Population Pharmacokinetics and Pharmacodynamics of Cisplatinum During Intraperitoneal Chemohyperthermia Using a Closed Abdominal Procedure

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Introduction

- HIPEC associated with high level of morbidity
- Rare data in literature concerning pk
- Objectives :
  - Study pK and pD of CDDP
  - Using population pharmacokinetic approach
  - Optimize dosage of CDDP

Patients

- **Jan 2003-dec 2004 : 40 patients :**

  14 with CDDP alone,

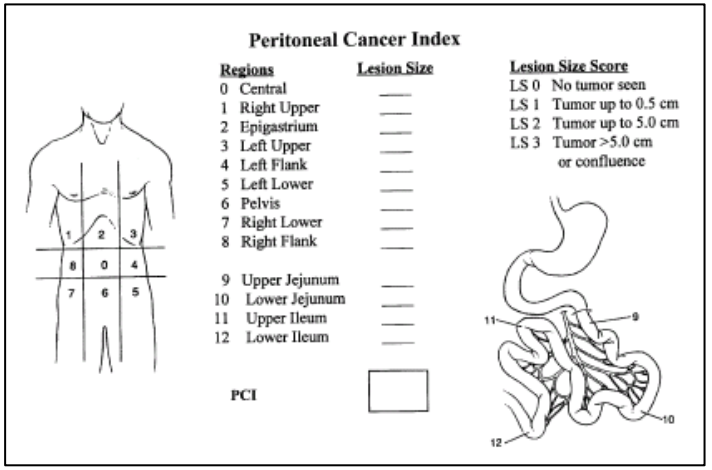
  26 CDDP + MMC

- **Origin of PC** : 16 pseudomyxoma, 13 ovarian origin, 4 mesothelioma, 7 various origin

Methods : surgical procedure

- **<u>Exploration</u> :** PC staging with **Gilly's classification** and **peritoneal cancer index of Sugarbaker (PCI)**

- **<u>Complete cytoreduction</u>**



Gilly's Classification	
Stage 0	Only positive cytology
Stage 1	< 5 mm, localized
Stage 2	< 5 mm, diffuse
Stage 3	5 mm up to 2 cm
Stage 4	Large malignant cakes

Methods : HIPEC

- **Closed technique** (CAVITHERM®)
- 4-6 litters of perfusate

- 1 to 1.5 mg/kg of CDDP used alone
- 0.8 to 1 mg/kg of CDDP associated with 0.5 to 0.6mg/kg of MMC

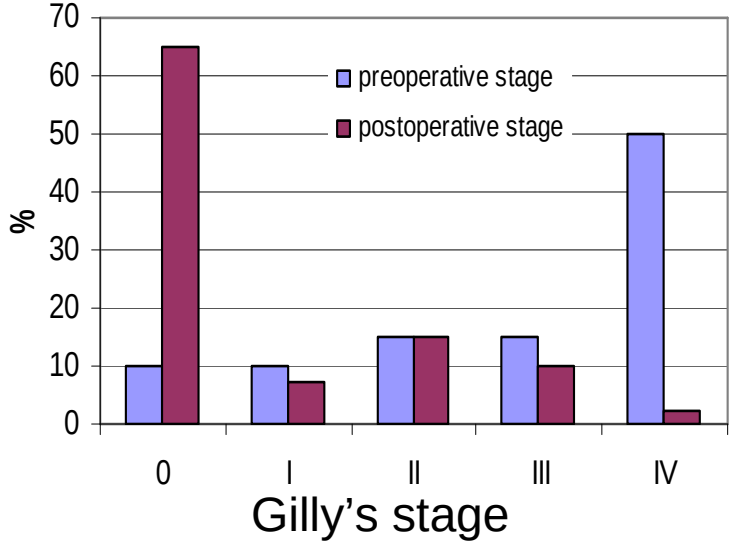
- During **90 min** with inflow temperature between **44 and 46 ℃**

