Thèse d'exercice

Université de Limoges

Thèse pour le diplôme d'État de docteur en Médecine

Présentée et soutenue publiquement

le 27 septembre 2019

Par Baptiste GIGUET

Né(e) le 07/05/1991 à Cherbourg en Cotentin

Description de l'évolution des concentrations plasmatiques et urinaires de l'iohexol dans une population de patients cirrhotiques. Etude pilote sur 9 patients.

Thèse dirigée par le Professeur Véronique LOUSTAUD RATTI

Examinateurs :

Mr le Professeur Denis SAUTEREAU	Président
Mme le Professeur LOUSTAUD RATTI	Juge
Mr le Docteur Paul CARRIER	Juge
Mr le Docteur Jérémie JACQUES	Juge
Mme le Docteur Caroline MONCHAUD	Membre invité
Mme le Docteur Maryline DEBETTE-GRATIEN	Membre invité
Mr le Docteur Romain LEGROS	Membre invité
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Le 1er janvier 2018

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De toutes les sciences que l'homme peut et doit savoir, la principale, c'est la science de vivre de manière à faire le moins de mal et le plus de bien possible.

Léon Tolstoï

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Droits d’auteurs

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Liste des abréviations

ACLF : Acute on Chronic Liver Failure.

AKI : Acute Kidney Injury.

ALKP : Alkalin Phosphatase.

ATN : Acute Tubular Necrosis.

AUC : Area Under the Curve.

BM : Brochner-Mortensen.

BMI : Body Mass index.

CIC : Clinical Investigation Center.

CKD : Chronic Kidney Disease.

CKD-EPI : Chronic Kidney Disease Epidemiology Collaboration.

CMAX : Maximal Concentration.

DBP : Diastolic Blood Pressure.

eGFR : estimated Glomerular Filtration rate.

FE Na : Sodium Excreted Fraction.

FE Urea : Urea Excreted Fraction.

GFR : Glomerular Filtration Rate.

HBV : Hepatitis B Virus.

HCV : Hepatitis C Virus.

HRS : Hepato-Renal Syndrom.

K plasm : plasmatic constant elimination.

LT : Liver Transplantation.

MELD : Model for End Stage Liver Disease.

MDRD 4 : Modification of Diet in Renal Disease 4.

MDRD 6 : Modification of Diet in Renal Disease 6.

mGFR : measured Glomerular Filtration Rate.

PK : Pharmacokinetic.

RFH : Royal Free Hospital.

SCr : Serum Creatinine.

SBP : Systolic Blood Pressure.

SLKT : Simultaneous Liver-Kidney Transplantation.

TDF : Tenofovir Disoproxil Fumarate.

UNOS : United Network for Organ Sharing.

Vd : Distribution Volume.

51 Cr-EDTA : 51 - Chromium EthyleneDiamineTetraacetic Acid.

Introduction

Impaired renal function is an independent prognostic factor in cirrhosis, particularly in decompensated patients. In addition, chronic renal impairment after liver transplantation (prevalence 15%) is also an independent factor of mortality [1] .

Serum creatinine has been incorporated as a prognostic factor into the Model for Endstage Liver Disease (MELD) score, a predictive model of mortality at 3 months. Finally, a double liver-kidney transplant should be considered in case of a measured Glomerular Filtration Rate (GFR) less than 30 ml/minute/1.73 m² [2]. An accurate evaluation of GFR is therefore essential to optimize the management of cirrhotic patients and to prioritize patients for liver transplantation and discuss double liver-kidney transplant [3]

Serum creatinine, creatinine clearance as well as SCr derived-equations (Cockcroft, modification of diet in renal disease 4 (MDRD-4), Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations and even MDRD-6 equation which seems more accurate usually tend to overestimate the cirrhotic patient's GFR by approximately 23 ± 23 ml / min / 1.73 m2 [4] especially in advanced diseases. Cystatin C-based or combining cystatin C and creatinine equations seem promising but are not validated. No calculated equations have today been demonstrated to be as efficient as direct evaluation of GFR.

Inulin, iohexol, or chromium-51 labelled ethylenediamine tetraacetic acid (51Cr-EDTA) clearance are the established gold standard measurement of GFR. Iohexol is a non toxic contrast agent, filtered by the glomerulus, without tubular secretion or reabsorption and is costless than inulin and CR-EDTA. However, few data are available in the cirrhotic population [5] [6] , and methodological limitations in these studies warrant confirmation of the validity of this tool for the measurement of GFR in cirrhotic patients: period of blood collections too short, existence of a third sector (ascites) in which iohexol concentrates over time, suggesting that the decrease in plasma concentrations does not only reflect renal elimination; application

of approximation methods (Brochner-Mortensen formula) for the calculation of iohexol clearance [7], not validated for the moment in the cirrhotic population.

Thus, our goal was to accurately describe the pharmacokinetic behavior of iohexol in patients with different stages of liver disease, by means of prolonged 24 hours kinetics. In parallel, we collected urine throughout the duration of the 24 hours to measure the renal clearance of iohexol and checked if the plasma decreasing concentrations corresponded to a total renal elimination of the product.

Finally, rich kinetics should allow the development of a population pharmacokinetic model and a derived bayesian estimator and a limited sampling strategy which could be easily applied in routine care.

I. Detailed Background.

1.1 Renal insufficiency and cirrhosis.

Cirrhosis can be complicated by renal insufficiency in many situations.

1.1.1. Renal diseases associated with cirrhosis.

First, some etiologies of cirrhosis may be directly or indirectly associated with various chronic kidney diseases [8]*. For example, particularly in the context of steatohepatitis and HCV infection* [9]*), cirrhosis is often linked to specific conditions, such as atherosclerosis, diabetes mellitus, elevated blood pressure, which can lead to renal failure. Hepatitis C virus infection is an independent factor of kidney disease development* [10] *. In a large cohort of US veterans, with a follow-up of more than fifteen years, HCV seropositivity doubled the risk of chronic renal insufficiency. Membranoproliferative glomerulopathy and cryoglobulinemia are specific immunological complications classically described in this population. Concerning hepatitis B virus, the renal diseases described since 1991* [11]*, include a large spectrum of lesions ranging from membranous nephropathy, which remains the most frequent, to membranoproliferative glomerulonephritis and mesangial proliferative glomerulonephritis. Polyarteritis nodosa* [12][13] *has also been described in this condition in the 1980's. The toxicity of antiviral drugs, particularly interferon, is possible* [14]*. Nucleotide analogues especially tenofovir disoproxil fumarate (TDF) may be responsible for proximal tubulopathies; Fanconi syndromes are mainly observed in HIV patients and exceptionally in HBV mono-infected patients* [15] [16] [17]*. Diabetes, which causes microvascular renal lesions, is also more common in cirrhotic patients* [18]*. Non-diabetic glomerulosclerosis is observed in cirrhosis* [8] [19]*. IgA nephropathy can occur, quite specific during alcoholic cirrhosis, and is probably underestimated* [19]*.*

1.1.2. Acute kidney injury and cirrhosis.

Acute kidney injury occurs in approximately 20% of hospitalized cirrhotic patients [20]*. Specific pathophysiological conditions of cirrhosis promote renal dysfunction: portal hypertension induces splanchnic vasodilation resulting in low renal perfusion and a decrease systemic blood volume* [21]*. Decreased renal perfusion activates a number of compensatory mechanisms including the renin-angiotensin-aldosterone system, arginine-vasopressin and the sympathetic nervous system* [22]*. The decrease in systemic vascular resistance is initially compensated by an increase in cardiac output. However, this compensation may be exceeded, particularly in the case of cirrhotic cardiomyopathy, and leads to a situation of uncontrollable hyperkinesia* [23]*. In addition, the presence of systemic inflammation, secondary to clinical or infra-clinical bacterial translocation, may also increase the risk of decompensation of cirrhosis by decreasing renal perfusion* [24] [25]*. All these conditions specifically promote hepato-renal syndrome, which is classified as an acute pre-renal lesion. Hepato-renal syndrome is the second leading cause of acute renal injury in cirrhotic patients after functional causes* [26] [27]*. There is usually a triggering factor such as a septic episode, a digestive hemorrhage* [21] [28]*, or underlying refractory ascites. Hepato-renal syndrome is one of the most serious complications encountered in cirrhosis with portal hypertension. Mortality remains high despite standard treatment consisting of the combination of terlipressin and albumin infusion* [29] [30]*. However, if HRS is a vascular disease potentially reversible after transplantation, cirrhosis is also characterized by a systemic inflammatory multiorgan disease correlated to the severity of liver disease and due to the translocation of bacteria most often without overt bacterial infection; 30% of patients with HRS have SIRS without bacterial documentation. So, the long term chronic vasoconstriction and inflammatory injury may lead to CKD and irreversibility of HRS. Hepato-renal syndrome concerns only 25% of AKI in cirrhosis. The other causes remain those encountered in non-cirrhotic patients: approximately 50% of AKI are due to a pre-renal origin (infections, hypovolemia, vasodilatators), 32% to intra-renal causes (tubulopathy, glomerulopathies). Finally, obstacles on the urinary tract are rare* [20] [31]*. Specific recommendations for the management of acute renal failure in cirrhotic patients have recently been updated, in accordance with the general recommendations and specific conditions for cirrhosis* [20] [30] [32]*.*

1.2. Role of renal insufficiency in cirrhosis course.

1.2.1. Renal function is prognostic in cirrhotic patients.

Serum creatinine is included in multiple cirrhosis prognostic criteria : it has a significant weight in specific liver transplantation scores such as the MELD score (Mayo model for end-stage liver disease) [33] [34]*, which is the current benchmark in Europe and the United States for graft allocation* [35].

