INDIVIDUALIZATION OF DRUG THERAPY

THE “HOLY GRAIL” OF CLINICAL PHARMACOLOGISTS

• THERAPEUTIC DRUG MONITORING

• PRACTICAL APPLICATION OF PK

• PHARMACOGENETIC/PHARMACOGENOMIC ERA

• BIOMARKERS & PATIENT RESPONSE – THE BOTTOM LINE
“... WHETHER BROMIDES ARE USED AS A SEDATIVE OR AS AN ANTIEPILEPTIC, THE PHYSICIAN WILL BE ENABLED BY THE CHEMICAL CONTROL TO HAVE A CLEAR RECORD OF THE CASE AND ALSO TO BE SAFEGUARDED AGAINST SELF-PREScribed CHANGES ON THE PART OF THE PATIENT. HE WILL BE ABLE TO AVOID INSUFFICIENT DOSES ON THE ONE HAND AND INTOXICATIONS ON THE OTHER HAND...”

FIRST US HOSPITAL TDM LAB
FLUORESCENCE POLARIZATION IMMUNOASSAY
ILLUSTRATIVE CASES

• CASE 1: CIMETIDINE IN RENAL FAILURE

• CASE 2: PHENYTOIN OVERDOSE
A 67-year-old veteran had been functionally anephric, requiring outpatient hemodialysis for several years. He was hospitalized for revision of his arteriovenous shunt and postoperatively complained of symptoms of gastroesophageal reflux. This complaint prompted institution of cimetidine therapy in a dose of 300 mg every 6 hours.
Rationale for Prescribed Cimetidine Dose:
At that time, 600 mg every 6 hours was the usual cimetidine dose for patients with normal renal function and the Physician’s Desk Reference recommended halving the usual cimetidine dose for patients “with creatinine clearance less than 30 cc/min”.
CIMETIDINE CASE HISTORY (cont.)

Three days later the patient was noted to be confused. The nephrology service made the diagnosis of dialysis dementia and informed the family that hemodialysis would be discontinued. The teaching attending suggested that cimetidine be discontinued. Two days later the patient was alert and was discharged from the hospital to resume outpatient hemodialysis therapy.
DOSAGE ADJUSTMENT
1/2 NORMAL DOSE IF $\text{CL}_{\text{Cr}} < 30 \text{ mL/min}$

PHARMACOKINETICS
FOLLOWING I.V. OR I.M. ADMINISTRATION, ~75% OF DRUG IS RECOVERED FROM THE URINE AFTER 24 hr AS PARENT COMPOUND

NOMOGRAM FOR CIMETIDINE DOSING*

DOSE ADJUSTMENT OPTIONS FOR PATIENTS WITH RENAL IMPAIRMENT

- MAINTAIN USUAL DOSING INTERVAL BUT REDUCE DOSE IN PROPORTION TO $\downarrow CL_E$
- MAINTAIN USUAL DOSE BUT INCREASE DOSING INTERVAL IN PROPORTION TO $\downarrow CL_E$
- ADJUST BOTH DOSE AND DOSING INTERVAL

\[ \bar{C}_{ss} = \frac{DOSE}{\tau} \frac{1}{CL_E} \]
ILLUSTRATIVE CASES

• CASE 1: CIMETIDINE IN RENAL FAILURE

• CASE 2: PHENYTOIN OVERDOSE
PHENYTOIN HYDROXYLATION

PHENYTOIN

\[ \text{CYP 2C9} \quad \text{CYP 2C19} \]

\( p - \text{HPPH} \)
SATURATION OF DPH HYDROXYLATION

PLASMA DPH (mcg/ml)

DPH ELIMINATION (mg/day)

URINE CREATININE (mg/day)

DPH DOSE (mg/day)

DAYS
RELATIONSHIP OF PLASMA LEVEL TO PHENYTOIN DOSE*

<table>
<thead>
<tr>
<th>PHENYTOIN DOSE (mg/day)</th>
<th>PLASMA LEVEL µg/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>300</td>
<td>10</td>
</tr>
<tr>
<td>400</td>
<td>20</td>
</tr>
<tr>
<td>500</td>
<td>30</td>
</tr>
</tbody>
</table>

(THERAPEUTIC RANGE: 10 – 20 µg/mL)

FIRST ORDER KINETICS

\[
\text{DOSE}/\tau = CL_E \cdot \bar{C}_{SS}
\]

