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Masterthesis / Review

Pharmacokinetics of Acetaminophen in patients with obesity compared to non-obese and overweight patients: a prospective observational cohort study

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Abstract

Background: **Drug dosing in obese patients can be challenging due to changes in pharmacokinetics. It is unclear which body mass descriptors can be used to describe paracetamol pharmacokinetics in obese patients.**
Objectives: **we sought to identify which body mass descriptor correlated best to specific pharmacokinetic parameters regarding paracetamol: the volume of distribution (Vd) and drug clearance (Cl). Secondly we aimed to identify the differences in pharmacokinetic parameters in obese and non- obese patients.**
Design: **we conducted a prospective observational cohort study at Ghent University Hospital.**
Methods: **25 obese patients (BMI> 35kg/m²) and 7 non-obese patients (BMI< 30 kg/m²), all undergoing laparoscopic abdominal surgery, received a two-gram loading dose of paracetamol. Blood sampling was performed at set intervals. Pharmacokinetic analysis was performed using PKSolver. Descriptive statistics were performed on both patient groups. Correlation coefficients and simple linear regression were calculated for different body mass descriptors and pharmacokinetic parameters**
Results: **Non obese patients exhibited significantly higher maximum plasma concentrations of paracetamol. Obese patients exhibited significantly higher Vd and Cl. The order of correlation to Vd in our study was LBM>TBW>IBW. Correlation between drug clearance and TBW was significant. There was a weak positive correlation between LBM and drug clearance, which was not statistically significant. There was a near absent correlation between IBW and drug clearance.**
Conclusions: **When statistically significant, correlations and predictive values between weight descriptors and pharmacokinetic parameters observed in our study were in general weak to very weak. We might conclude that LBM can be used to calculate loading dose of paracetamol and TBW might be suited for calculation of maintenance doses of paracetamol. . Larger randomised controlled trials with less confounders (e.g. liver surgery) and with assessment of toxic metabolites and hepatotoxicity are needed to improve the clinical relevance of our findings.**

Keywords: **Pharmacokinetics, Obesity, Acetaminophen.**

Manuscript will be submitted at University Ghent as a thesis.
The study has been conducted in the University Hospital of Ghent and was approved by its ethics committee (Corneel Heymanslaan 10, 9000 Ghent, Belgium. Chairperson: Prof. Dr. R. Peleman. Protocol number BC-07469) Approval was obtained on April 20th 2020. Written informed consent was obtained from all included patients. Data was collected from the 1st of September 2020 until the 31st of March 2024.
This study was registered on www.clinicaltrials.gov, Unique Protocol ID: BC-07469

Introduction

Paracetamol is one of the most widely used analgesic agents in the world. It is well known for its anti-pyretic and analgesic properties. It is generally considered a safe and effective analgesic[1].

Paracetamol is the first step in the WHO (World Health Organisation) pain ladder and can be used as mono therapy in moderate to mild pain, and in combination with other analgesics in mild to severe pain. It is therefore frequently used in the perioperative period[2].

Its mechanism of action is not fully understood. It is believed to act on a centrally expressed COX (cyclooxygenase) enzyme. Flower and Vane demonstrated a potent inhibition of brain PGE2 (prostaglandin E2) synthesis compared to PGE2 in the spleen, by paracetamol. They estimated an 8x more potent inhibition of brain PGE2 synthesis than the PGE2 synthesis in the spleen. In vitro experiments showed however, that paracetamol had weak inhibitory activity on the COX-1 and -2 enzymes. This is contradictory to the in vivo findings of paracetamol inhibiting the formation of COX 1 and 2 enzyme products[1]. Chandrasekharan et al. proposed that paracetamol might act on the COX-3 enzyme, a variant of the COX-1 enzyme[3]. These are however theories, and other different mechanisms of action have been proposed, showing that the true mechanism of action is still somewhat of a mystery.

Paracetamol has a favourable safety profile and has little contra-indications and low potency to trigger allergic reactions. It can therefore be used in a large spectrum of patients. It is however important to note that these characteristics are true within the prescribed dosage of 4g/24h[4]. When taken in higher doses, paracetamol is known to cause liver toxicity due to its metabolites. One of these toxic metabolites is NAPQI (N-acetyl-p-benzoquinone imine). When paracetamol is taken in normal doses, the resulting NAPQI reacts with GSH (glutathione), thus causing a detoxification of this metabolite and its urinary excretion as cysteine and mercapturic acid conjugates. When this pathway is exhausted, the NAPQI concentration rises, resulting in the formation of protein adducts causing liver toxicity[4,5]. Paracetamol intoxication is a major cause of acute liver failure in developed countries such as the UK (United Kingdom) and the USA (United States of America)[5].