Renal failure is described as a prognostic factor, regardless of its evolution, chronic or acute [36]*. Among the causes, hepato-renal syndrome is associated with the worst prognosis, while parenchymal kidney disease appears to have a better prognosis* [37]*. This has been well established in acute kidney injury, according to the recent AKI classification* [38]. *In the CANNONIC cohort, a cohort of patients with acute on chronic liver failure (ACLF), renal insufficiency is very closely associated with one month mortality* [39].

In addition, Cullaro et al. recently demonstrated that persistence of a basal serum creatinine within "normal range" (meaning an overestimated GFR), predicted the survival of patients waiting for a liver transplant [3] [40].

1.2.2 Impact on the management of liver transplantation.

Renal failure is also a major problem after liver transplantation, particularly in cases of previous renal disease, with an overall incidence of 15 to 25% of the stage ≥ 4 CKD (chronic renal disease) [41] [42] *5 years after liver transplantation; it is predictive of post-transplant mortality and increases health care costs* [43].

A cohort study of 19,261 patients from the United Network for Organ Sharing (UNOS) registry evaluated the impact of pre-transplant renal insufficiency on post-transplant survival. Rates of primary graft dysfunction and 30-day mortality were significantly higher in patients with moderate (20 to 39.9 mL/min) or severe (<20 mL/ min) renal impairment. The same was true for graft and patient survival rates at 1, 2

and 5 years. The multivariate analysis showed that pre-transplant renal failure was an independent factor in mortality at 30 days and 2 years after adjustment for age, gender, etiology of cirrhosis, presence of diabetes, body mass index and time of cold ischemia. This study, although old, had confirmed the use of serum creatine in prognostic cirrhosis scores and the use of the MELD score for graft allocation. Since then, many studies have validated the prognostic impact of renal insufficiency on the survival of the graft and the patient in post-liver transplantation [44].

Post-liver transplantation renal insufficiency is influenced by renal function, particularly acute kidney injury occurring before liver transplantation [42] [45] [46]. *Transplant algorithms for simultaneous liver-kidney transplantation (SLK) depend on our still imperfect ability to predict, with certitude, the etiology of renal insufficiency before LT. An American study by Nadim and al showed the importance of distinguishing the different etiologies of AKI occurring in pre-transplantation. Patient survival and renal outcomes at 1 and 5 years after LT were significantly worse for patients with Acute Tubular Necrosis (ATN). After 5 years, the incidence of chronic renal failure (stage 4 or 5) was statistically higher in the ATN group than in the HRS-AKI group (56% versus 16%, P < 0.001). In patients with renal dysfunction at the time of LT, it is important to know if their renal function will improve, stabilize or deteriorate. For those who will not recover, combined liver/kidney transplantation may be justified* [47].

Simultaneous liver and kidney transplantation in the case of pre-existing kidney disease meets specific criteria for selecting the right patients [48] [49] [50] [2]. *They are based on renal function, and possibly on a renal sample, mainly in cases of multifactorial renal failure. They help to select the most severe patients, but remain drastic and do not clearly help to assess the full reversibility of HRS, the main renal complication of end-stage cirrhosis. Finally, renal biopsy (most often transjugular) is not always accessible or dangerous because of bleeding disorders. Most authors consider SLKT in patients with endstage liver disease and chronic kidney disease (CKD) with measured GFR <30 mL/min/1.73 m2 for at least 3 months or CKD with measured GFR between 30 and 40 mL/min/1.73 m2 and biopsy showing severe*

kidney parenchymal lesions including interstitial fibrosis, glomerulosclerosis, and vascular arterial lesions [5].

1.3. How to assess renal function in cirrhotic patients.

1.3.1. Serum creatinine and its limitations.

Renal function assessment is based on serum creatinine, which is a highly reproducible and easy-to-use tool.

Nevertheless, serum creatinine, creatinine clearance as well as serum creatinine derived-equations (Cockcroft, modification of diet in renal disease 4 (MDRD-4), Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations that evaluate the glomerular filtration rate (GFR) by calculation, tend to overestimate the cirrhotic patient's GFR by approximately 23 ± 23 ml / min / 1.73 m2 especially in advanced diseases [51] [52] [5] [53]. *MDRD-6 equation may be more accurate and has been proposed as the reference according to the US consensus guidelines to identify candidates for simultaneous liver and kidney (SLK) transplantation* [49]

The specific limitations of creatinine should be highlighted [51]. *A recent South Korean study showed that kidney function was overestimated in nearly half of the 779 patients* [54]. *Factors associated with overestimation of renal function were sex, muscle mass and stage B or C of the CHILD PUGH score. There are several explanations:*

- First, a decrease in the hepatic secretion of creatine - the precursor of creatinine in connection with an hypermetabolic state due to pro-inflammatoiry cytokines, endotoxinemia and sympathetic hyperactivity.

- Second, sarcopenia is more common in cirrhotic patients and is associated with a decrease in creatinine production [55]. *An increase in tubular creatinine secretion has been assumed in cirrhotic patients, but these data remain questionable.*

- Third, there is possible interference between bilirubin and creatinine dosage – bilirubin acts as a chromogen in spectrophotometry, giving an overestimation of renal

function [8] [56] *Overestimation of renal function is mainly described in the case of high serum bilirubin levels, but also in the case of refractory ascites and advanced liver cirrhosis* [8]*. Some laboratory techniques are useful in case of high serum bilirubin levels, such as deproteinization, addition of sodium dodecyl sulfate and use of enzyme methods (bilirubin oxidase or specific alkaline kinetic picrate)* [57] [58] [59]*.*

- Fourth, the presence of ascites is also responsible for an overestimation of renal function due to changes in vascularization [60]*.*

1.3.2. Other simple markers.

Since serum creatinine appears to be inaccurate in the estimation of renal function, other tools are needed, particularly to assess prognosis, especially in the case of a liver transplant project [51] [52] *or a combined liver-kidney transplant.*

Standard tools such as blood urea nitrogen are less accurate than serum creatinine, [61]*. The excretion fraction of sodium (FENa) or urea (FEurea) appears to be helpful, but cannot accurately estimate renal function* [62]*.*

Cystatin C, a low molecular weight non-glycosylated protein from the family of cysteine protease inhibitors, is the most studied marker in cirrhotic patients [63]*. It is eliminated by glomerular filtration, but reabsorbed and metabolized by tubular cells so that its clearance cannot be calculated* [64]*. Serum cystatin C levels appear to increase earlier than creatinine in acute renal lesions, particularly in patients with normal serum creatinine and ascites* [65] *and are more closely related to mortality* [66] *although different studies remain controversial* [67]*. The cut-off value of 1.1 mg/dl could provide an appropriate reference level for the early detection of renal dysfunction in these patients* [68]*. In patients with low muscle mass, it is more accurate than serum creatinine and is independent of age, muscle weight, inflammation and serum bilirubin concentration* [69]*. Limits are the absence of standardization of the dosage and its cost.*

Equations based on Cystatin C, combined or not with serum creatinine have been proposed recently. The main ones used are: CKD-EPI-Creatinine Cystatin C and CKD-EPI-Cystatin C [70] [71] [72] [73] [74]*. CKD-EPI-Cystatin C appears to be more accurate than the MDRD6 formula in cirrhosis, and is predictive of mortality after liver transplantation* [63]*.*

More recently, Kalafatelli et al. proposed a new specific equation = $45.9 \times (creatinine^{-0.836} \times urea^{-0.229} \times INR^{-0.113} \times age^{-0.129} \times sodium^{-0.972} \times 0.809$ *(if female)* $\times$ *0,92 (if moderate/severe ascites),* *called the Royal Free Hospital (RFH) score. In 469 patients, this score appeared to be more accurate than creatinine based equations* [75]*.*

In conclusion, among classical tools, Cystatin C and Cystatin C based equations seem to be interesting, but are not considered yet as referent by the scientific community [76]*.*

1.3.3. Gold standards.

Beyond all these specific markers, referent tools provide direct measurement of GFR [51]*.*

These exogenous renal markers have an exclusive renal elimination, with free filtration in the glomerulus and neither secretion nor reabsorption through the tubules. However, the procedure is long, expensive, cumbersome to implement and only used in clinical trials or rarely in patients with particularly difficult situations requiring a precise assessment of renal function.

The renal clearance of inulin is the first gold standard used [77] [78]*, but it is long, costly and cumbersome as its derivative, Sinistrin* [76]*.*

51-chromium-EDTA (ethylenediaminetetraacetic acid) [79] [80] *and other radioactive markers can help assess renal function* [81] [82] *(125I-iothomalate and 99mTc-diethylene triamine pentaacetic). However they are costly and some are*

associated with strict regulations regarding distribution, handling and administration to patients [83]

Iohexol, a non-ionic contrast agent, is most suited to replace inulin as the marker of choice for GFR determination

1.4 Iohexol.

1.4.1. Properties of iohexol.

Iohexol is a radiological contrast product with a low extra-renal excretion, low protein binding and is neither secreted nor reabsorbed by the kidney. In addition, iohexol is virtually non-toxic and carries a low cost. As iohexol is stable in plasma, administration and sample analysis can be separated in both space and time, allowing access to GFR determination across different settings.