MICHAELIS - MENTEN KINETICS

\[
\text{DOSE}/\tau = \left[ \frac{V_{\text{max}}}{K_m + \bar{C}_{SS}} \right] \bar{C}_{SS}
\]
After inpatient evaluation for a generalized seizure, a 28-year-old woman was discharged on phenytoin therapy at a dose of 300 mg/day. After 5 days of therapy, she presented to the hospital’s emergency department with marked ataxia. Her phenytoin plasma concentration was found to be 27 μg/mL. She was sent home on a reduced phenytoin dose of 200 mg/day.
Two days later, she returned to the emergency department with more severe ataxia. Her phenytoin plasma concentration was now 32 μg/mL. Non-compliance was suspected but a clinical pharmacology evaluation was requested.
RELATIONSHIP OF PLASMA LEVEL TO PHENYTOIN DOSE

- $K_M = 15 \, \mu g/mL$
- $V_{MAX} = 738 \, mg/day$
PATIENT WITH VERY LOW $V_{\text{MAX}}$

$K_M = 14 \, \mu\text{g/mL}$

$V_{\text{MAX}} = 132 \, \text{mg/day}$
CYP2C9*3 VARIANT: ALLELE FREQUENCY = 6% - 10%

HETEROZYGOTE (CYP2C9*1*3)†

\[ K_M = 11.5 \, \mu g/mL \]
\[ V_{\text{MAX}} = 254 \, \text{mg/day} \]

PATIENT (? CYP2C9*3*3)

\[ K_M = 14 \, \mu g/mL \]
\[ V_{\text{MAX}} = 132 \, \text{mg/day} \]

BASIS OF APPARENT FIRST-ORDER KINETICS

\[
\frac{dC}{dt} = \left[ \frac{V_{\text{max}}}{K_m + C} \right] C
\]

If \( K_m > C \): \[
\frac{dC}{dt} = \left[ \frac{V_{\text{max}}}{K_m} \right] C = \"k\" C
\]
FUTURE OF INDIVIDUALIZED THERAPY

SELECT DRUG (PGX)

ESTIMATE INITIAL DOSE (PK OR PGX)

TARGET LEVEL
LOADING DOSE
MAINTENANCE DOSE

BEGIN THERAPY

ASSESS THERAPY
PATIENT RESPONSE
DRUG LEVEL (TDM)

REFINE DOSE ESTIMATE (PK)

ADJUST DOSE
INDIVIDUALIZATION OF DRUG THERAPY

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NIH CLINICAL CENTER - BUILDING 10
CRYPTOCOCCAL MENINGITIS IN 1965

DIAGNOSTIC AND PROGNOSTIC VALUE OF CLINICAL AND LABORATORY FINDINGS IN CRYPTOCOCCAL MENINGITIS* 

A Follow-up Study of Forty Patients

William T. Butler, M.D.,† David W. Alling, M.D., Ph.D.,‡ Anderson Spickard, M.D.,§ and John P. Utz, M.D.¶

BETHESDA, MARYLAND

PRIOR TO AMPHOTERICIN B

MENINGITIS ALMOST UNIFORMLY FATAL
75% OF PATIENTS DIED WITHIN 1 YEAR

DIAGNOSTIC APPROACH

INDIA INK PREP - IMMEDIATE

CULTURE – 2 WEEKS
CSF CHANGES IN CRYPTO MENINGITIS

INCREASED WBC

INCREASED PROTEIN (NORMAL: 15 - 45 mg/dL*)

REDUCED GLUCOSE ? NORMAL

50 - 75 mg/dL*

½ - ⅔ BLOOD GLUCOSE†

† Goodwin GM, Shelley HJ. Arch Int Med 1925;84:242
CSF GLUCOSE QUESTIONS

• WHAT IS NORMAL [CSF GLUCOSE]?

• WHY IS $R_{CSF}$ NORMALLY $< 1$?

• WHY DOES [CSF GLUCOSE] FALL IN PATIENTS WITH MENINGITIS?

• WHY DOES $R_{CSF}$ FALL IN PATIENTS WITH MENINGITIS AT THE SAME TIME THAT [CSF PROTEIN] RISES?
MODEL FOR ANALYZING BLOOD/CSF GLUCOSE TRANSFER

\[ \frac{dC_S}{dt} = k_d(C_S - C_B) - k_f C_S \]

at SS: \( R_{CSF} = \frac{C_S}{C_B} = \frac{k_d}{k_d + k_f} \)

**CHOROID PLEXUS**

\( \rho_{csf} = 0.50 \text{ mL/min} \)

**ARACHNOID VILLI**

\( \rho_{CSF} = k_f \times V_{CSF} \)

**Bulk Flow**

\( \rho_{CSF} = \frac{0.50 \text{ mL/min}}{150 \text{ mL}} = 0.0033 \text{ mL/min/mL} \)
PLATEAU $R_{CSF}$ VALUES IN 8 PATIENTS

