PK, pharmacokinetic; PD, pharmacodynamic.

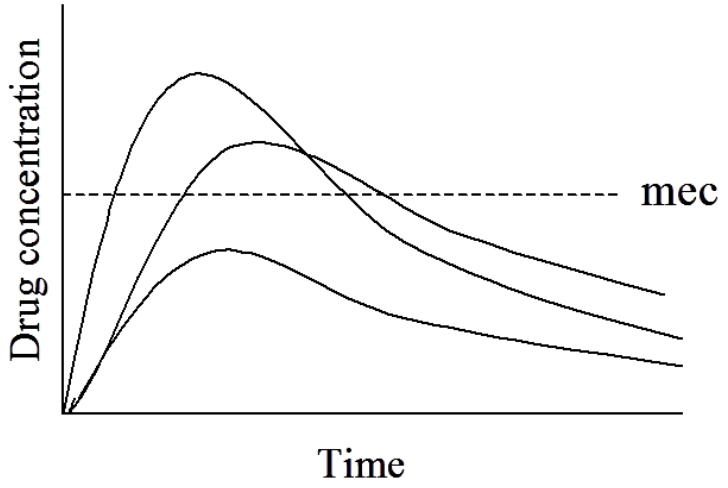
PK/PD ROLE IN DRUG DEVELOPMENT - SUMMARY

AS A DRUG DISCOVERY PROJECT MOVES INTO A DEVELOPMENT PHASE, A SOUND UNDERSTANDING OF THE LEAD COMPOUND'S PK/PD RELATIONSHIP WILL PROVIDE FOR A BASIS FOR ANTICIPATING THE THERAPEUTIC INDEX AND AID IN PK AND BIOMARKER DRIVEN DESIGN OF EFFICACIOUS DOSE REGIMENS FOR CLINICAL PROOF OF CONCEPT STUDIES

THERAPEUTIC DRUG MONITORING

"optimization of the therapeutic effect of a drug to prevent exposure to toxic or sub-therapeutic concentrations, through dosage adjustments based on plasma concentrations in individual patients"





TDM STUDIES IN ONCOLOGY – METHOTREXATE

CONVENTIONAL COMPARED WITH INDIVIDUALIZED CHEMOTHERAPY FOR CHILDHOOD ACUTE LYMPHOBLASTIC LEUKEMIA

WILLIAM E. EVANS, PHARM.D., MARY V. RELLING, PHARM.D., JOHN H. RODMAN, PHARM.D., WILLIAM R. CROM, PHARM.D., JAMES M. BOYETT, PH.D., AND CHING-HON PUI, M.D.

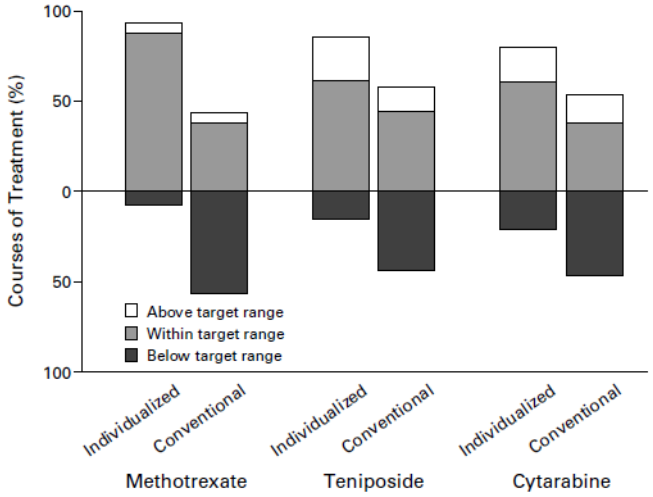


Figure 2. Percentage of Treatment Courses during Which Systemic Exposures Were below, within, or above the Target Range in the 91 Patients Receiving Individualized Doses of Methotrexate, Teniposide, and Cytarabine and the 91 Receiving Conventional Doses.