The clearance of iohexol is promising and and gives similar results as inulin and 51-Cr-EDTA [84]*. However, few data are available in the cirrhotic population* [4] [6] *and methodological limitations in these studies warrant confirmation of the validity of this tool for the measurement of GFR in cirrhotic patients: period of blood collections too short, limited to 5 hours, while the product is not completely eliminated; existence of a third sector (ascites) in which iohexol concentrates over time, suggesting that the decrease in plasma concentrations does not only reflect renal elimination; application of approximation methods (Brochner-Mortensen formula) for the calculation of iohexol clearance, not validated yet in the cirrhotic population.*

Henriksen et al [85] *, suggested that the use of a plasmatic clearance of iohexol in patients with fluid retention and ascites may lead to an overestimation of GFR urinary clearance. While urinary clearance may be the most physiologic and accurate method to measure the filtering capacity of the kidney, it is time consuming and prone to errors; urinary clearance may itself also slightly underestimate GFR. We had thus to check the discrepancies between plasma clearance and urinary*

clearance of iohexol even if plasma clearance methods represent the best compromise between physiology and feasibility in clinical routine.

Thus, our goal was to accurately describe the pharmacokinetic behavior of iohexol in patients with different stages of liver disease, by means of complete prolonged 24H kinetics. These multiple early and late samples should objectify the existence and the intensity of the possible rebounds of concentration related to the 3rd sector as well as to determine the duration of samples necessary and sufficient to capture the phase of terminal elimination of the iohexol. In parallel, we collected urine throughout the duration of the kinetics to measure the renal clearance of iohexol and check if the plasma decreasing concentrations corresponded to a total renal elimination of the product.

II. Material and method.

2.1. Study Objective.

The main objective was to describe the urinary and plasma concentrations of Iohexol in a population of 9 cirrhotic patients, based on a rich kinetics of samples.

After measuring the urinary and plasma clearance of iohexol, the secondary objectives were to compare the renal clearance obtained from the plasma and urinary clearance of Iohexol and to assess the concordance between the plasma clearance of iohexol and different methods estimating GFR (CKD-EPI, MDRD4 and 6, RFH, Brochner-Mortensen formula). Finally, the impact of relevant covariates on the measurement of plasma clearance of Iohexol, particularly ascites and prognostic cirrhosis scores, have been studied.

2.2. Patients and samples.

The eligible patients had to be over 18 years old, had advanced liver disease with different grades of ascites (3 patients without ascites, 3 patients with grade I ascites and 3 patients with grade II or III ascites) and a potential indication for liver transplantation. All the inclusion and exclusion criteria are detailed in Appendix 1. The study was conducted in full compliance with the European and French guidelines of Good Clinical Practices, the most up to date Declaration of Helsinki (Seoul 2008) and the International Conference on Harmonization, Harmonized Tripartite Guideline for Good Clinical Practices in the European Community. It was approved by the Independent Ethics Committee of Limoges and by the relevant authorities and registered under EudraCT number 2018-002778-35. All patients gave their written informed consent for study participation and blood sample conservation. The study was registered on the site ClinicalTrials.gov. with the identifier: NCT03769597.

Details of the procedure are described in Appendix 1.

Screening of eligible patients was done during routine consultations in the hepatogastroenterology department of the Limoges University Hospital ("V-1 visit"). After a period of reflection, the patient's consent was obtained and the inclusion and exclusion criteria were checked during a second visit ("V0 visit"). Finally, patient's inclusion was achieved during the "V1 visit" at the clinical investigation center (CIC). Clinical and biologic data were collected prior to the injection of iohexol.

Patients received a single 5 mL bolus of iohexol (Omnipaque® GE HEALTHCARE 5 mL). Over the next 24 hours, 11 blood samples were taken to record plasma Iohexol concentrations : at 15, 30, 60, 90 minutes and then, at 2, 3, 4, 6, 8, 12 and 24 hours. In addition, urine was collected at 4, 8, 12 and 24 hours with the different voiding volumes reported. Oral intakes were quantified and an oral intake of 300 mL of water was systematic at 3 and 6 hours. Patient's hydration was also adapted by the responsible physician according to the clinical condition.

Iohexol was measured in serum and urine samples with a very sensitive and specific method based on liquid chromatography coupled with tandem mass spectrometry in the Pharmacology unit of the University hospital of Limoges. The internal standard was ioversol and the limit of quantification was 10 ng/mL.

2.3. Statistical analysis.

A non compartmental analysis was applied to determine the plasma and urinary clearance of iohexol (calculated as Dose/AUC) in PKanalix (Lixoft, Antony, France). Comparisons between reference iohexol clearance and other methods were performed using linear correlation and bland altman plots. Covariates were investigated on reference clearance using linear regression and scatter plot (continuous covariates) or Mann Whitney and boxplots (categorical covariates).

III. Results.

3.1. Description of patients.

A total of 9 patients were consecutively included in our study, exclusively men. It should be noted that during the inclusion period, 3 other patients were screened, signed their informed consent at the V0 visit, but secondarily withdrew their consent. The characteristics of the patients are shown in table 1.

3.2. Primary outcome : Description of the pharmacological curves of plasma and urinary concentrations of iohexol as a function of time.

The non-compartmental analysis of blood and urine concentrations of iohexol, are presented in Table 2.

Overall, the plasma concentration decay is homogeneous for all patients with typically two phases a rapid phase 1 corresponding to the distribution phase (first two hours) and a slower phase II corresponding to the elimination phase (figure 1). Iohexol is almost no longer detected in plasma at the 24th hour which allowed us to extrapolate the AUC 0 - 24 hours to AUC 0 - ∞.

It should be noted that patient #7 presented a high and isolated concentration at 2 hours, perhaps because he had received a not scheduled iodine injection for radiographic examination 15 days before inclusion.

The urinary curves are also homogeneous with an inverse behavior of the plasma curves. However, at the 24th hour, the urinary elimination was not complete varying at H24 from 60 to 90% of the overall dose administered. Thus the urinary clearance of iohexol was not directly measurable and the urine clearance was extrapolated from the plasma clearance and the total urinary excretion of iohexol, according to the formula :

Urinary clearance of iohexol = Measured Plasma clearance X Total urinary excretion of iohexol in 24 hours / total dose of iohexol injected

Of note, the Patient #1 with grade 2-3 ascites had a iohexol measurement in ascites at H24 and showed a low concentration (14 mg/L) not in favor of an accumulation in ascites.

3.3. Secondary outcome.

3.3.1. Plasma and urinary clearances of iohexol obtained by non-compartmental analysis.

The median plasma and urinary clearance [min; max] of iohexol over 24 hours were 63.7 mL/min [41.3 ; 111.3] and 53.6 mL/min [32.7 ; 76.7] respectively. Indexed to body surface area for each patient, the median plasma clearance was 59.4 mL/min/1.73 m2 [30.6 ; 103.3].

The median bias between plasma and urinary clearance was -16.5 mL/min, with 95% concordance limits of - 35 to 2 mL/min.

The linear regression and Bland-Altman comparisons are shown in Figure 2.

3.3.2. Concordance between the measured plasma clearance of iohexol and other formulas estimating the GFR.

All comparisons between the measured plasma clearance of Iohexol and creatinine based equations are presented in Figure 3. In the same way we compared the measured plasma clearance with the renal clearance estimated by the RHF and the plasma clearance of iohexol extrapolated with the Brochner-Mortensen formula.

3.3.2.1. Comparison between measured plasma clearance of Iohexol and CKD-EPI equation.

The median bias between measured plasma clearance of Iohexol versus estimated clearance according to CKD-EPI equation is + 24.3 mL/min/1.73m2 with 95% concordance limits of - 12.5 to 61.1 mL/min/1.73m2.

3.3.2.2. Comparison between measured plasma clearance of Iohexol and MDRD4 and MDRD 6 equations.

The median bias between measured plasma clearance of Iohexol versus estimated clearance by MDRD 4 equation is + 35.0 mL/min/1.73m2 with 95% concordance limits of - 16.1 to + 86.1 mL/min/1.73m2.

The median bias between measured plasma clearance of Iohexol versus estimated clearance by MDRD 6 equation is + 28.1 mL/min/1.73m2 with 95% concordance limits of - 13.2 to + 69.4 mL/min/1.73m2.

3.3.2.3. Comparison between measured plasma clearance of Iohexol and RFH equation.

The median bias between measured plasma clearance of Iohexol versus estimated renal clearance according to RFH equation is + 5,8 mL/min/1.73m2 with 95% concordance limits of - 17.5 to + 29.1 mL/min/1.73m2.

3.3.2.4. Comparison between measured plasma clearance of Iohexol and plasma clearance of iohexol extrapolated with the Brochner-Mortensen formula.

The median bias between measured plasma clearance of Iohexol versus plasma clearance of iohexol extrapolated with the Brochner-Mortensen formula is + 6,6 mL/min/1.73m2 with 95% concordance limits of - 4.9 to + 18.1 mL/min/1.73m2.

3.3.3. Evaluation of covariates.

All comparisons are presented in Appendix 2. None of the clinically and biologically relevant covariates appear to significantly influence the measured plasma clearance of iohexol.

In addition, the volume of distribution of iohexol for the nine patients was compared according to the presence or not of ascites : grade I to III versus absence of ascites. This comparison is presented in Figure 4. The volume of distribution does not differ significantly between the two groups.