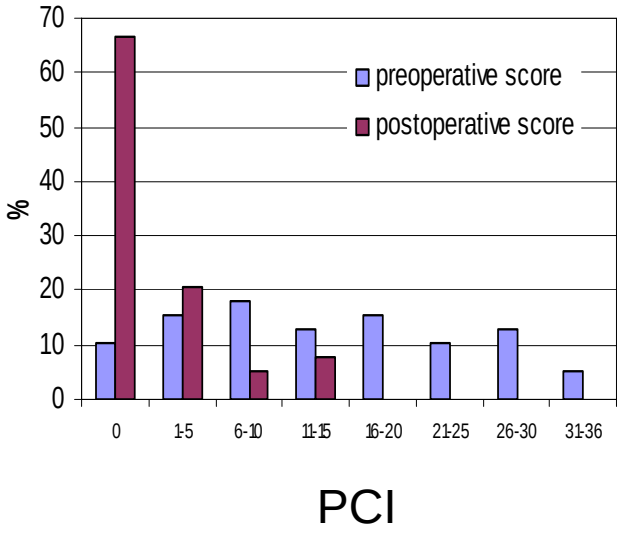
Methods : pK and pD studies

- **Pharmacokinetics** :
  - **Blood, perfusate and urine samples** : 1 min, 45 min, 90 min, 3h, 6h, 24h, 48h, 72h, 120h and 240h
  - **NONMEM ®** for pharmacokinetics and **X-Pose ®** for covariate detection
- **Pharmacodynamics** :
  - **AUC** of CDDP = organism exposure
  - **Toxicity** : renal and haematological complications
  - **Long term effectiveness** : survival and disease free survival