The percentage of courses during which systemic exposures were below the target range was significantly lower in patients receiving individualized therapy ($P<0.001$ for all three medications).

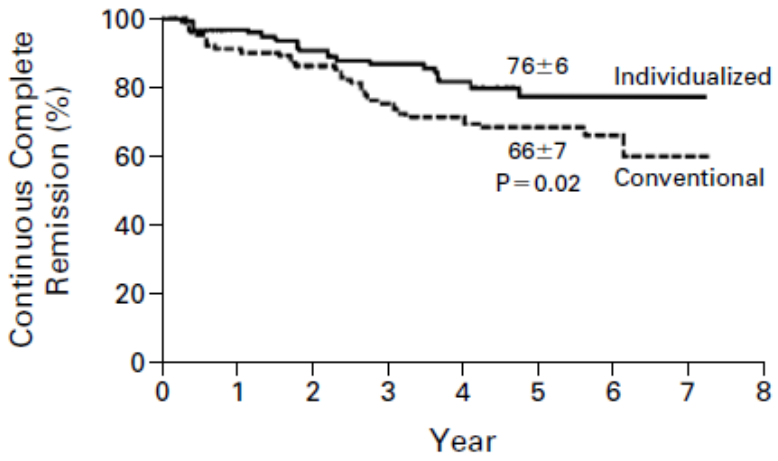
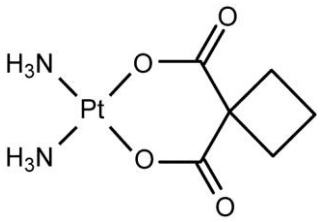


Figure 4. Kaplan–Meier Estimates of Continuous Complete Remission in Patients with B-Lineage Acute Lymphoblastic Leukemia.

- 182 children with ALL – improved outcomes for patients with B-lineage leukaemia

TDM STUDIES IN ONCOLOGY - CARBOPLATIN



Adaptive dosing and platinum–DNA adduct formation in children receiving high-dose carboplatin for the treatment of solid tumours

GJ Veal[1], J Errington[1], MJ Tilby[1], ADJ Pearson[2], ABM Foot[3], H McDowell[4], C Ellershaw[5], B Pizer[4], GM Nowell[6], DG Pearson[6] and AV Boddy[*,1], on behalf of the UKCCSG Pharmacology Working Group

[1]Northern Institute for Cancer Research, University of Newcastle upon Tyne, Newcastle upon Tyne, NE2 4HH, UK; [2]Royal Marsden Hospital, Surrey, SM2 5PT, UK; [3]Bristol Royal Hospital for Children, Bristol, BS2 8BJ, UK; [4]Alder Hey Children's Hospital, Liverpool, L12 2AP, UK; [5]United Kingdom Children's Cancer Study Group, Leicester, LE1 6TP, UK; [6]Department of Earth Sciences, Durham University, Durham, DH1 3LE, UK

