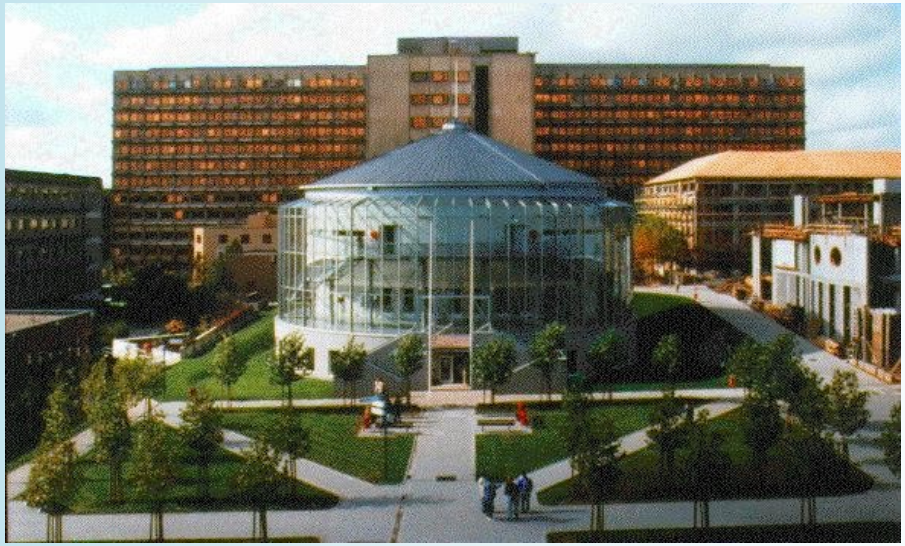
Pharmacokinetics of Oral Oseltamivir in Critically Ill Patients



Hites M[1], Taccone FS[2], Deprez G[3], Beumier M[2], De Backer D[2], Delforge ML[4], Vincent JL[2], Cotton F[3], Jacobs F[1]
Erasme Hospital
Université Libre de Bruxelles, Brussels, Belgium

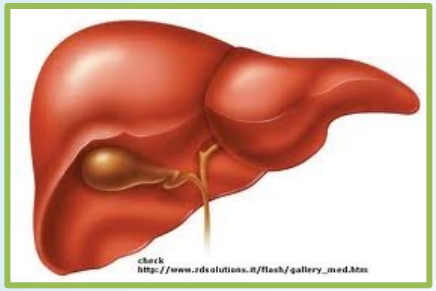
[1]Dept of Infectious Diseases,
[2]Dept of Intensive Care, [3]Laboratory of Clinical Chemistry,
[4]Laboratory of Virology
E-mail: Maya.Hites@erasme.ulb.ac.be

Introduction

- Standard drug (SD) regimens are established based on pharmacokinetic (PK) studies in healthy individuals

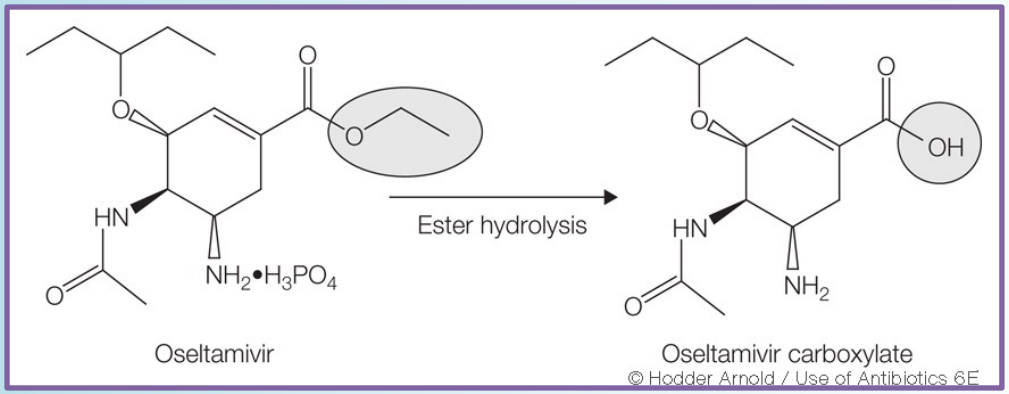
Introduction

- PK of many drugs are altered in critically ill patients
  - Δ Absorption
  - Δ Metabolism
  - Δ Drug distribution
  - Δ Clearance



Introduction

- Oseltamivir phosphate (OP) is a treatment of choice for severe Influenza infections
  - Only oral formulations existed at the time of the study
  - The drug is absorbed as a pro-drug, and must be metabolized to its active form: oseltamivir carboxylate (OC)



- WHO recommends to increase SD regimens (75 mg BID) to 150 mg BID for severe cases (not based on any clinical data)

Objectives

- To perform a PK study of oseltamivir in critically ill patients to establish whether:
  - Oral administration
  - SD regimens (75 mg BID)

  achieved therapeutic serum concentrations in these patients

- More precisely:
  - Was OP absorbed?
  - Was OP metabolized into OC in all patients?
  - Does OC reach therapeutic serum concentrations?

