A PHARMACOKINETIC AND PHARMACODYNAMIC RATIONALE FOR PERIOPERATIVE INTRAPERITONEAL CHEMOTHERAPY

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PHARMACOKINETICS
EXPLORES WHAT THE BODY DOES TO THE CHEMOTHERAPY DRUG

PHARMACODYNAMICS
EXPLORES WHAT THE DRUG DOES TO THE BODY
Pharmacokinetic

1. PERITONEUM OR PERITONEAL MEMBRANE
2. THE PERITONEAL PLASMA BARRIER
3. DEDRICK DIFFUSION MODELS
4. AUC and AUCratio
1. Peritoneum or Peritoneal Membrane

ANATOMY

• Monolayer mesothelial cells
• Basement membrane
• Five layers connective tissue made by a matrix of collagen, hyaluron and proteoglycans and cellular component with blood capillaries

PHYSIOLOGICAL FUNCTIONS

• Reduces friction between intra-abdominal contact surfaces
• Host defence against intra-abdominal infections
• First line of defence against peritoneal carcinomatosis (Sugabaker J Surg Onc 2007)
2. Peritoneal plasma barrier

peritoneal plasma barrier

is represented by the

blood capillary wall and the surrounding interstitium

rather than the first mesothelial lining.

(Stelin G. 1990)

peritoneectomy procedures

consisting of only mesothelium removal do not change

the mass transfer coefficient over the barrier.

(de Lima Vasquez V. 2003)
Dedrick’s diffusion model and AUC ratio

\[ \text{AUC ratio} = \frac{\text{AUC}_{\text{IP}}}{\text{AUC}_{\text{IV}}} \]

**AUC ratio** and clinical advantage

*AUC ip*: intraperitoneal concentration

*AUC iv*: plasma concentration

Traditional two-compartment model of peritoneal transport  Dedrick RL, 1978
The peritoneal permeability of a chemotherapy drug is inversely proportional to the square root of its molecular weight Dedrick 1978
Peritoneal plasma transport barrier

1) Specific tissue permeability
2) Surface area

Fig. 3. Illustration of how drug transfer from the peritoneal cavity into surrounding tissues can be divided into parallel paths governed by tissue-specific permeabilities, $P_i$'s, and areas, $A_i$'s, where the subscript $i$ can be $L$ for liver, $V$ for hollow viscera, and $P$ for parietal tissue. Low-molecular-weight drugs move from the peritoneal tissues into the rest of the body primarily via blood flow [adapted from (25)].
Pharmacokinetic: variables

1. DOSE
2. CARRIER SOLUTION
3. VOLUME
4. TIMING
5. DURATION
6. PRESSURE
7. VASOACTIVE AGENTS
1. Dose

- drug dose is based on body surface area (mg/m²)
- It’s an accurate predictor of drug metabolism/ drug toxicity.
- Gender-bias: peritoneal surface in females is 10% larger than in males, in proportion to the body surface*
- Some institutions calculate the dose of the drugs per liter by body surface area (mg/m²/L)**

* Rubin et. al. 1988  **Baratti et al 2007
2. Carrier solution

Mohamed et al. in 2003, showed that an isotonic high molecular weight dextrose solution prolongs the intraperitoneal retention of artificial ascites.

The carrier solution most widely employed is 1.5% dextrose isotonic peritoneal dialysis solution.

*Pestieau et al. 2001*
The use of variable volume is a dangerous practice with unpredictable systemic toxicity Sugarbaker (2006)

Volume of carrier solution must be related to body surface area to allow prediction of both systemic drug toxicity and exposure of tumore nodule.

2 L/m² (Elias D. 2002) or 1,5 L/m² (Sugarbaker P. 2005)
4. Timing of chemotherapy in relation to surgery

- **Hyperthermic Intraperitoneal Peroperative Chemotherapy** is the most widely used.
- **Early Post-operative Intraperitoneal Chemotherapy**
- **Sequential Post-operative Intraperitoneal Chemotherapy**
5. Duration

• The destruction of tumor cells reaches a plateau above which a longer exposure time does not offer any cytotoxic advantage*

The duration of perioperative chemotherapy should be related to the systemic toxicity.

* Cancer Res 2000

Range from 30-120 minutes
6. Pressure

High intra-abdominal pressure increases penetration of cisplatin*, doxorubicin** and oxaliplatin ° into the tumor nodule.

Respiratory and hemodynamic tolerance limit this procedure so much that it is currently utilized only for palliating refractory malignant ascites in PC patients in laparoscopic HIPEC°°

7. Vasoactive agents

Epinephrine*  Vasopressin**

Dedrick’s two-compartment model describes the transfer of the fluid between the two compartments over the peritoneal-plasma barrier but it inadequately explains both the specific penetration of the drug into the tumor nodule and the value of the effective contact area.
Pharmacokinetic: conclusions

A greater concentration of the drug into the peritoneal cavity does not necessarily mean a greater concentration into the peritoneal tumor nodule
Pharmacodynamic

Dedrick and Flessner’s mathematical model of tissue penetration applied to the tumor nodule
Drug diffuses until it is "deep" in the tissue (tumor nodule) under a concentration gradient determined by the peritoneal cavity and the plasma concentration.