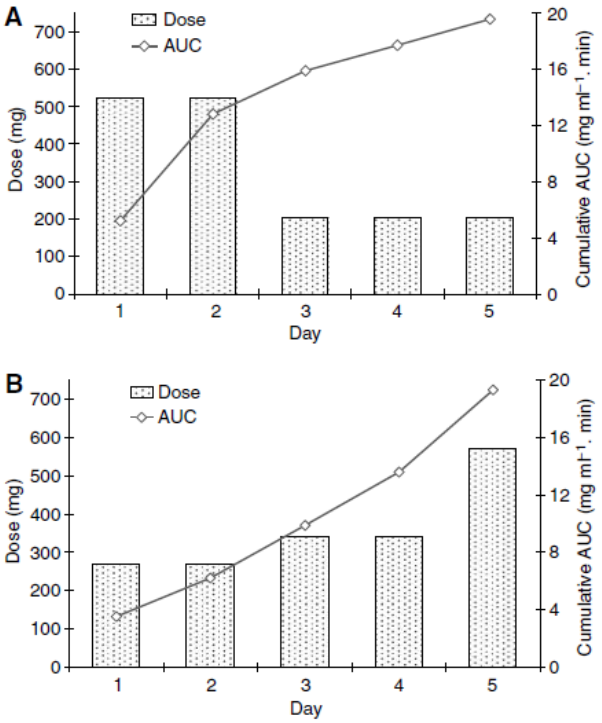


Figure 1 Examples of carboplatin pharmacokinetically guided dosing and exposure (AUC) in individual patients showing (**A**) a dose reduction implemented on day 3 to achieve a cumulative AUC of 19.6 $\mu g\,ml^{-1}$.min over 5 days of treatment and (**B**) dose increases on days 3 and 5 resulting in a cumulative AUC of 19.3 $\mu g\,ml^{-1}$.min.