Age	60 (47 - 70)
Sexe ratio (M:F)	1,0
Etiology	Alcohol 78% - Mixte 22%
MELD	17 (8 - 33)
Child Pugh	7 (5 - 12)
Serum creatinine (micromol/L)	87 (53 - 142)
CKD - EPI (mL/min/1,73m2)	83 (46 - 120)
MDRD4 (mL/min/1,73m2)	82,7 (47 - 153,9)
MDRD6 (mL/min/1,73m2)	77,2 (46,5 - 134)
RFH (mL/min/1,73m2)	54,6 (31,9 - 105)
BM formula (mL/min/1,73m2)	59,7 (38,4 - 115,1)
mCl plas (mL/min)	63,7 (41,3 - 111,3)
mCl urin (mL/min)	53,6 (32,7 - 76,7)
Serum albumin (g/L)	34,2 (26 - 37,7)
SBP (mmHg)	120 (101 - 140)
DBP (mmHg)	70 (60 - 89)
Weight (kg)	96 (70 - 143)
BMI (kg/m2)	32,8 (22,3 - 48,3)
Natremia (mmol/L)	132 (118 - 139)
Diuretics	yes : 56% ; no : 44%
Bilirubine (micromol/L)	29,9 (10,2 - 159)
ALKP (UI/L)	136 (73 - 323)

Table 1. Patient's main characteristics median (min-max).

RHF : Royal Free Hospital formula, BM : Brochner-Mortensen formula, mCl plas : measured plasmatic clearance, mCl urin : extrapolated urinary clearance, SBP : systolic blood pressure, DBP : diastolic blood pressure, BMI : Body Mass Index, ALKP : Alkaline Phosphatase.

Patient no.	Cl plas (mL/min)	Cl urin (mL/min)	*k* plas (min-1)	C max (mg/L)	Vd (mL)	AUC 0 > inf (mg/h/L)	AUC 0 > 24h (mg/h/L)	%
1	63,71	35,30	0,003211	284	19839,7	846,26	830,171	- 1.9
2	55,92	40,07	0,002345	196	23852,5	964,113	924,802	- 4.1
3	58,70	46,38	0,002031	148	28897,5	918,45	860,117	- 6.4
4	76,25	65,98	0,002644	154	28830,0	707,119	686,323	- 2.9
5	111,26	76,69	0,003635	227	30607,4	484,599	480,014	- 0.9
6	79,01	58,60	0,004057	202	19475,6	682,396	680,013	- 0.3
7	41,27	32,68	0,001994	173	20689,5	1306,38	1226,09	- 6.1
8	79,88	71,44	0,003817	247	20924,1	674,929	671,568	- 0.5
9	63,39	53,64	0,001947	140	32556,8	850,604	779,724	- 8.3
Median	63,71	53,64	0,002644	196	23853	846,3	779,7	-5
Min - Max	41,27 - 111,3	32,68 - 76,69	0,001947 - 0,004057	140 - 284	19476 - 32557	484,6 - 1306	480 - 1226	-9 ; -1,9

Table 2. Non - compartmental Analysis (NCA) : iohexol pharmacokinetic parameters. Cl plas : measured plasma clearance of Iohexol, Cl urin : extrapolated urinary clearance of Iohexol, k plas : plasmatic elimination constant, C max : plasma maximal concentration, Vd : distribution volume, AUC : Area Under the Curve.

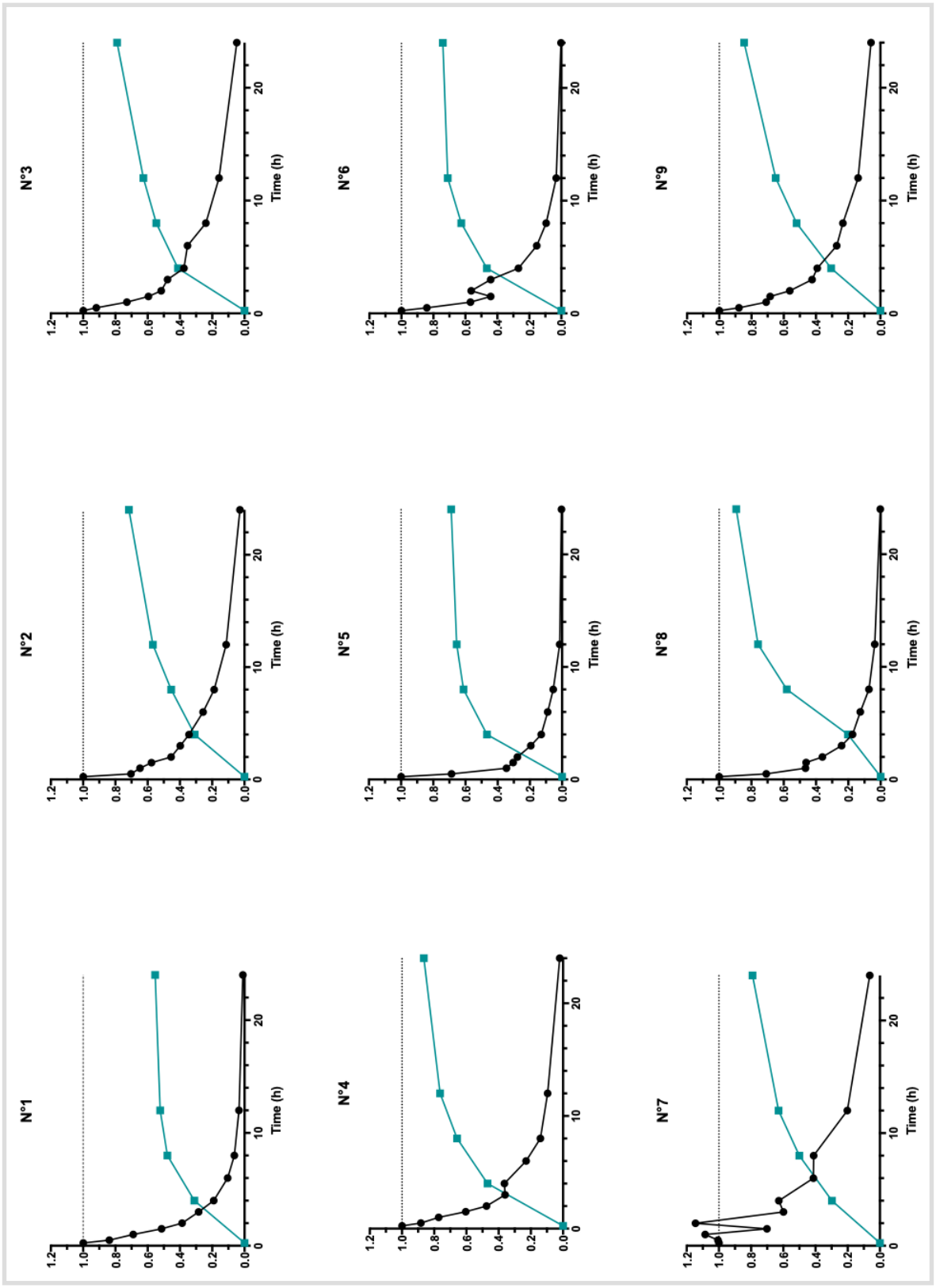


Figure 1. Plasma and urinary iohexol concentration curves as a function of time for each patient.