➔ Were SD regimens adequate in these critically ill patients?

Patients and methods

- Prospective observational PK study
  - in critically ill patients hospitalized in the Dept. of intensive care of the Erasme hospital, Université Libre de Bruxelles, Belgium
  - from October 2009 to January 2010
- Inclusion criteria
  - all consecutive patients, 18 years or older
  - with suspected or confirmed Influenza infection
  - treated with OP:
    - 75 mg BID
    - 150 mg BID

    Given orally or via naso-gastric tube

Choice of dosage regimen: case by case discussion between intensivists and infectious disease specialists

Patients and methods

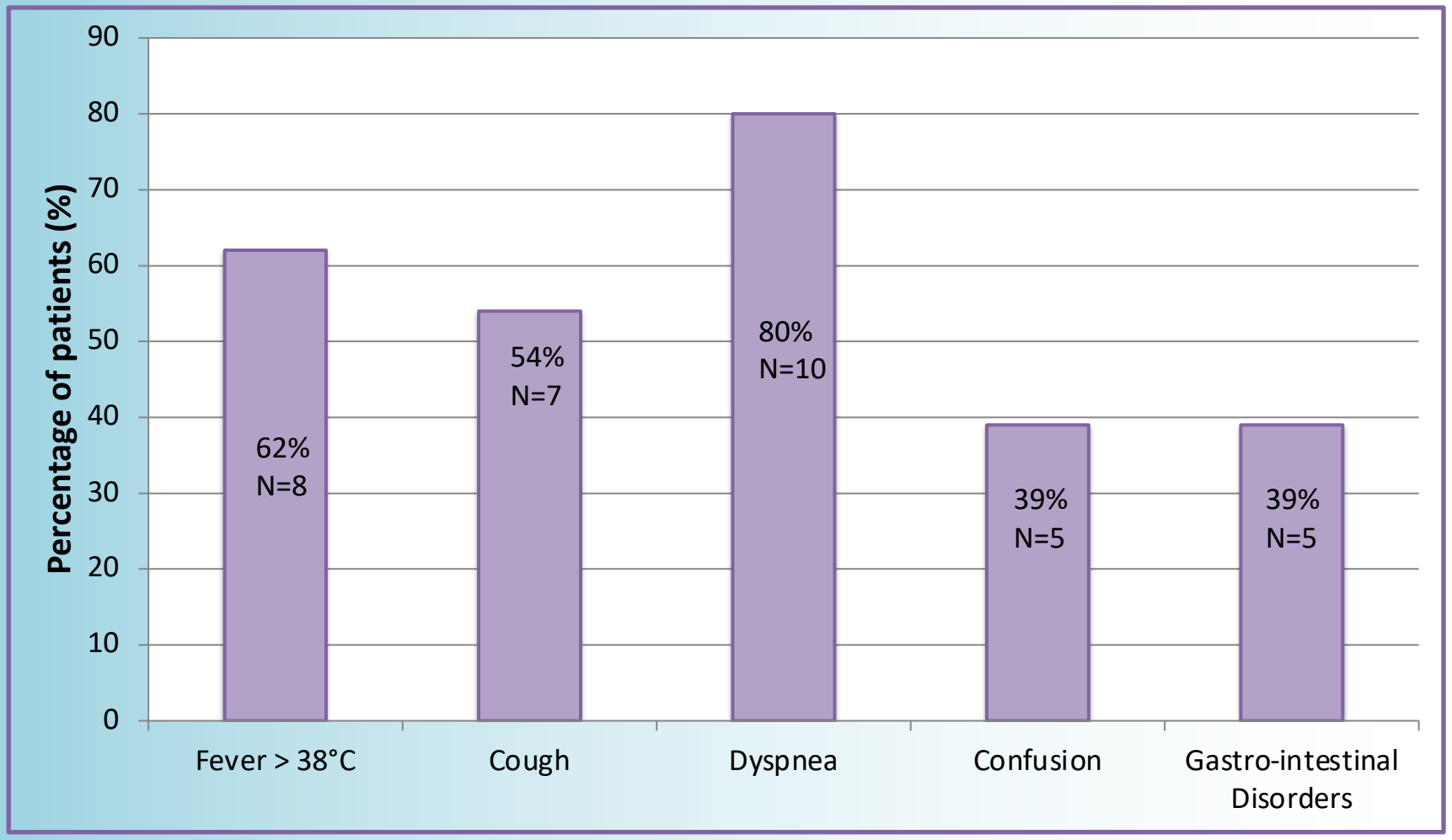
- 13 patients were included:
  - 6 (46%) cases of confirmed flu infection