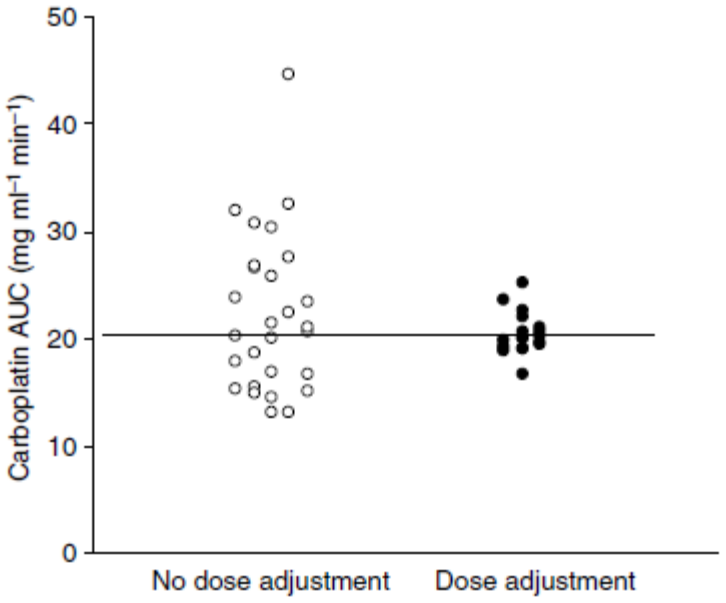
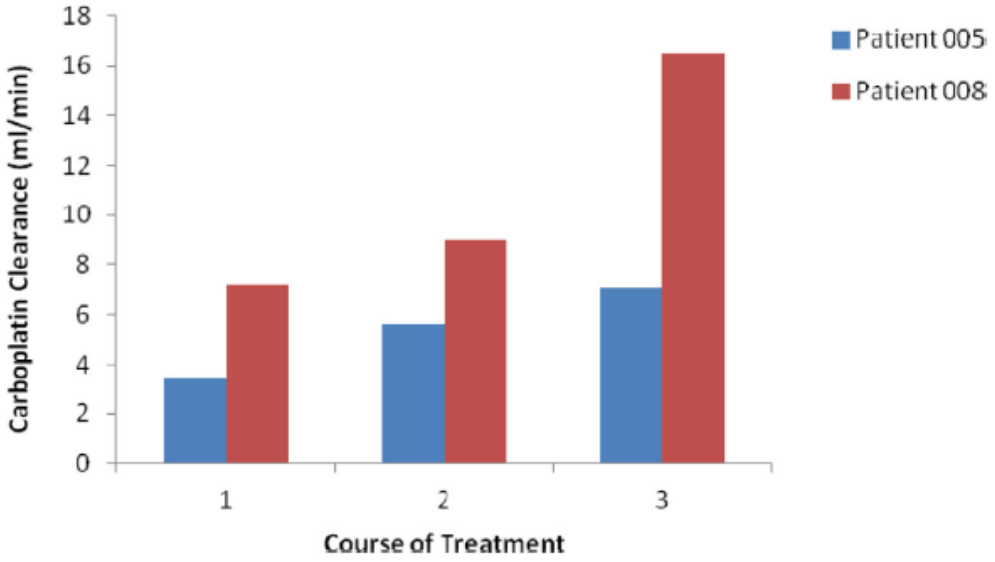
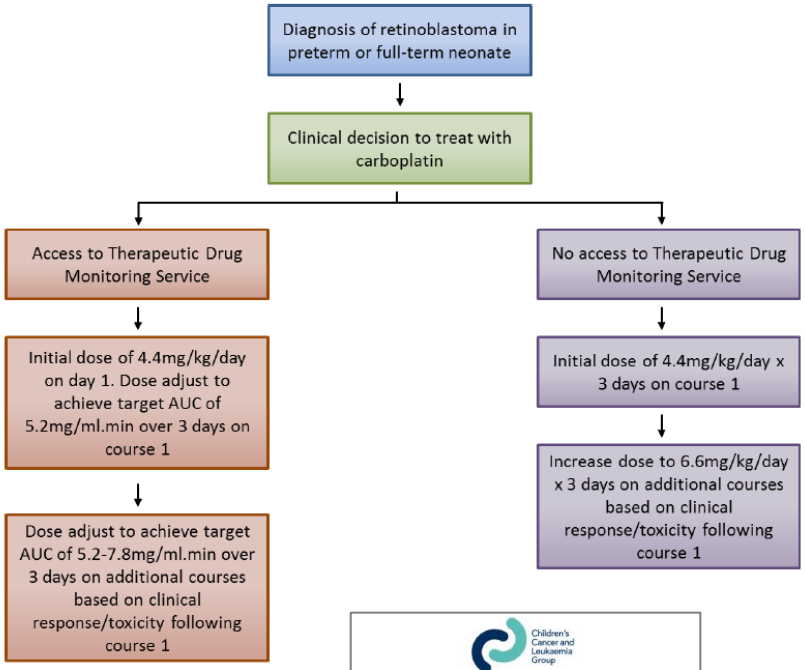
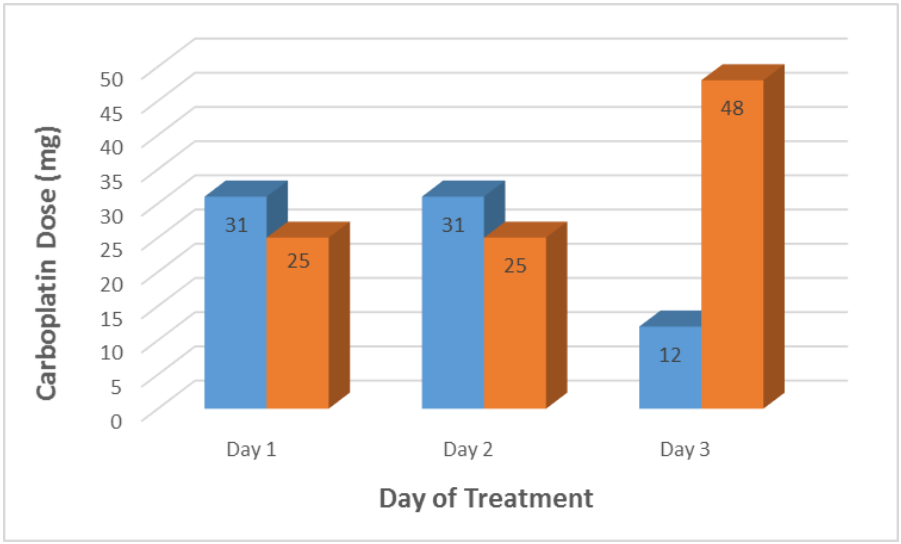


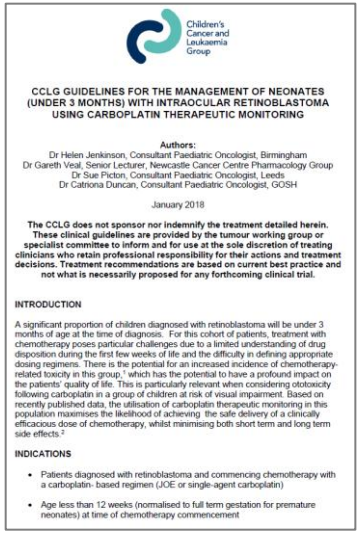
Figure 2 Predicted *vs* actual carboplatin exposures following pharmacokinetically guided dosage adjustment in children receiving high-dose carboplatin chemotherapy ($n = 28$).