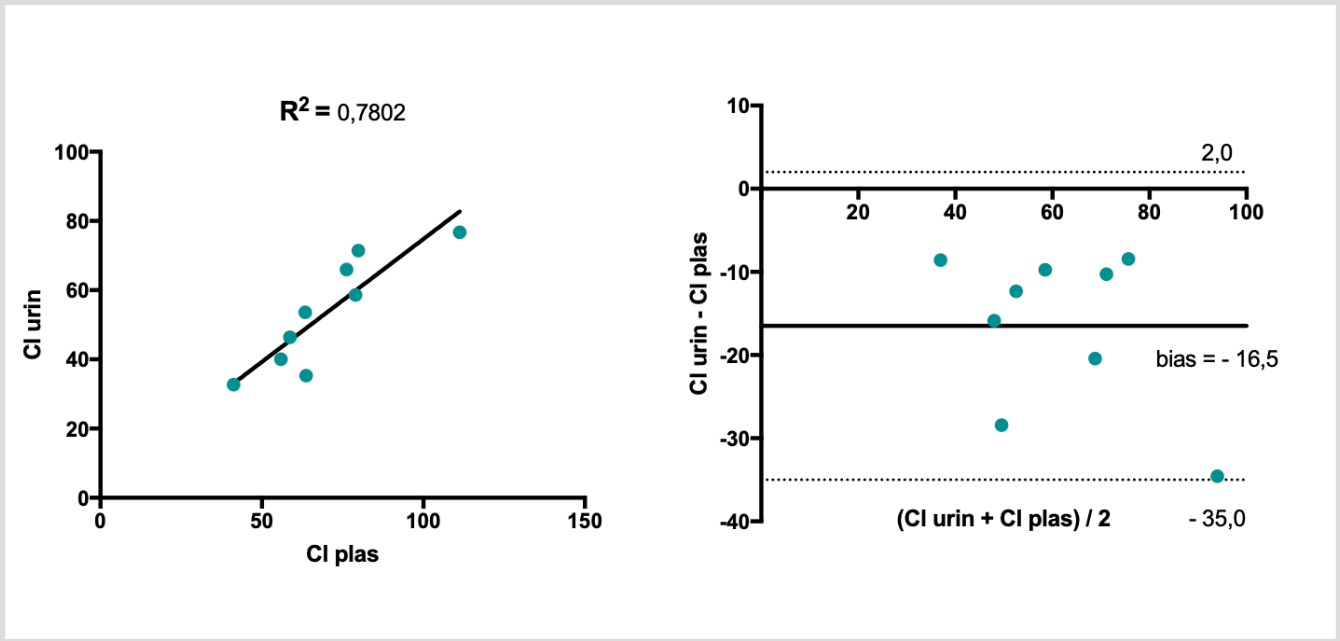
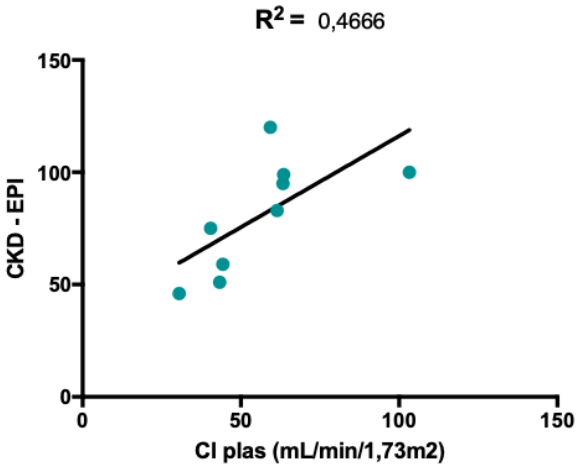
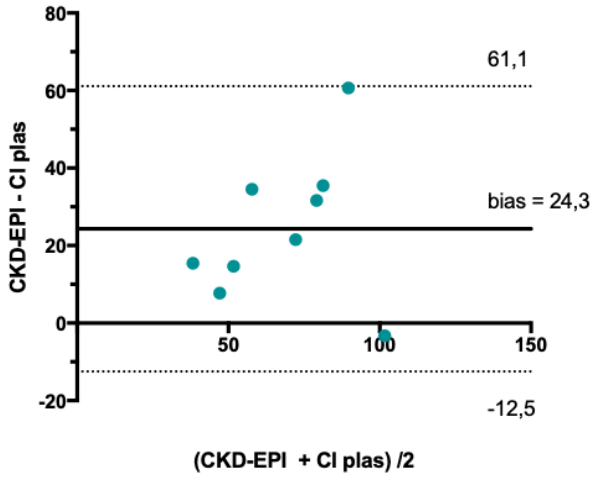
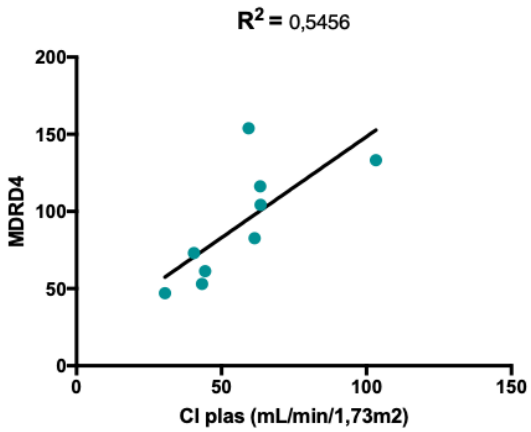
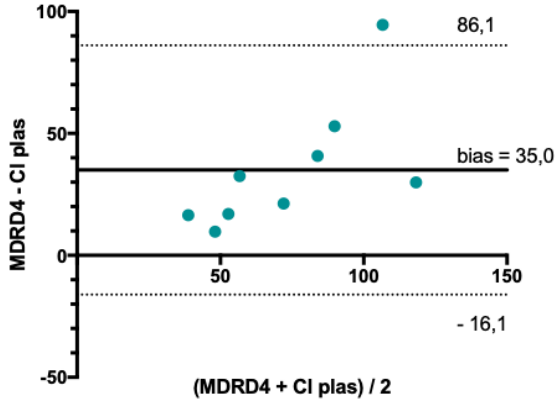


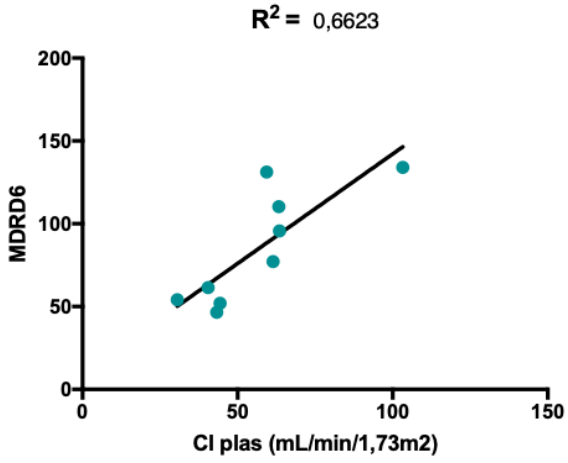
Figure 2. Comparison between plasma and urinary clearances of Iohexol by linear regression and Bland-Altman method. Clearances are expressed in mL/min.

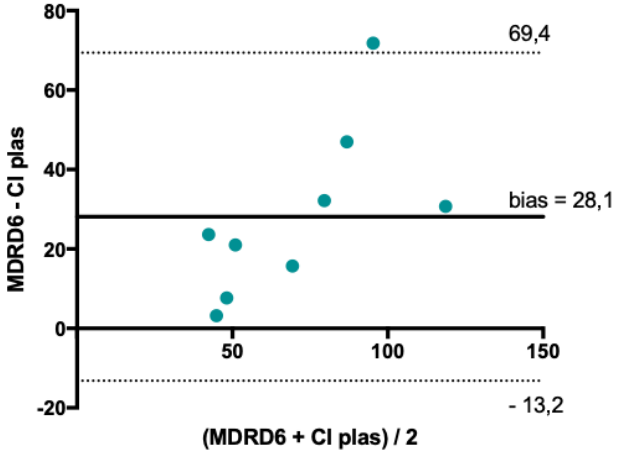












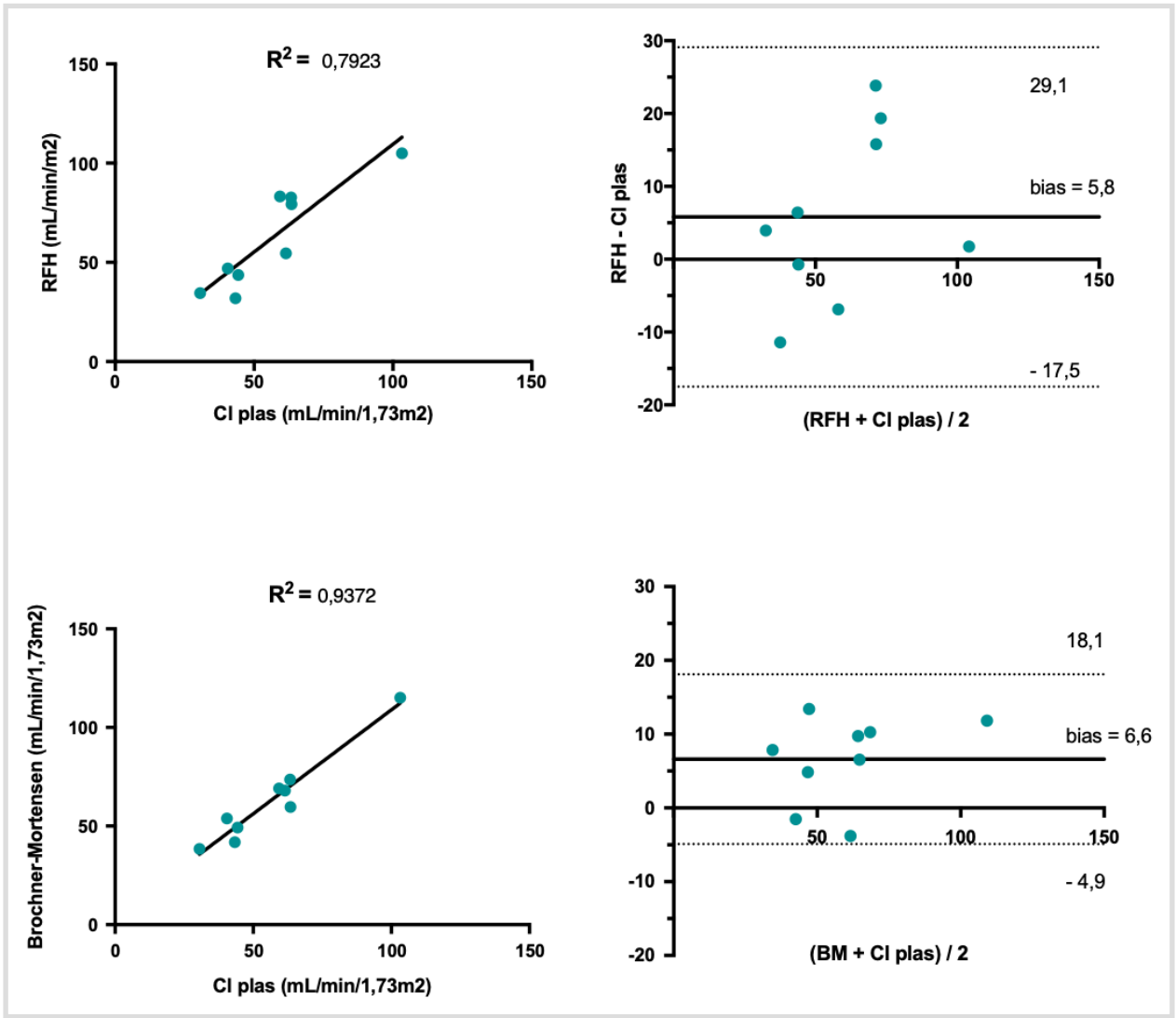


Figure 3. Comparisons between the measured plasma clearance of Iohexol and creatinine based equations by linear regression and Bland-Altman method.