Conceptual diagram of the drug diffusion in the tissue adjacent the peritoneal cavity.
Ce is the concentration in the tumor nodule

In this Dedrick & Flessner model the solid line shows that Ce decreases exponentially approaching the concentration of the plasma and that this decrease is directly correlated to the distance (X₀ and 3X₀) in cm from the serosal surface.

Conceptual diagram of the drug diffusion in the tissue adjacent to the peritoneal cavity
Pharmacodynamic: variables

1. TEMPERATURE

2. TUMOR NODULE

3. DENSITY and BINDING

4. INTERSTICIAL FLUID PRESSURE
Hyperthermia (41-43 °C) increase tumor response

1) by a direct cytotoxicity on tumor cells

2) by increasing the membrane permeability and consequently drug uptake in tumor nodules.

3) by increasing the penetration depth of the drug solution into tumor nodules.
2. Tumor nodule

The levels of doxorubicin inside the tumor nodules were higher than expected from the AUCratio, suggesting that this ratio might not be the most appropriate way of assessing treatment efficiency.

Fig. 1 Doxorubicin concentration in plasma, peritoneal fluid, tumor nodules and normal adjacent tissues. Data obtained from a single patient.
The evidence that different histologic subtypes of appendiceal malignancy sequester different levels of doxorubicin shows that the simple diffusion of Dedrick’s two-compartment model is inadequate.

Active transport or irreversible binding of the drug at the level of the tumor nodule were proposed as possible solutions.

Figure 12. Doxorubicin levels in appendiceal tumor tissue showing diffuse peritoneal adenomucinosis (DPAM) versus peritoneal mucinous carcinoma (PMCA). Peritoneal fluid concentrations are also shown. TN = tumor nodule, PF = peritoneal fluid.
New Conceptual four-compartment model of intraoperative chemotherapy

In this model the **tumor nodule** is a more appropriate pharmacological end-point and **pharmacokinetic and pharmacodynamic** variables are combined.

- **Plasma**
  - Plasmatic blood flow
  - PharmacoKinetic variables and Pharmacodynamic Variables
    - Drug dose
    - Solution carrier
    - Volume and duration
    - Size and penetration depth
    - Interstitial fluid pressure
    - Cell Binding, density, temperature

- **Subperitoneal Compartment**

- **Peritoneal fluid**

- **Tumor nodule**

- **Organs of Metabolism** (liver and/or kidney)

- **Portal venous blood flow**
Pharmacokinetic and pharmacodynamic characteristics of the drugs used in HIPEC for ovarian cancer

<table>
<thead>
<tr>
<th>Drug</th>
<th>Molecular weight</th>
<th>AUC ratio</th>
<th>Hyperthermia</th>
<th>Penetration depth into tumor tissue</th>
</tr>
</thead>
<tbody>
<tr>
<td>CDDP</td>
<td>300,1</td>
<td>10</td>
<td>+++ *</td>
<td>3-5 mm **</td>
</tr>
<tr>
<td>DXR</td>
<td>579,99</td>
<td>290</td>
<td>+++</td>
<td>From few layers to 1 mm</td>
</tr>
<tr>
<td>PACLITAXEL</td>
<td>853,9</td>
<td>1000</td>
<td>-- - ?</td>
<td>From 40 (in 4 hours) a 80 cell layers (in 24h)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>+ if ↑ duration</td>
<td></td>
</tr>
</tbody>
</table>

*Urano et al 1999  **Van der Waart (1998)
Toxicity dose limiting

CDDP
• Dose can be escalated until systemic toxic effects become the dose limiting factor

DXR
• Dose limiting toxicity is abdominal pain and peritoneal sclerosis from direct peritoneal irritation
• No cardiotoxicity when i.p.

PACLITAXEL
• No vesicant effect for direct peritoneal cavity instillation
• Even if severe abdominal pain is the dose-limiting toxicity
AUC ratio: paclitaxel
Ideal Drug?

Active against a particular tumor with a direct cytotoxic effect

High capacity of penetration into tumor nodule
Conclusion 1

The main pharmacokinetic advantage of intraperitoneal chemotherapy is the **high concentrations** delivered to the **tumor site** with minimal systemic drug exposure and bone marrow toxicity.
Conclusion 2

• A disadvantage of i.p. chemotherapy is the limited tissue penetration.
• The penetration depth of the drugs is estimated to range from a few cell layers to a few millimeters (1-3 mm).
• Hypertermia increases cytotoxic effect of CDDP and DXR but not for Paclitaxel
Conclusion 3

• An adequate cytoreductive surgery should precede the i.p. administration

• **Cytoreduction** can be considered optimal and therefore useful to address our patient to HIPEC
  when the threshold of 2.5 mm in the largest diameter for residual tumor nodule is obtained