Paracetamol is a hydrophilic drug that binds plasma proteins to a small extent and has a plasma half-life of 1.5-3 hours. Most of the drug is eliminated by glucuronide and sulphate conjugation (55% and 30% respectively) in the liver, or as unchanged drug (5%). A small amount (5-15%) is oxidised to the before mentioned toxic metabolite NAPQI. In healthy subjects 85 to 95% of a therapeutic dose is excreted in the urine within 24 hours as free paracetamol, glucuronide and sulphate conjugates, mercapturic acid and cysteine[4,6].

Obesity is a chronic disease characterized by an abnormal or excessive fat accumulation. It is usually classified using the BMI (body mass index). The WHO defines obesity as having a BMI >30 kg/m2, a BMI >25 kg/m2 but < 30 kg/m2 is considered as being overweight[7,8]. It is important to note that the use of BMI does not reflect the same degree of adiposity across different people, nor does it correlate to a person's health. For example body constitution (fat mass), skeletal muscle mass, metabolic state and comorbidities should be considered when defining obesity as a disease[9]. BMI is however the most useful measure of defining obesity on a population level, as it is the same for both sexes and all ages in adults. Obesity is associated with a range of comorbidities such as diabetes, cardiovascular disease and several cancers. It is a risk factor for all-cause mortality. These patients therefore often require medication in order to mitigate the effects of these comorbidities. Drug dosing can be challenging in this patient group[7].

In our daily practice, drug dosing is often based on the actual weight of the patient. These dosing regimens usually originate from studies on healthy volunteers. We know that obese patients are underrepresented or excluded in these studies. It is therefore difficult to extrapolate these dosing regimens to obese patients[7]. For some drugs it might be useful to choose a different dosing scalar, not based on TBW (total body weight), as to not over or underdose the chosen drug.

One factor to consider is the lipophilic property of a drug and its effect on the volume of distribution. Lipophilic drugs like for example midazolam, distribute easily in the adipose tissue. In obese patients the volume of distribution will be greater, and the overall plasma concentration for a given dose will be lower. Lipophilic drugs often require a loading dose, more closely related to TBW, in order to achieve an effective steady state[7]. Once this steady state is reached, the clearance of the drug will define the pharmacokinetic properties of the drug. Since we know that paracetamol is a hydrophilic drug, and thus less affected by a given fat mass, TBW might not be the ideal dosing scalar.

Drug clearance is more related to LBM (lean body mass), which describes the weight of all 'non-fat' body components such as muscle, bones and organs, than TBW. It contributes to the majority

of drug clearance, since adipose tissue has little metabolic activity. When LBM increases, so does the clearance[10]. This is especially important when calculating maintenance doses. In obese patients, the excess adipose weight is generally correlated to a 20–40% increase in LBM11.

Combining these factors indicates the importance of knowing which body mass descriptor correlates best to the metabolism of the chosen drug. On the one hand, we want to avoid toxic dosing, on the other hand we want an effective and safe plasma concentration.

In general, there's a lack of sufficient data regarding how obesity affects the drug PK (pharmacokinetics). This deficiency largely stems from clinical studies that historically excluded individuals with obesity, leading to a scarcity of dosing information for this population.

The objectives of this study were to assess if PK of paracetamol is altered in obese as compared to non-obese adults. We sought to confirm, and elaborate on, previous work by Van Rongen et al.[12] and Abernethy et al.[13] Secondary objective includes assessment of correlations between different body mass descriptors and PK parameters.

Methods

This observational study, consisted of two patient groups. One group consists of obese patients (BMI> 30 kg/m²) undergoing laparoscopic abdominal surgery, the other group consists of non-obese patients (BMI< 30 kg/m²) undergoing laparoscopic abdominal surgery. This study was approved by the Ethics Committee of Ghent University Hospital on 20/04/2020, reference number: BC-07469.

Inclusion criteria were:

- Adult 18-70 years old.
- Obese or non-obese scheduled for laparoscopic surgery.
- Control group BMI ≥18.5 kg/m² and < 30 kg/m² or Obese group BMI > 30kg/m².
- ASA (American Society of Anaesthesiologists) Class I, II or III as assigned by the anesthesiologist.