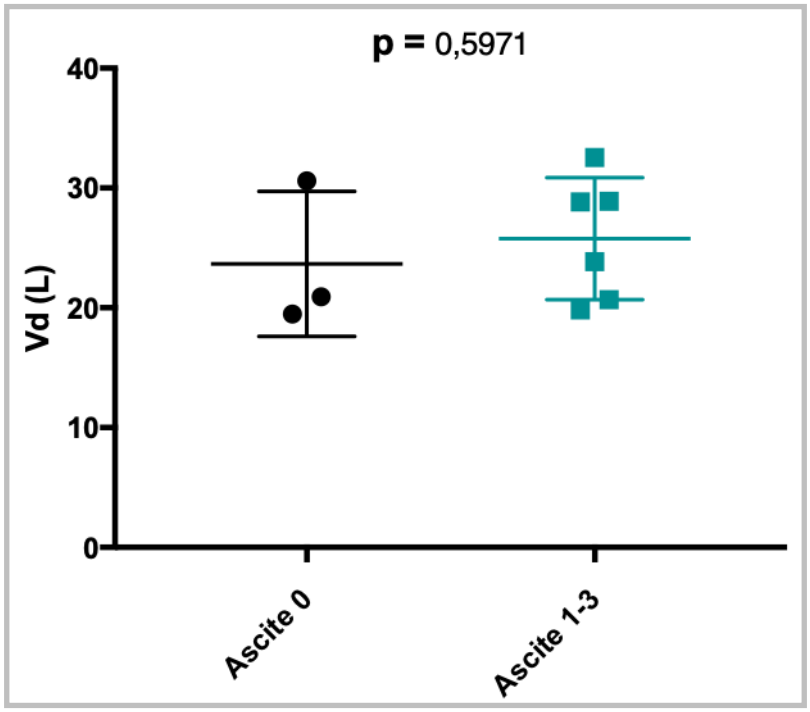


Figure 4. Comparison of the influence of ascite or not on the distribution volume.

IV. Discussion.

Impaired renal function is an independent prognostic factor in cirrhosis, particularly in decompensated patients. In addition, chronic renal impairment after liver transplantation (prevalence 15%) is also an independent factor of mortality [43]. It is so crucial to accurately evaluate GFR in this population.

In this study, we achieved our goal of describing, after a single injection, the evolution of iohexol kinetics in blood and urine obtained from rich samples collected over a 24 hour period.

To our knowledge, no study has so far described both the plasma and the urinary clearance of iohexol using complete rich pharmacokinetics (eleven samples) in a population of cirrhotic patients with different grades of ascites. In fact few data are available in the cirrhotic population [6], and methodological limitations in these studies warrant confirmation of the validity of iohexol for the measurement of GFR in this setting: period of blood collections too short, limited to 5 hours, while the product is not completely eliminated; second, very early plasma sampling reflecting the distribution phase are often lacking.

Urinary or plasma clearance of iohexol ?

Our data highlighted that urinary clearance of iohexol could not be directly measured as iohexol was not completely eliminated at H24 in the urine.

Urinary clearance is theorically the most physiologic and accurate method to measure the filtering capacity of the kidney especially in patients presenting a third sector like ascites and voluminous edema. Theoretically, urinary samples should be collected until the complete elimination of iohexol in urine if we want to conclude that plasma clearance is equal to urinary clearance.

Our first observation was that the urinary elimination of iohexol was very slow, all patients still having iohexol in urine in significant proportions at H24, regardless of the grade of ascites. Urinary elimination was between 60 and 90% and three patients only achieved 90% elimination of iohexol while none of our patients had an estimated GFR < 30 mL/min/1.73m2 at baseline. Therefore, we could not optimally measure the urinary clearance of iohexol in order to use it as a gold standard.

By observing the urinary elimination curves, three hypotheses can be advanced. The first would be that iohexol is not a good marker for GFR measurement. However, numerous publications showed that the clearance of iohexol gives similar results as inulin and 51-Cr-EDTA [8] [84]. Furthermore, it appears clearly as a reference tool in GFR measurement in the literature and plasma clearance is generally considered as accurate as urinary clearance [86] [87].

The second would be that samples should have been extended over more than 48 hours until the complete elimination of iohexol in the urine, which is difficult to do in routine practice. Most studies focusing on the urinary clearance of other markers such as inulin or CR EDTA demonstrated that they were systematically subject to the difficulties of urine collection that is rarely complete, and thus the interpretation of results was prone to errors. In our study, we encountered difficulties in obtaining full urine in patient number 1 and we had approximately sixty percent of the initially injected dose collected in urine at 24 hours. The third hypothesis is that iohexol is stored in a massive way in ascites or edema. Slack and al. were the first to analyze iohexol concentrations in the ascites of three patients at the same time as in the plasma. Iohexol equilibrated between blood and ascitic compartments after 4 h, but unfortunately, in this study blood and ascites samples were not available beyond 4 h, limiting the interpretation of the results. The authors also compared simultaneously GFR obtained with iohexol and chrome EDTA and showed a very small bias (-1.3 mL/min/1.73m2 (18 to.16)). The design of our study did not include a dosage of iohexol in ascites but we evaluated the ascites concentration of iohexol in one patient with grade 2-3 ascites who had benefited from a paracentesis, immediately after the collection of plasma and urine samples at H24: iohexol was present but at low concentration (14mg/L). Finally, the volume of distribution was not

impacted by the presence of ascites (Figure 4) within the estimated GFR of our patients who did not include values lower than 30 ml/min/1.73m2 or higher than 120 ml/min/1.73m2.

A strong point of this study is that we were able to collect all plasma samples which allowed us to very accurately describe the plasma concentration curves of Iohexol over time. Plasma elimination of iohexol in phase 2 (elimination phase) followed a constant linear or "first order" elimination and the amount of iohexol detected in blood at H24 was under or at the limit of detection (10ng/mL). Thus the half-life of iohexol, integrating clinical conditions and volume of distribution, did not vary significantly between ascites grades and between the presence or absence of ascites. This suggests that the specificities of cirrhotic patients, such as ascites, seem to have a minor impact on the plasma and urinary clearance of iohexol. We so calculated urinary clearance of iohexol from the plasma clearance, the total urinary excretion and the total injected dose of iohexol. However this proposal is only acceptable for the estimated values of GFR above 30 mL/min/1.73m² and under 120 mL/min/1.73m². In practice, a very precise evaluation of the true GFR is mainly useful in this value range and patients with an eGFR < 30mL/min/1.73m² are immediately considered for double transplantation [49].

We thus conclude that plasma clearance is probably accurate, less cumbersome and more feasible that urinary clearance of iohexol to measure GFR in cirrhotic patients taking into account the restrictions mentioned above. We therefore chose rich plasma clearance as a reference for the GFR assessment and for the different comparisons in this study.

Comparison of plasma clearance of iohexol and eGFR obtained with creatinine-based equations.

Taking the measured plasma clearance as a reference, we noticed that creatinine-based equations were, as expected, not relevant except perhaps for the RHF. An unexpected result was the good correlation between the measured plasma clearance and the GFR evaluated by the Brochner-Mortensen equation.

The coefficient of correlation between the complete plasma clearance of iohexol and the GFR estimated from serum creatinine derived formulas, was low. The coefficients ranged from 0.46 for CKD-EPI to 0.66 for MDRD6. This is in agreement with the data from the literature, concluding that MDRD-6 equation is probably, for lack of better, the most accurate formula. Indeed, it has been proposed as the reference according to the US consensus guidelines to identify candidates for simultaneous liver and kidney (SLK) transplantation [49]. RFH, which has been more recently described [75] seemed to be the most accurate creatinine-based equation to evaluate GFR in our population (R^2 = 0.79) [61] but showed individual bias from -10 to 25 mL/min/1.73m² which is quite large. Moreover, RFH has not been widely validated yet.

Comparison of plasma clearance of iohexol and GFR obtained by Brochner-Mortensen equation.

The approximation method (Brochner-Mortensen formula) for the calculation of the iohexol plasma clearance, largely used in the literature has never been applied in the cirrhotic population and should be tested.

We compared the measured iohexol plasma clearance to the GFR calculation with the one-pool correction equation for slope-intercept measurement of glomerular filtration rate (GFR) (Brochner-Mortensen equation) widely used in Europe but not studied in cirrhotic patients. This correction allows to avoid the first rapid exponential phase of the plasma clearance of iohexol corresponding to the distribution phase (very early samples). Thus, the formula uses a reduced number of plasma samples (on average 4 to 6 samples), obtained during the phase 2 (elimination) and gives in the literature a good evaluation of the GFR and has been validated outside the presence of a 3rd sector. In our study, the comparison between the measured plasma clearance of Iohexol (i.e., using the AUC formula) and the GFR estimated by the Brochner-Mortensen equation (R^2 = 0,93) showed a very good correlation, the lower individual bias (from -5 to 14 mL/min/1.73m²) and the less patient dispersion on the Bland Altman, for clearance values between 30 and 60 mL/min/1.73m².

Limitations.

The main one is the number of patients included. However the design of this study was pilot and descriptive, aiming to describe the behavior of iohexol in plasma and urine with rich kinetics, including early and late samples over a period of at least 24 hours, which had not been done yet in the cirrhotic population.

A recruitment bias is also related to gender. Patients with different grades of ascites were recruited prospectively and successively, with only men unfortunately. Although cirrhosis mainly affects men, women are equally affected by overestimation of GFR by serum creatinine based formulas, especially in the pre-transplant period. Women have relatively low serum creatinine levels and are therefore likely to be disadvantaged by graft allocation systems based on Meld's score. For illustration, after the adoption of the Meld's score in the allocation of liver transplants, the proportion of male transplant recipients increased, and the waiting list mortality rate for women was much higher than for men. Women scored higher when Cr was switched to mGFR in the MELD scoring system. It is therefore an essential precaution in ensuring equal access to liver transplantation between genders [54] [61] [88].