Results : surgery

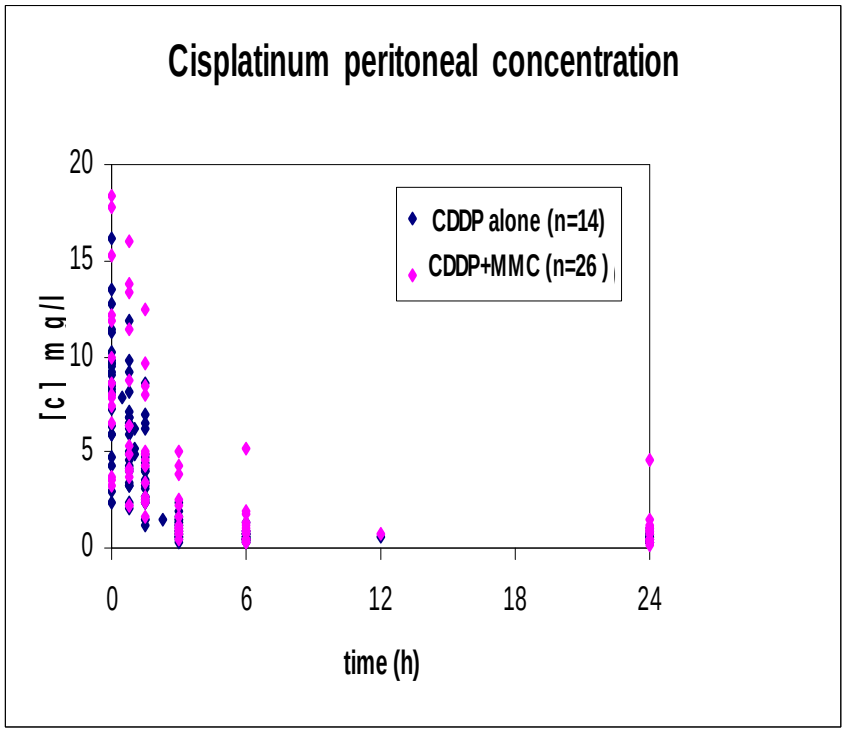
- **Carcinomatosis staging :**

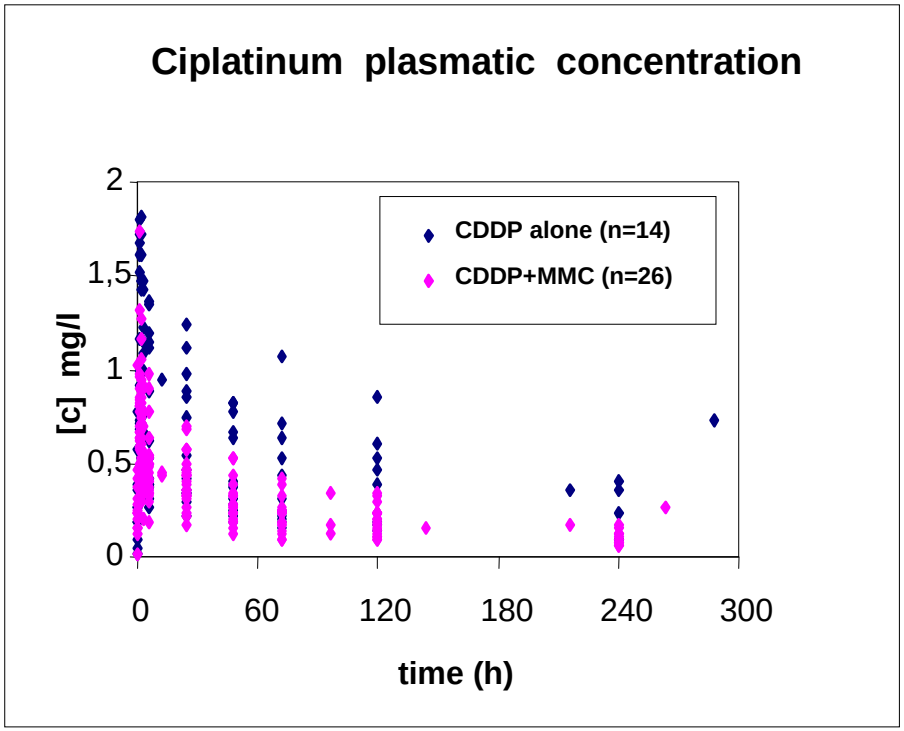




- **Assessement of completness cytoreduction :**
  - CC-0 (no residue) = 26 patients (65%)
  - CC-1 (residue<5mm) = 8 patients
  - CC-2 (residue >5mm) = 6 patients