Exclusion criteria were:

- Allergy or inability to tolerate paracetamol.
- Documented liver disease or liver enzymes > 3 times normal value.
- Kidney disease: eGFR (estimated Glomerular Filtration Rate) < 30ml/min.
- Participation in a clinical trial within the past 30 days.
- Chronic alcohol abuse or alcohol intake <72hrs.
- Gilbert-Meulengracht-syndroom.
- Chronic malnutrition.
- Intake of medication with influence on CYP2E1 (Cytochrome P450 2E1) or UGT (UDP-glucuronosyltransferase).
- Pregnancy.

Patient consent was obtained preoperatively through a pre-operative consultation or through informative telephone contact and subsequent e-mail.

All patients had laboratory records <3 months old including liver enzymes, bilirubine, coagulation tests and full blood counts obtained via preoperative blood sampling in the hospital (University Hospital Gent) or via the collaborative care platform 'COZO'.

Standard of care pain management in our hospital for laparoscopic surgery follows the WHO pain ladder, starting with paracetamol 4g/day with six hour intervals, supplemented by NSAIDs (Non-steroidal anti-inflammatory drugs) (e.g. ibuprofen) and opioids (weak and/or strong, e.g. tramadol or oxycodone) if necessary.

All patients received a two gram loading dose of paracetamol based on earlier work by Juhl et al.14 and Gregoire et al.[15] Doses were administered intraoperatively via a volumetric pump over a 15min period. After this, the two groups both received the standard dose of one gram of paracetamol at six hour intervals.

Both groups received the same anesthetic care intraoperatively consisting of vapor anesthesia using sevoflurane, combined with a short acting opioid, in this case remifentanil. Rocuronium was used as a muscle relaxant, reversal of neuromuscular block was achieved by administration of sugammadex. BISTM (Bispectral IndexTM) monitoring ensured an adequate depth of anesthesia.

Postoperative pain management orders outside of paracetamol were identical in both groups, and consisted of the before mentioned pain protocol. A rescue PCIA (Patient Controlled Intravenous Analgesia) pump with piritramide, was given to each patient in both treatment groups.

Blood sampling (lithium heparine) was conducted at set intervals after the infusion of paracetamol. These intervals were at 0 min, the baseline; 15min, 30min, 45min, 60min, 90min, 120min, 180min, 240min, 300min and 360min. Blood sampling was performed using a dedicated IV (intravenous) line preferably placed in the patients forearm, opposite to the site of paracetamol infusion. The blood samples were stored in a refrigerator and send to the laboratory the same day. Samples were carefully labelled with correct timestamps and pseudonymised patient numbering.

PK analysis was performed using PKSolver, a freely available menu-driven add-in program for Microsoft Excel. The program includes different modules for PK and PD (Pharmacodynamics) analysis. In this investigation we used the IV bolus non compartmental analysis module.

LBM was calculated by using an online calculator using the Janmahasatian formula. IBW (Ideal Body Weight) was calculated using an online calculator utilising the Devine formula.

Statistical analysis was performed using IBM® SPSS® Statistics 29.0.

Statistical analysis of patient characteristics and pharmacokinetic parameters was performed using the Student's T test.

Scatter plots were made in SPSS, to see the distribution of our observed data. Normality was tested using the Shapiro-Wilk Test since our sample size was less than 50. Correlation between three body mass descriptors, drug clearance and volume of distribution was objectified using the Pearson correlation coefficient and performing simple linear regression. These three descriptors were: TBW, IBW and LBM.

Results

32 patients were recruited and enrolled in the study. Seven patients were non-obese, consisting of five females and two males. 25 patients were obese, 12 participants were female and 13 were male.

Mean TBW in the non-obese group was 75.57kg ± 9.78. The mean TBW in the obese group was 123,73kg ± 15,04. Mean BMI was 25,8 ± 2,66 in the non-obese group, with the mean BMI in the obese group being 41,3 ± 4,51. Extensive patient characteristics are noted in Table I.

Distribution of parameters

P-values of tested parameters were all >0.05 using the Shapiro-Wilk test, confirming normality of distribution.

Table I. — Patient characteristics are expressed as mean (SD) or number of patients.