Finally, we noted that one patient experienced a Cmax superior to the iohexol measured at the end of the perfusion (patient #7). We explained it by an injection of iodine for a CT scan 15 days before. We so need to warn about the fact that patients with severe cirrhosis are likely to benefit from radiological examinations with iodine injection that may interfere with plasma iohexol clearance.

Perspectives : how to use plasma iohexol clearance routinely for all patients ?

The application of kinetics based on full plasma samples remains difficult in clinical practice as 11 samples are needed over a 24 hours period and this method can be reserved only for a small number of patients with a very complex profile

especially before liver transplantation.

Several issues may be relevant: first, test the Brochner-Mortensen equation in a larger cohort of cirrhotic patients, second, specifically build a new population PK model for cirrhotic patients that will allow a reduced number of plasma samples (3 or 4) in the same cohort. This model would have the advantage of reducing the number of samples required for the use of the Brochner-Mortensen equation.

In addition, it would seem that capillary sampling on filter paper are an alternative method to traditional blood samples, thus making it possible to avoid keeping patients in hospital. This method is already used in CKD paediatric populations and seems simpler while remaining accurate [89] [90].

Conclusion

Accurate evaluation of GFR in cirrhotic patients is a critical issue and the review of the literature shows that up to now no formula or direct method of measurement has emerged consensually (apart from the MDRD6 recommended in the pre- transplantation setting despite its limits).

Even if we were unable to measure the true urinary clearance of iohexol (which is supposed to be the gold standard) with a collection time of 24H given the obstacles described above, we finally concluded that the use of iohexol plasma clearance with rich samples is relevant.

The second important step will be to validate in a larger cohort of liver pre-transplant patients who are offered a rich plasma kinetics taken as a reference, the good preliminary results obtained with the Brochner-Mortensen equation. Finally, we will compare the relevance of these results with those of a population pharmacokinetic model needing a more reduced number of plasma samples, model built specifically for cirrhotic patients.

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Annexes

APPENDIX 1.

Judgment criteria.

Main :

Description of the pharmacological curves of plasma and urinary concentrations of iohexol as a function of time.

Secondary:

- Plasma clearance of iohexol obtained by non-compartmental analysis.
- Urinary clearance of iohexol obtained by non-compartmental analysis.
- Comparison of the renal clearance obtained from the plasma and urinary clearance of Iohexol respectively.
- Coefficients of linear correlations between measured plasma clearance of iohexol and DFG calculated by different methods. Bland Altman curves will also be drawn.
- Comparing the estimation of the iohexol clearance by the Brochner-Mortensen formula in our population.
- Evaluation of covariates by linear regression and scatter plots (continuous covariates) or Mann Whitney and box plots (categorical covariates) : grade of intensity of ascites, BMI, natrémie, albumin, biological stigmata of hepatic insufficiency or portal hypertension : bilirubin, albumin, INR, alkalin phosphatase, Child Pugh score, MELD score.

Study design :

Single center open prospective pilot study .

Study population :

All the patient included were taken care of in the Hepato-Gastroenterology department of the University Hospital of Limoges and presented an advanced liver disease with a potential indication for liver transplantation and had ascites or not.

1. Inclusion criteria :

- Patients with advanced liver disease, with potential indication for liver transplantation, with or without ascites:
- Absence of ascites: 3 patients.
- Grade 1 OMS (mild) ascites: only detectable by ultrasound examination (3 patients).
- Grade 2 (moderate) and Grade 3 OMS (wide) ascites: clinically significant ascites, causing moderate symmetrical distension of the abdomen (3 patients), or causing severe abdominal distension (3 patients).
- If possible, different representative GFR profiles were desired; however, this criterion was not decisive.
- Moreover, patients were over 18 years old, affiliated to a social security system, and gave their informed consent.

2. Exclusion criteria :

- Hypersensitivity to the active substance, to iodinated contrast agents, or any of the excipients.
- History of major immediate, or delayed cutaneous hypersensitivity to the injection of the iodinated contrast product (Omnipaque).
- Patients with thyrotoxicosis.
- Asthmatic patients.
- Patients with severe cardiovascular disease.

- Patients with central nervous system disorders, especially vascular.
- Patients with pheochromocytoma.
- Patients with myasthenia.
- Patients with sickle cell disease.
- Patients requiring anesthesia on the first day of sampling.
- Patients requiring iodinated contrast injection during hospitalization and in the previous two weeks. Gadolinium injections are not contraindicated.
- Patients under tutorship or curatorship or unable to give informed consent.
- Patients already included in another interventional research protocol or in exclusion period.
- Pregnant or lactating women.

Procedure :

As a first step, a complete oral information was delivered to the patient by the medical doctor, and the information notice given during a routine consultation in the Hepato-gastro-enterology department of Limoges University Hospital: « V-1 visit ».

In order to give the patient time to think about whether or not to participate to the study, the informed consent was signed during another second routine medical consultation: « V0 visit ». The inclusion and non-inclusion criteria were checked before any recruitment.

The visit V1 took place at CIC (Clinical Investigation Center) of the University Hospital center of Limoges. During this visit, clinical data (medical history, current treatments…) were collected and a clinical examination was performed and blood samples taken before the injection of iohexol.

Biological data collected before the injection of Iohexol were: serum creatinine, blood urea, blood electrolytes, alkaline reserve, cells blood count, INR, prothrombin time, blood calcium, blood phosphor, serum albumin and pre-albumin, ALAT, AST,

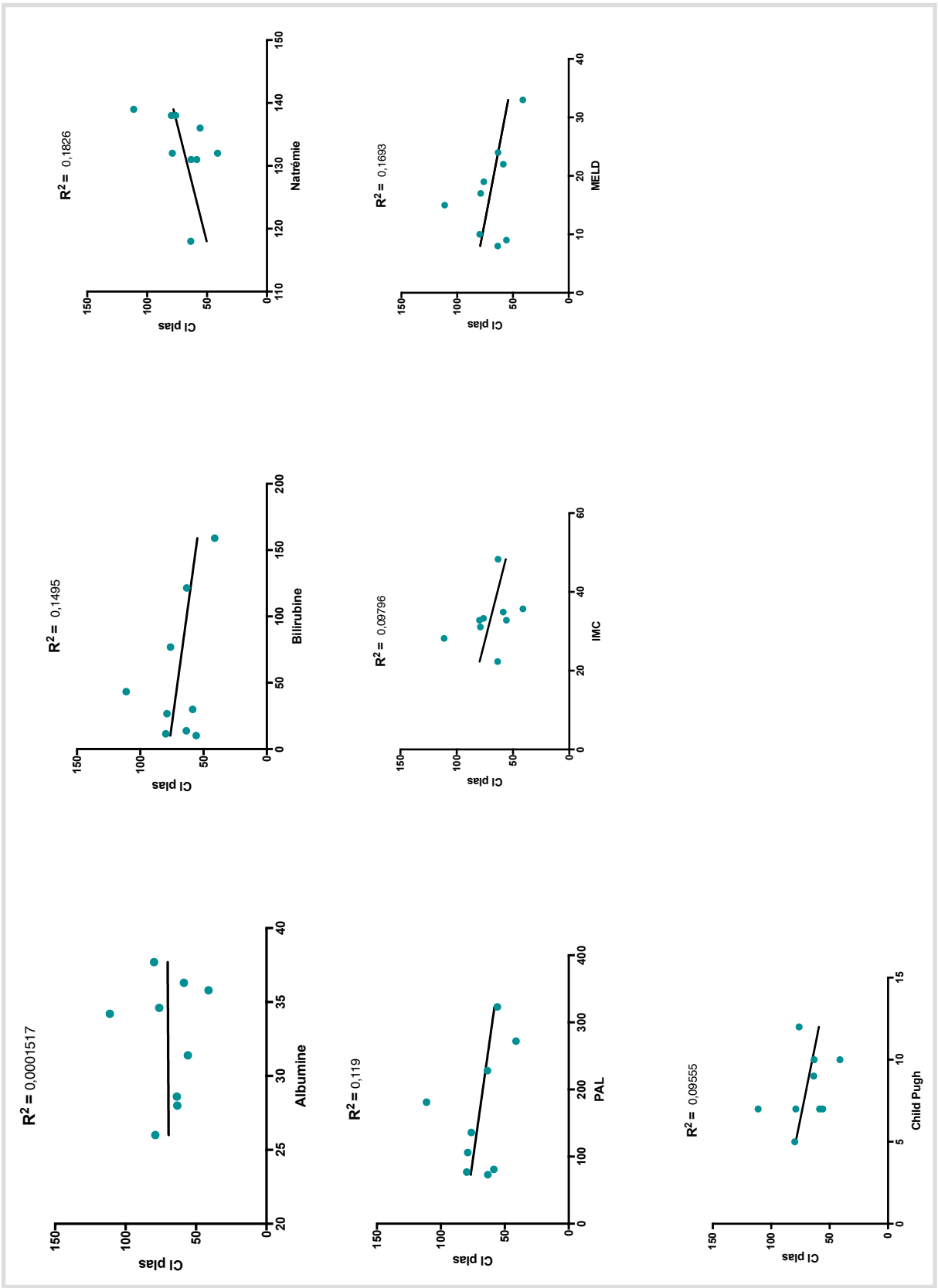
alkaline phosphatase, gamma-glutamyl-transferase, serum bilirubin, proteinuria, urine creatinine, urine electrolytes.