- 15 PK studies performed:
  - **10 series** with SD regimens: 75 mg BID
  - **5 series** with increased dosage regimens: 150 mg BID

Patient Characteristics	Median (range) or Number
Sex	6M / 7F
Age	60 (35-84)
Weight (Kg)	65 (40-136)
Body Mass Index (kg/m^2)	22 (15-51)
Creatinine clearance (ml/minute)	50 (10-192)
SOFA score (1st day of PK study)	11 (2-18)
APACHE II upon admission to ICU	26 (15-41)
Co-morbidities	
Immunosuppressive treatment	5
Diabetes	2
Chronic renal insufficiency (Cr > 2.5 mg/dl)	3: 1 chronic dialysis
Cardiopathy	3
Cirrhosis	1: Child C
Pregnancy	1

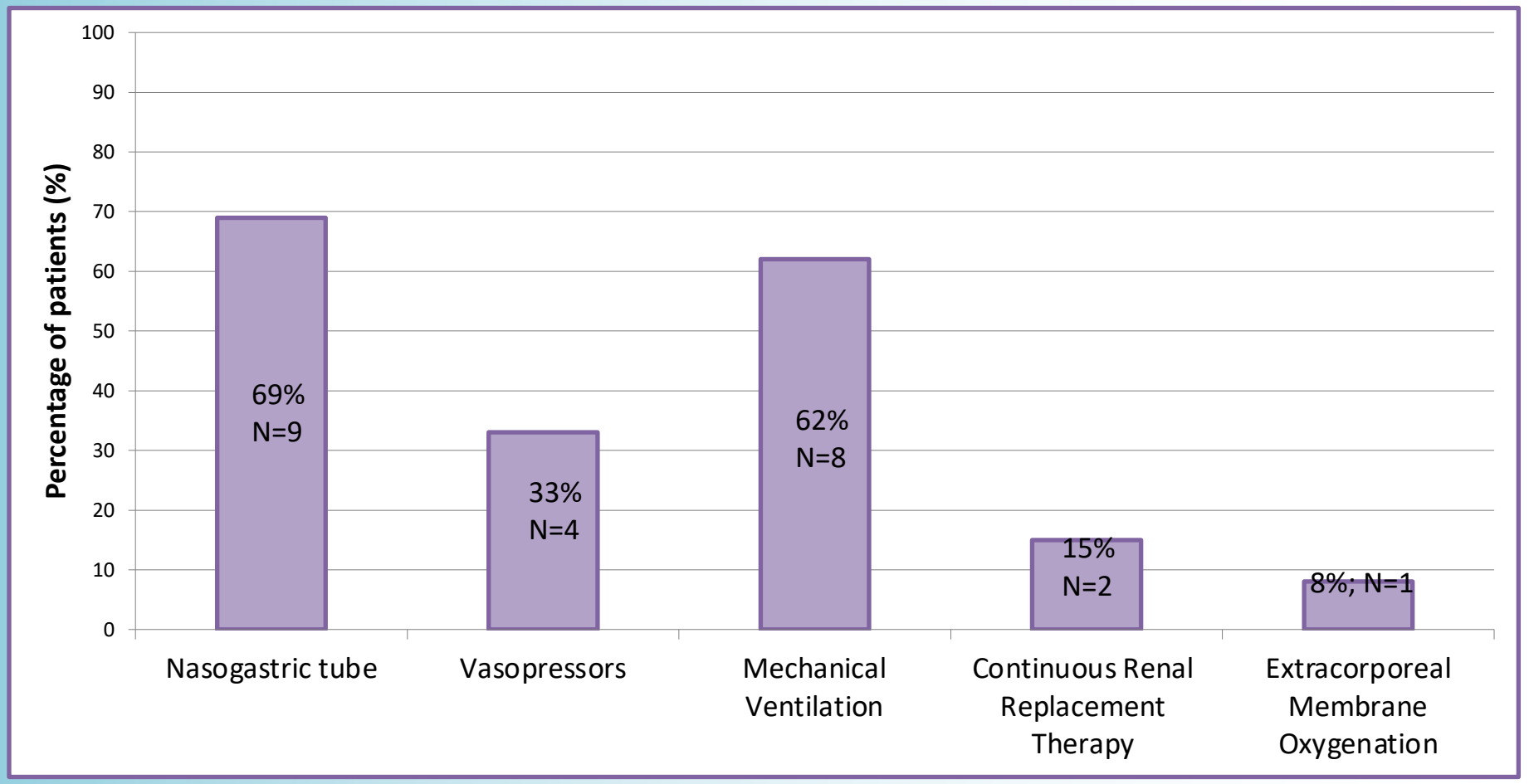
Patients and methods

- Clinical presentation



Patients and methods

- Concomitant treatments