	Obese	Non-obese
Male	13 (52%)	5 (71%)
Female	12 (48%)	2 (29%)
Age (years)	43,76 (15,09)	49,71 (13,92)
Smoker	4 (16%)	4 (57%)
ASA-score	2,32 (0,56)	2
BMI	41,3 (4,51)	25,8 (2,66)
TBW (kg)	123,73 (15,04)	75,57 (9,78)
IBW (kg)	168 (9,52)	63,86 (9,48)
LBM (kg)	67,69 (11,08)	49,74 (9,68)

SD (Standard Deviation); ASA (American Society of Anaesthesiologists); BMI (Body Mass Index); TBW (Total Body Weight); IBW (Ideal Body Weight); LBM (Lean Body Mass).

PK parameters

Non-obese patients exhibited a higher mean Cmax (maximum plasma concentration) of paracetamol (74.79 mg/L ± 12.37) compared to obese patients (58.71 mg/L ± 18.45). This difference was statistically significant (t(30) = 2.16, p= 0.039). Figures 7 and 8 show the plasma concentrations over time in both groups.

The mean Vd (volume of distribution) was significantly lower in non-obese participants (36.91L ± 7.34) compared to obese patients (54.16L, ± 10.98), (t(30) = -3,90, p < .001). These findings are in line with the significantly higher plasma concentrations in non-obese patients.

Non-obese patients had a mean drug clearance of 0.18 L/min ± 0.04, whereas obese patients had a significantly higher mean clearance of 0.28 L/min ± 0.07, (t(30) = -3,55, p < .001), suggesting differences in drug metabolism between the two groups (Table II).

Correlation

In our results we observed that LBM correlated the strongest to Vd (r(30) = .736, p < .001). Being a statistically significant predictor for Vd (R2 =0,542, F= 35,5, p < .001), Fig 1. TBW showed the second strongest correlation with Vd (r(30) = .633, p < .001), being the second strongest predictor for Vd (R2 =0,401, F= 20,1, p < .001), Fig 2. We observed the weakest correlation between IBW and Vd (r(30) = .490, p= .004), showing that IBW was the weakest predictor of Vd (R2 =0,241, F= 9,5, p= .004), Fig 3.

There was a moderate positive correlation between LBM and drug clearance, which was not statistically significant (r(30) = .320, p=.075). LBM was not a statistically significant predictor of drug clearance (R2 =0,102, F= 3,4, p = .075), Fig 4. Similarly there was a near absent correlation between IBW and drug clearance, which was not statistically significant (r(30) = .053, p = .774). Linear regression analysis clearly showed no predictive value of IBW regarding drug clearance

Table II. — PK parameters are expressed as mean (SD).

	Obese	Non-obese	P value*
Cmax (mg/L)	58,71 (18,45)	74,79 (12,37)	.039
Vd (L)	54,16 (10,98)	36,91 (7,34)	<.001
Drug clearance (L/min)	0,28 (,07)	0,18 (,04)	.001

SD (Standard Deviation); Cmax (Maximum plasma concentration); Vd (Volume of distribution);*P value from Independent Student's T-test.