CARBOPLATIN CLEARANCE ACROSS COURSES AND DOSING GUIDELINES









Children's Cancer and Leukaemia Group

CCLG GUIDELINES FOR THE MANAGEMENT OF NEONATES (UNDER 3 MONTHS) WITH INTRAOCULAR RETINOBLASTOMA USING CARBOPLATIN THERAPEUTIC MONITORING

Authors:
Dr Helen Jenkinson, Consultant Paediatric Oncologist, Birmingham
Dr Gareth Veal, Senior Lecturer, Newcastle Cancer Centre Pharmacology Group
Dr Sue Picton, Consultant Paediatric Oncologist, Leeds
Dr Catriona Duncan, Consultant Paediatric Oncologist, GOSH

January 2018

The CCLG does not sponsor nor indemnify the treatment detailed herein. These clinical guidelines are provided by the tumour working group or specialist committee to inform and for use at the sole discretion of treating clinicians who retain professional responsibility for their actions and treatment decisions. Treatment recommendations are based on current best practice and not what is necessarily proposed for any forthcoming clinical trial.

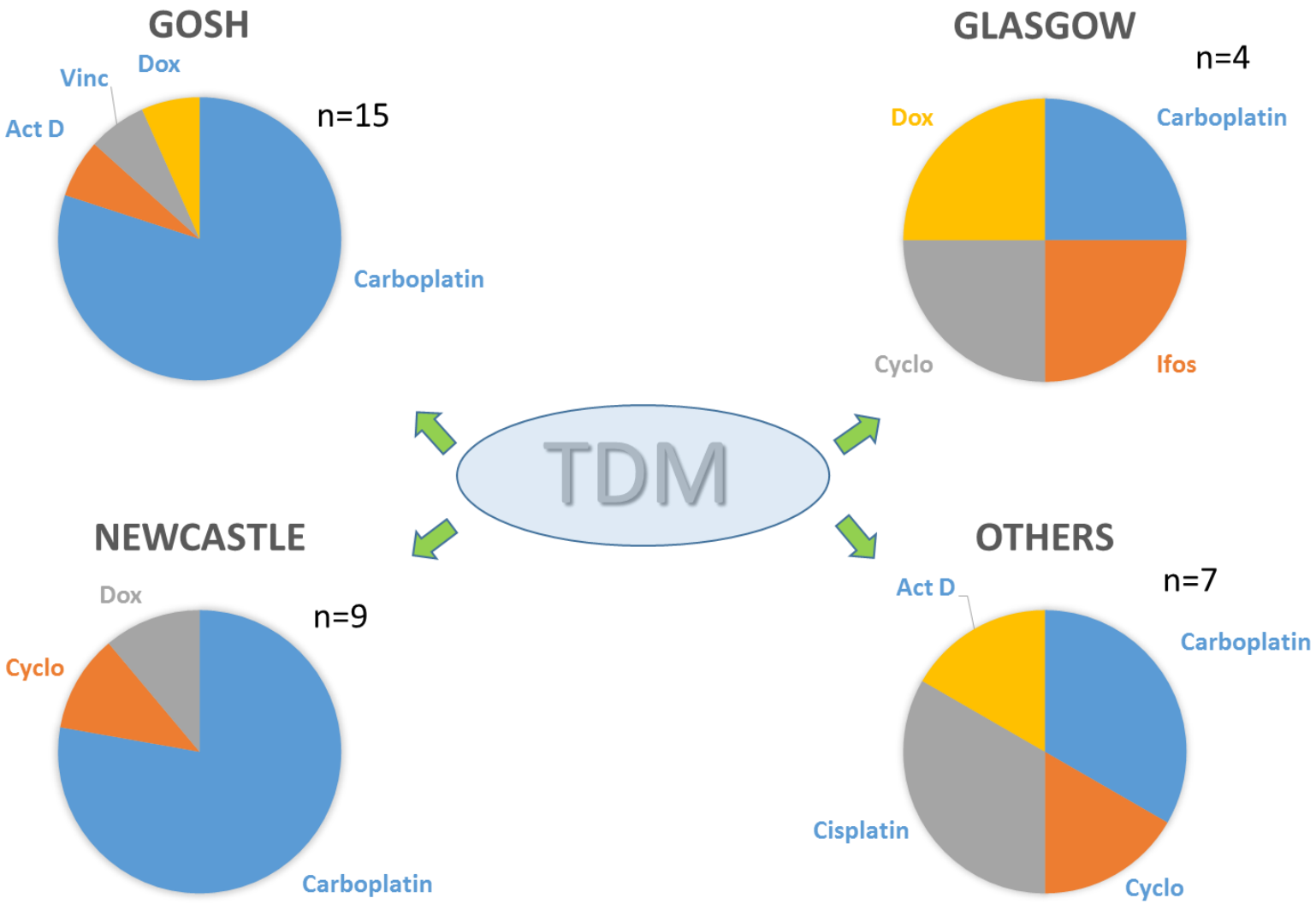
INTRODUCTION

A significant proportion of children diagnosed with retinoblastoma will be under 3 months of age at the time of diagnosis. For this cohort of patients, treatment with chemotherapy poses particular challenges due to a limited understanding of drug disposition during the first few weeks of life and the difficulty in defining appropriate dosing regimens. There is the potential for an increased incidence of chemotherapy-related toxicity in this group,[1] which has the potential to have a profound impact on the patients' quality of life. This is particularly relevant when considering ototoxicity following carboplatin in a group of children at risk of visual impairment. Based on recently published data, the utilisation of carboplatin therapeutic monitoring in this population maximises the likelihood of achieving the safe delivery of a clinically efficacious dose of chemotherapy, whilst minimising both short term and long term side effects.[2]

INDICATIONS

- Patients diagnosed with retinoblastoma and commencing chemotherapy with a carboplatin- based regimen (JOE or single-agent carboplatin)
- Age less than 12 weeks (normalised to full term gestation for premature neonates) at time of chemotherapy commencement

TDM ACROSS CENTRES 2017



- Dose adjustments carried out in >75% cases

QUESTIONS?

TDM CASE STUDY – INFANT HEPATOBLASTOMA

- Neonate born at 37 weeks with retroperitoneal mass and elevated AFP levels
- Tumour biopsy at day 9 confirmed diagnosis of hepatoblastoma with no extra-hepatic disease
- Standard risk treatment with cisplatin initiated according to SIOPEL3
- First cycle at 16 days of age: 1.6 mg/kg cisplatin
- Cisplatin pharmacokinetic studies were carried out on each of 6 courses of treatment between weeks 2 and 17 of life
- Samples for pharmacokinetic studies (UF) collected at 3h, 6h (end of drug infusion) and 24h

TDM CASE STUDY – INFANT HEPATOBLASTOMA

- Cisplatin AUC of 535 µg/ml.min on cycle 1 was well tolerated and encouraging response observed (decrease in AFP)
- Dose of 1.7 mg/kg for cycles 2/3 with target AUC defined as that observed on cycle 1
- >2-fold increase in cisplatin clearance (despite weight gain of approximately 10%) resulted in lower AUC values and subsequent increase in dose to 2.5 mg/kg
- Highlights the marked evolution of cisplatin clearance observed in neonates during the first few weeks of life
- Clear rationale for TDM dosing approach