Patients and methods

- Blood samples:

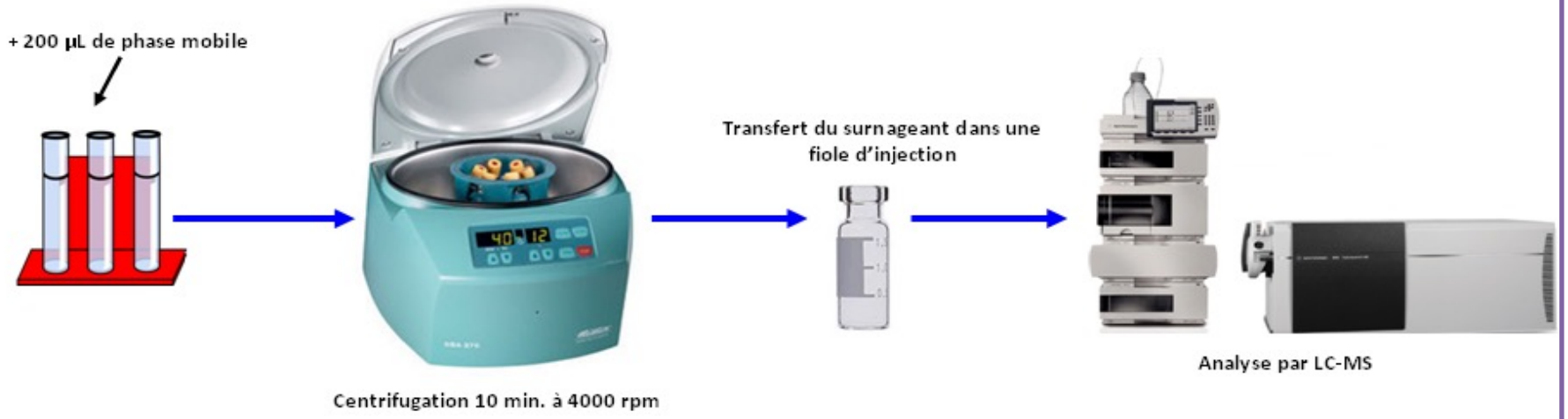
Dose of Oseltamivir phosphate

T0 | T1,T2, T3, T4, T5, T6, T8 | T12 | T24 | T36 | T48

Exact time of blood sampling was recorded!!

Patients and methods

- Measurement of OP and OC by liquid chromatography/ tandem mass spectrometry



Coefficient of variation: **OP:** 3%, **OC:** 6%
Limit of quantification: 1 µg/L for OP and OC

Patients and methods

- Data analysis:
  - Peak concentrations of OP and time to peak concentrations
  - Trough concentrations of OC
  - Area under the curve (0-12 hours) ($AUC_{0\text{-}12}$) of OP and OC
  - Serum concentrations were « normalized » to SD, as PK of OP and OC are linear[1]