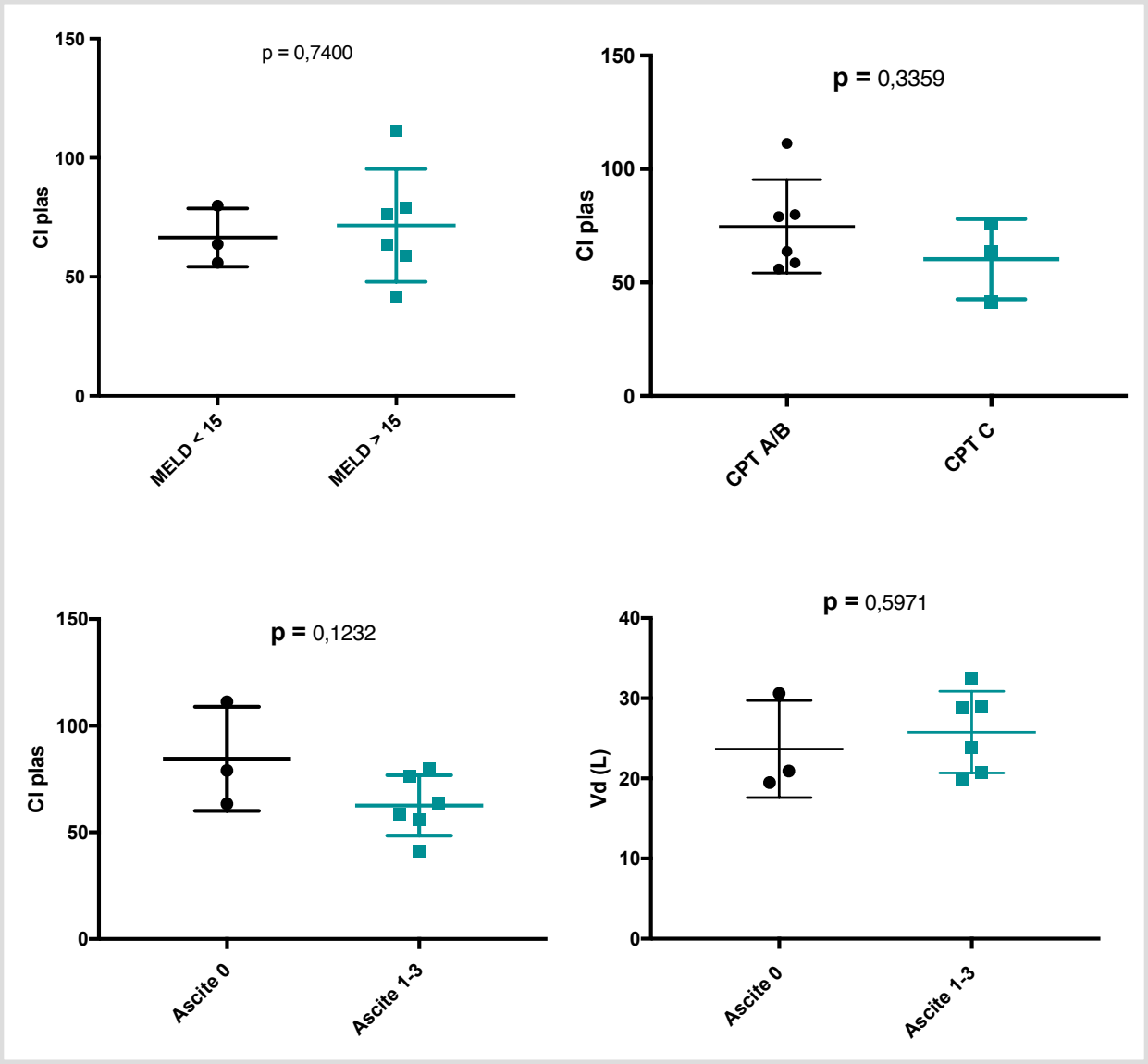
After injection of a bolus of 5mL of iohexol, blood samples were taken at given times for 24 hours. All the urinary samples were taken at each urination, with exact volume and time recording:

- Blood samples were collected in order to measure Iohexol blood concentration at 15, 30, 60, 90 minutes, 2, 3, 4, 6, 8, 12 and 24 hours (from S1 at 15 minutes to S11 at 24 hours.).
- Urine samples were collected in order to measure iohexol urine concentration at 4, 8, 12 and 24 hours.
- The patient's fluid intake was accounted. A systematic oral hydration of 300 ml of oral water, aiming to trigger diuresis was given at 3 and 6 hours (the hydration was adapted by the doctor according to the clinical condition of the patient).

Iohexol was measured in serum and urine samples with a very sensitive and specific method based on liquid chromatography coupled with tandem mass spectrometry in the Pharmacology unit of the University hospital of Limoges. The internal standard was ioversol and the limit of quantification was 10 ng/mL.

APPENDIX 2.





Serment d’Hippocrate

En présence des maîtres de cette école, de mes condisciples, je promets et je jure d’être fidèle aux lois de l’honneur et de la probité dans l’exercice de la médecine.

Je dispenserai mes soins sans distinction de race, de religion, d’idéologie ou de situation sociale.

Admis à l’intérieur des maisons, mes yeux ne verront pas ce qui s’y passe, ma langue taira les secrets qui me seront confiés et mon état ne servira pas à corrompre les moeurs ni à favoriser les crimes.

Je serai reconnaissant envers mes maîtres, et solidaire moralement de mes confrères. Conscient de mes responsabilités envers les patients, je continuerai à perfectionner mon savoir.

Si je remplis ce serment sans l’enfreindre, qu’il me soit donné de jouir de l’estime des hommes et de mes condisciples, si je le viole et que je me parjure, puissé-je avoir un sort contraire.

Description de l'évolution des concentrations plasmatiques et urinaires de l'iohexol dans une population de patients cirrhotiques. Etude pilote sur 9 patients.

Introduction : L'insuffisance rénale est un facteur pronostic indépendant de survie dans la cirrhose. La créatinine sérique et les équations associées surestiment significativement le débit de filtration glomérulaire (GFR). La mesure de la clairance urinaire par marqueurs directs reste le gold standard pour l'évaluation du GFR. Cette étude pilote prospective décrit les concentrations plasmatiques et urinaires du iohexol, au moyen de prélèvements riches sur 24 heures chez des patients cirrhotiques avec des grades d'ascites.

Méthode : Une dose d'iohexol (5 mL) a été injectée par voie intraveineuse et 11 concentrations plasmatiques ont été mesurées sur 24 heures. Parallèlement, la concentration urinaire du iohexol a été mesurée sur les urines recueillies toutes les 6 heures.

Résultats : Les courbes plasmatiques et urinaires de iohexol de nos 9 patients sont homogènes, avec cependant, une élimination urinaire incomplète à 24H. Dans les limites des clairances de notre population (> 30 mL/min/1.73m² et < 120 mL/min/1.73m²), la clairance plasmatique mesurée (mGFR), était adaptée pour évaluer le GFR. La mGFR médiane était de 59,4 mL/min/1,73 m2 [30,6-103,3]. Les formules basées sur la créatinine surévaluaient le mGFR. L'équation de Brochner-Mortensen montrait par contre une très bonne corrélation (R2 = 0,93) avec le mGFR.

Conclusion : Aujourd'hui, aucune stratégie n'a le consensus pour l'évaluation du GFR. Dans notre étude, l'utilisation de la clearance plasmatique du iohexol avec cinétique riche, semble un outil pertinent. Nos perspectives sont la construction dans une autre étude, d'un modèle pharmacocinétique de population applicable en clinique et la validation de l'équation de Brochner-Mortensen.

Mots-clés : cirrhose, taux de filtration glomérulaire, iohexol, pharmacocinétique, Brochner-Mortensen.

Description of the evolution of iohexol plasma and urinary concentrations in cirrhotic patients. Study pilot concerning 9 patients.

Introduction : Renal failure is an independent prognostic factor for survival in cirrhosis. Serum creatinine and associated equations significantly overestimate glomerular filtration rate (GFR). The measurement of urinary clearance (Clu) by direct markers remains the gold standard for the assessment of GFR. This prospective pilot study describes the plasma and urinary concentrations of iohexol, using 24H-rich samples in cirrhotic patients with the 3 ascites grades.

Method : One dose of iohexol (5 mL) was injected intravenously and 11 plasma concentrations were measured over 24 hours. In parallel, the urinary concentration of iohexol was measured in the urine collected every 6 hours.

Results : The plasma and urinary curves of iohexol in our 9 patients are homogeneous, with, however, incomplete urinary excretion at 24H. Within the clearance limits of our population (> 30 mL / min / 1.73m² and < 120 mL / min / 1.73m²), the measured rich plasma clearance (mGFR) was adapted to assess GFR. The median mGFR was 59.4 mL / min / 1.73 m2 [30.6-103.3]. Creatinine-based formulas overestimated mGFR. On the other hand, the Brochner-Mortensen equation showed a very good correlation (R2 = 0.93) with the mGFR

Conclusion : Today, no strategy has the consensus for the assessment of the GFR. In our study, the use of iohexol plasmatic clearance with rich kinetics, seems a relevant tool. Our perspectives are, in a future study, the construction of a clinically applicable population pharmacokinetic model and the validation of the Brochner-Mortensen equation.

Keywords : cirrhosis, glomerular filtration rate, iohexol, pharmacokinetic, Brochner-Mortensen.