$\rho_{\text{CSF}}$ IN A DIABETIC PATIENT

<table>
<thead>
<tr>
<th>PATIENT NO.</th>
<th>% / DAY</th>
</tr>
</thead>
<tbody>
<tr>
<td>199</td>
<td>1.5</td>
</tr>
<tr>
<td>203</td>
<td>1.5</td>
</tr>
<tr>
<td>205</td>
<td>1.4</td>
</tr>
<tr>
<td>206</td>
<td>1.4</td>
</tr>
<tr>
<td>207</td>
<td>1.2</td>
</tr>
<tr>
<td>208</td>
<td>1.3</td>
</tr>
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<td>211</td>
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<tr>
<td>216</td>
<td>0.9</td>
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<tr>
<td>218</td>
<td>1.1</td>
</tr>
<tr>
<td>225</td>
<td>1.2</td>
</tr>
</tbody>
</table>

**MEAN ± SD**  
1.3 ± 0.2
EARLY WARNING OF TREATMENT FAILURE

BIOLOGICAL MARKER: A PHYSICAL SIGN OR LABORATORY MEASUREMENT THAT OCCURS IN ASSOCIATION WITH A PATHOLOGICAL PROCESS AND THAT HAS PUTATIVE DIAGNOSTIC AND/OR PROGNOSTIC UTILITY.
CRYPTOCOCCAL MENINGITIS

ANTIFUNGAL THERAPY

CRYPTOCOCCAL MENINGITIS

\( R_{CSF} \)

POS CSF CULTURE

DEATH
QUALIFICATION OF BIOMARKERS

STATISTICAL CRITERIA
• Changes in marker must be correlated with clinical outcome

BIOLOGICAL PLAUSIBILITY
• Epidemiologic evidence that marker is a risk factor
• Marker must be consistent with pathophysiology
• Marker must be on causal pathway
• Changes in marker reflect changes in prognosis
GLUCOSE KINETICS AFTER IT LOAD

![Graph showing glucose concentration over time](image)
MODEL FOR ANALYZING BLOOD/CSF GLUCOSE TRANSFER

CHOROID PLEXUS

$\rho_{csf} = 0.50 \text{ mL/min}$

CSF
(150 mL)

BLOOD

ARACHNOID VILLI

$\frac{dC_S}{dt} = k_d(C_S - C_B) - k_f C_S$

at SS: $R_{CSF} = \frac{C_S}{C_B} = \frac{k_d}{k_d + k_f}$
## RESULTS OF KINETIC ANALYSIS

<table>
<thead>
<tr>
<th>DATE</th>
<th>$R_{CSF}$</th>
<th>$K_d$ min $^{-1}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>12/16’66</td>
<td>0.40</td>
<td>0.00188</td>
</tr>
<tr>
<td>12/27’66</td>
<td>0.17</td>
<td>0.00079</td>
</tr>
</tbody>
</table>

APPARENT PARADOX

WITH MENINGEAL INFECTION, THE BLOOD-CSF BARRIER BECOMES:

• **MORE PERMEABLE TO PROTEIN**

• **LESS PERMEABLE TO GLUCOSE**
STEADY STATE RELATIONSHIP BETWEEN CSF AND BLOOD GLUCOSE CONCENTRATIONS

\[ K_M = 182 \text{ mg/dL} \]
\[ = 10 \text{ mM} \]

MODEL OF FACILITATED DIFFUSION OF GLUCOSE BETWEEN CSF AND BLOOD

CONCLUSION

• CARRIER TRANSPORT OF GLUCOSE ACROSS MENINGES IS MUCH MORE RAPID THAN SIMPLE DIFFUSION.

• THEREFORE, NET GLUCOSE TRANSPORT ACROSS MENINGES DECREASES WHEN CARRIER FUNCTION IS IMPAIRED, EVEN THOUGH SIMPLE DIFFUSION PROBABLY IS INCREASED.
ROLE OF BIOMARKERS IN DDRU

- DISCOVERY
- PRE CLINICAL
- PHASE I–II
- PHASE III
- PHASE IV

- TARGET & CANDIDATE SELECTION
- EFFICACY BIOMARKERS
- SAFETY BIOMARKERS
- CLINICAL PRACTICE

- BIOMARKER SELECTION
- PK/PD MODELING
- DOSE SELECTION
- POST-APPROVAL SURVEILLANCE

- PATIENT SELECTION

- CANDIDATE ATTRITION & REFINEMENT DECISIONS
- OTHER INDICATIONS & DIFFERENTIATION
PHASE IV STUDY: IT ARA-C IN PML *

- SPONSOR: AIDS CLINICAL TRIALS GROUP

- GOAL: IS INTRATHECAL ADMINISTRATION OF CYTARABINE (ARA-C) EFFECTIVE IN PATIENTS WITH PML?

PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY

- JC VIRUS PRESENT IN 80% NORMAL SUBJECTS
- PML OCCURS IN 4% OF PATIENTS WITH AIDS
- THERE IS NO ESTABLISHED EFFECTIVE THERAPY
- SURVIVAL AVERAGES 2.5 TO 4 MONTHS
- OCCURRED IN PATIENTS RX'D WITH TYSABRI
- OCCURRED IN PATIENTS RX'D WITH RITUXAN
- OCCURRED IN PATIENTS RX'D WITH RAPTIVA
LABELLED INDICATIONS FOR CYTARABINE (ARA-C)

- IV for remission induction of acute non-lymphocytic leukemia (in combination with other approved cancer drugs).
- IV for treatment of acute lymphocytic leukemia.
- IV for treatment of blast phase of chronic myelocytic leukemia.
- IT for prophylaxis and treatment of meningeal leukemia.
• The JC virus (etiologic agent of progressive multifocal leukoencephalopathy) is sensitive to ARA-C *in vitro*.

• ARA-C crosses the blood-brain barrier (BBB) only slowly.

• Intrathecal/intraventricular administration might improve the therapeutic efficacy of ARA-C by circumventing the BBB.
PATIENT ENROLLMENT

- 57 patients with PML randomized in multicenter ACTG trial

- Three treatment groups
  - Only continue antiretroviral drugs
  - Add 4 mg/kg ARA-C daily IV for 5 d q 21 d
  - Add intrathecal ARA-C
“GROUP 3 RECEIVED ANTIRETROVIAL THERAPY PLUS 50 MG OF CYTARABINE, ADMINISTRED INTRATHECALLY WITH AN OMMAYA RESERVOIR, ONCE A WEEK FOR FOUR WEEKS, THEN ONCE EVERY 2 WEEKS FOR 8 WEEKS, THEN ONCE EVERY 4 WEEKS FOR THE REMAINDER OF THE STUDY.”
REPEETITIVE IT ADMINISTRATION IS NON-TRIVIAL

OMMAYA PUMP
SCHEMATIC OF PUMP PLACEMENT

Lateral view of brain.
RESERVOIR PLACEMENT
ELEMENTS OF STUDY DESIGN

• STATISTICAL SAFEGUARDS
  - RANDOMIZATION OF PATIENTS
  - BALANCED TREATMENT GROUPS
  - INTENTION TO TREAT ANALYSIS
  - DATA ANALYZERS BLINDED

• JUSTIFICATION FOR IT DOSE REGIMEN
  - NONE PROVIDED
THE MOST WIDELY USED BIOMARKER/SURROGATE ENDPOINT

DRUG LEVELS USED AS A SURROGATE FOR CLINICAL EFFICACY AND TOXICITY IN THE EVALUATION OF GENERIC DRUGS *

* Comment by Carl Peck: CDDS WORKSHOP, McLean, VA, May 13, 1998
INTRATHECAL AMPHOTERICIN B PHARMACOKINETICS

MIC C. neoformans

MODEL FOR ANALYZING INTRATHECAL AMPHOTERICIN B PHARMACOKINETICS

\[ \rho_{\text{csf}} = 0.54 \, \text{mL/min} \]

CSF (139 mL)

BRAIN ECF (677 mL)

INTRATHECAL CYTARABINE
PHARMACOKINETICS


CL_E = 0.42 mL/min

30 mg ARA-C, IT
SIMULATED CYTARABINE
INTRATHECAL DOSE REGIMENS

30 mg qd x 3
70 mg

IN VITRO EFFECTIVE LEVEL FOR JC VIRUS

“FAILURE” OF IT CYTARABINE IN PML ASSOCIATED WITH HIV INFECTION*

FAILURE OF CYTARABINE IN PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY ASSOCIATED WITH HIV INFECTION

COLIN D. HALL, M.B., CH.B., URANIA DAFNI, SC.D., DAVID SIMPSON, M.D., DAVID CLIFFORD, M.D., PATRICIA E. WETHERILL, M.D., BRUCE COHEN, M.D., JUSTIN McARTHUR, M.B., B.S., M.P.H., HARRY HOLLANDER, M.D., CONSTANTIN YAINNOUTSOS, PH.D., EUGENE MAJOR, PH.D., LINDA MILLAR, B.S., JOSEPH TIMPONE, M.D., AND THE AIDS CLINICAL TRIALS GROUP 243 TEAM*

SINCE THE CHOSEN IT DOSE HAD NO POSSIBILITY OF BEING EFFECTIVE, IT IS ERRONEOUS TO CONCLUDE THAT THE DRUG IS INEFFECTIVE.

POC: 30 mg/DAY BY CONTINUOUS IT INFUSION

\[ [\text{ARA-C}] \mu g/mL \]

\[ l \text{ (hours)} \]

MIC