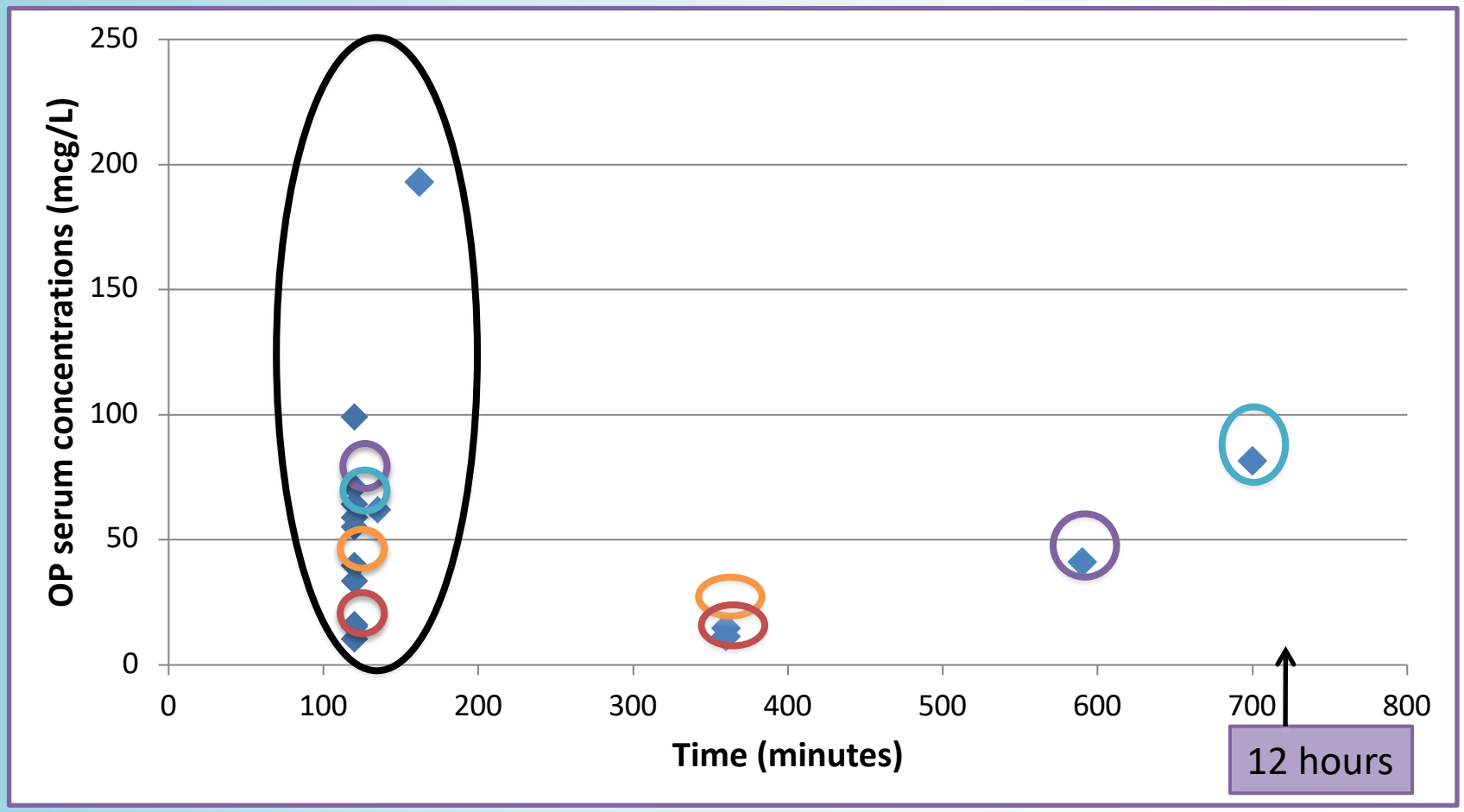
- « Adequate » trough concentrations of OC defined as:

> 1.86 µg/L (=MIC_{90}) for A(H1N1) virus

[1]Wattanagoon and al. Pharmacokinetics of high-dose Oseltamivir in Healthy Volunteers. *AAC.* 2009. 53(3): 945-952.

Results and discussion

- Was OP absorbed?



Results and discussion

- $AUC_{0\text{-}12}$ of OP in critically ill patients

147 µg.h/L (51-616)