Results : pharmacokinetics



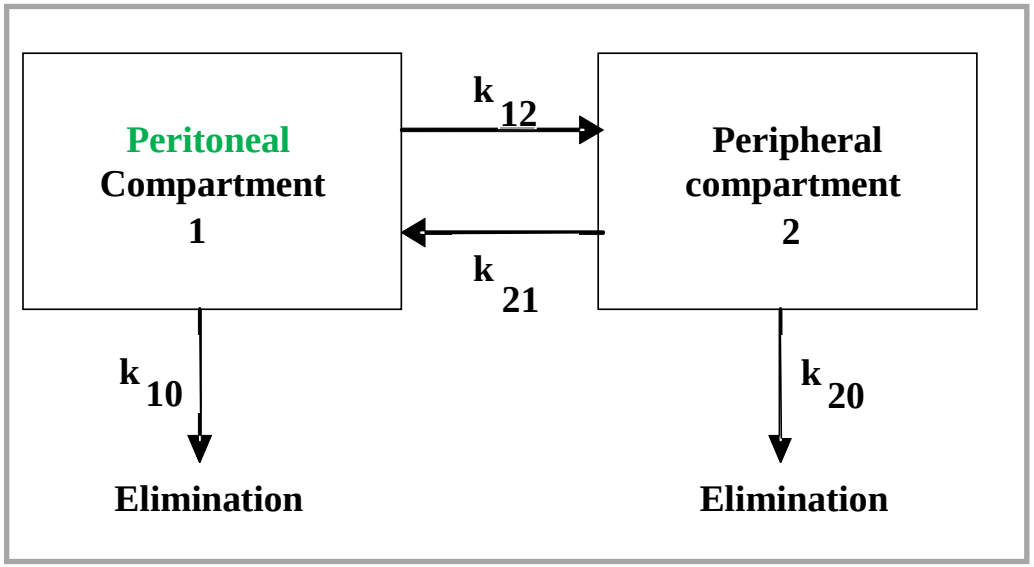


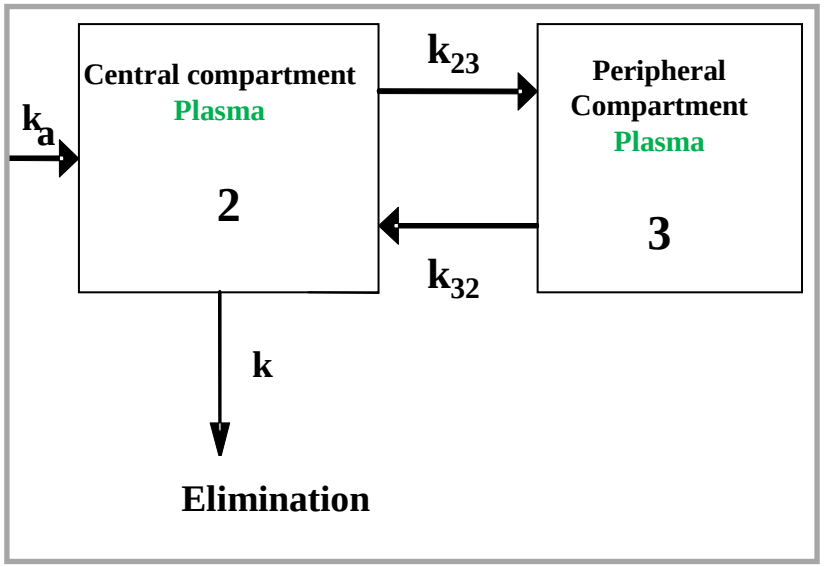
Peritoneal resorption = 24h

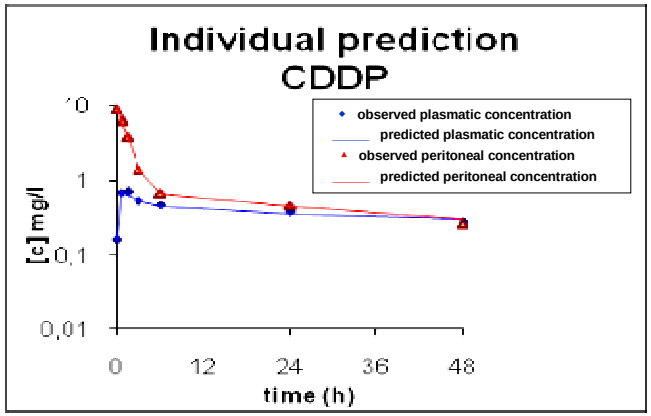
Plasmatic resorption > 10 days

Results : pharmacokinetics

→ **2 separated models : population pharmacokinetics**

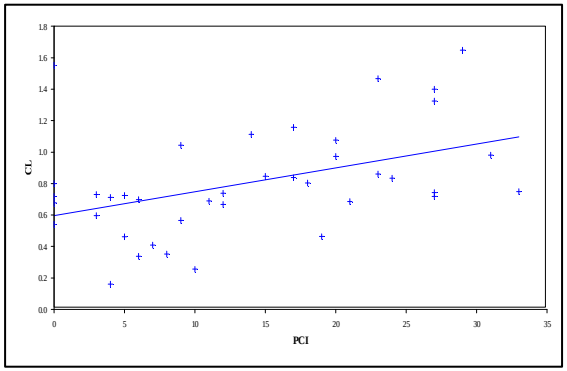






Covariates analysis :

- Weight and PCI : plasmatic clearance
- ALAT : Ka



Results : pharmacodynamics

	AUC CDDP	
	plasmatic	peritoneal
mean	97.91	90.87
sd	90.93	76.55
median	67.28	68.41

Peritoneal / Plasmatic AUC ratio ≈ 1

- **Haematologic toxicity :**
  - Anemia grade 1 or 2 : 75%
  - Leucopenia grade ≤1 : 84 % (61 % grade 0)
  - Thrombopenia grade 1 : 34 % (55 % grade 0)

No relationship with plasmatic or peritoneal AUC

- **Renal toxicity :**
  - 10 Acute Renal Failure : **No correlation with plasmatic or peritoneal AUC**
  - **Insufficient hydration and digestive preparation**

- **Long term Survival**
  - **No direct relationship with organism exposure with CDDP**

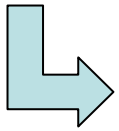
Discussion

- **Plasmatic/Peritoneal AUC** ratio near 1 : concept of **peritoneo-plasmatic barrier** for CDDP ??

- **Maximal systemic tolerated dosage of CDDP = maximal HIPEC dosage**

- **Renal** and **haematologic toxicity** are **multifactorial** (surgical and medical complications)

- **Long term survival also multifactorial** (origin of CP, CP stage, …)



difficulty +++ to show a direct relationship with CDDP exposure

Conclusions

- Pharmacokinetic study for HIPEC is possible using 2 bicompartimental models with **population pharmacokinetic approach**.

- The large number of parameters linked with toxicity or survival make difficult the research of direct interaction between pharmacokinetic and pharmacodynamic.

- Peritoneal surface doesn’t constitute, as supposed, a barrier between peritoneal cavity and plasmatic compartment for CDDP.
- **Cisplatinum HIPEC is equivalent in term of drug exposure as a systemic perfusion.**

- Future works :
  - develop a **single model** integrating plasmatic and peritoneal compartments
  - integrate **volume of abdomen** measured with CT scan as a covariate
  - **adapt precisely drug dosage** with individual parameters to reduce toxicity and optimize effectiveness