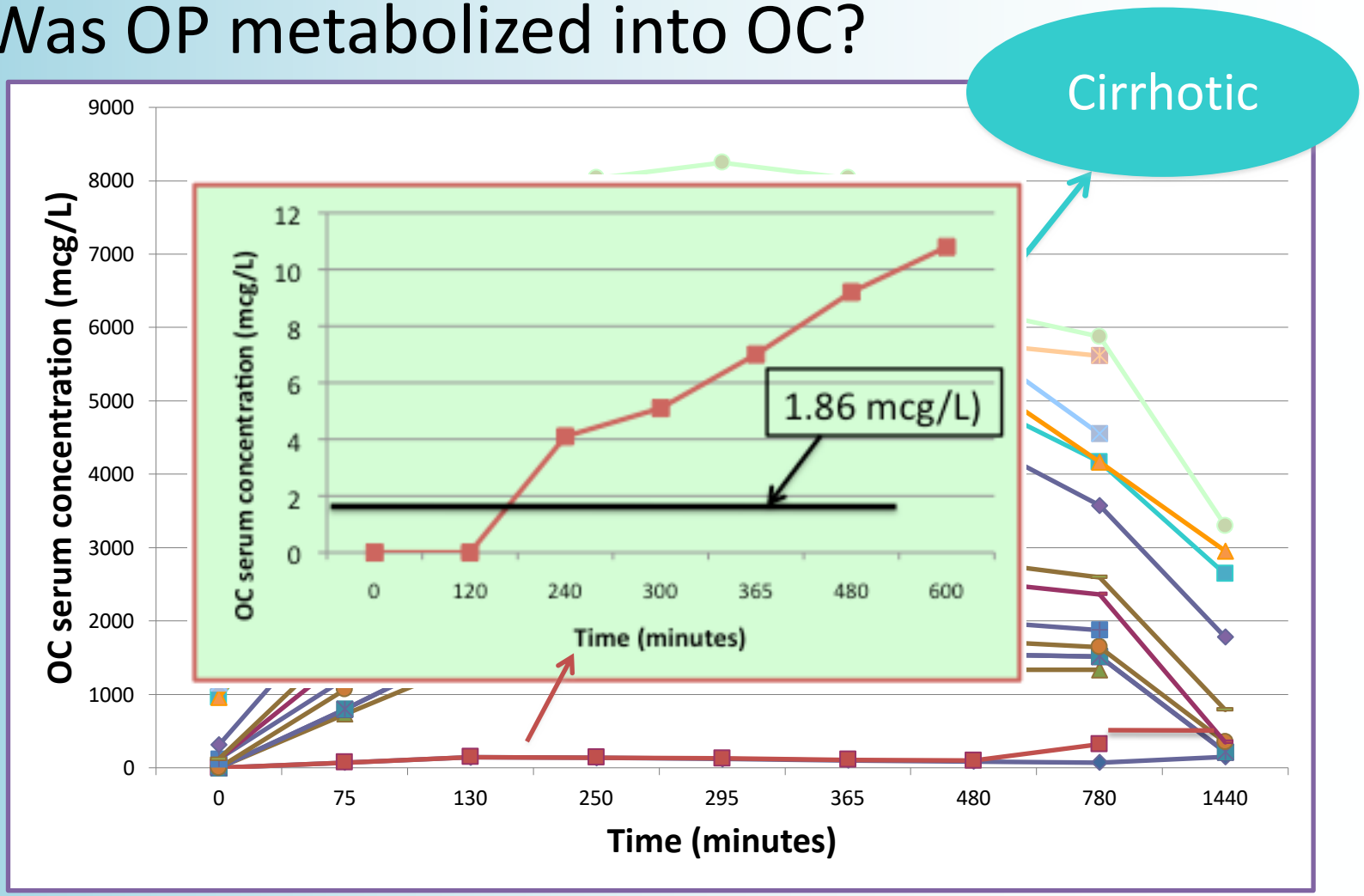
- $AUC_{0\text{-}12}$ of OP in healthy individuals

112 µg.h/L[1]

[1]Roche Scientific notice for Oseltamivir phosphate.

Results and discussion

- Was OP metabolized into OC?



Results and discussion

- Does OC reach therapeutic serum concentrations?
  - Median trough concentrations of OC:

269 µg/L (6.3-743) >>> 1.86 µg/L (=MIC_{90} for A(H1N1)

  - AUC_{0-12} of OC:

critically ill	healthy volunteers
2261 µg.h/L (11-14068)	2270 µg.h/L[1]

1. He G, Massarella J, Ward P. Clinical pharmacokinetics of the prodrug oseltamivir and its active metabolite Ro 64-0802. *Clin Pharmacokinet*. 1999. **37**: 471-484.

Conclusions

- Our results indicate that in critically ill patients, OP is:
  - well absorbed, yet delayed in some patients
  - well metabolized into OC
- Despite large variability in OC concentrations, oral administration of SD of OP resulted in therapeutic concentrations in every patient.

Conclusions

- 75 mg BID is an optimal dose of OP in critically ill patients.

- An IV loading dose may be needed in critically ill patients as absorption is delayed in some patients.

Thank you for your attention!