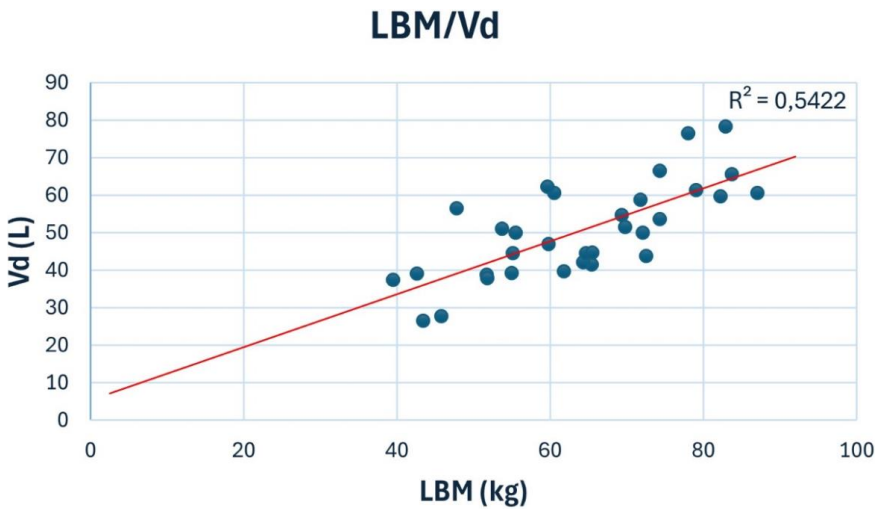

Fig. 1

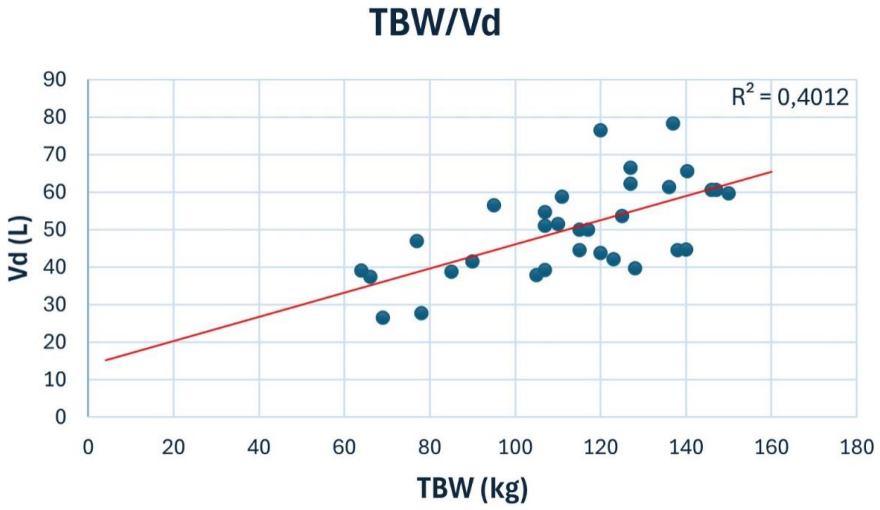

Fig. 2

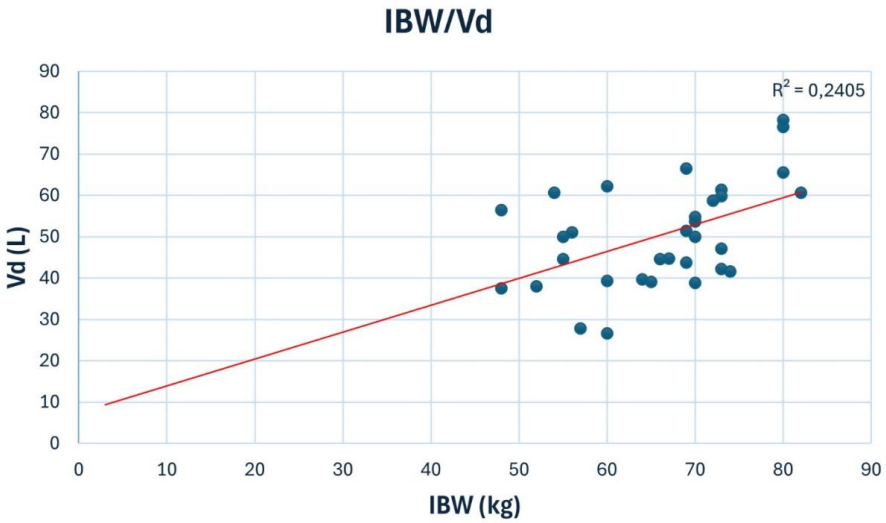

Fig. 3

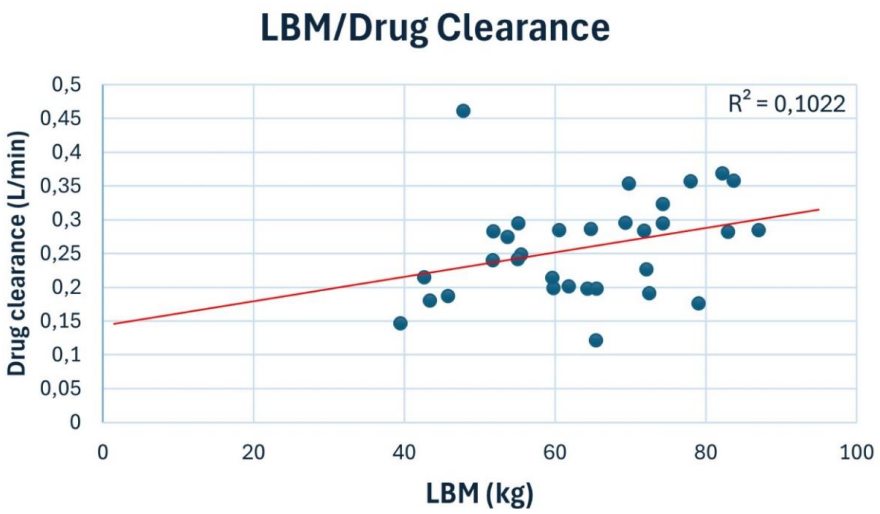

Fig. 4

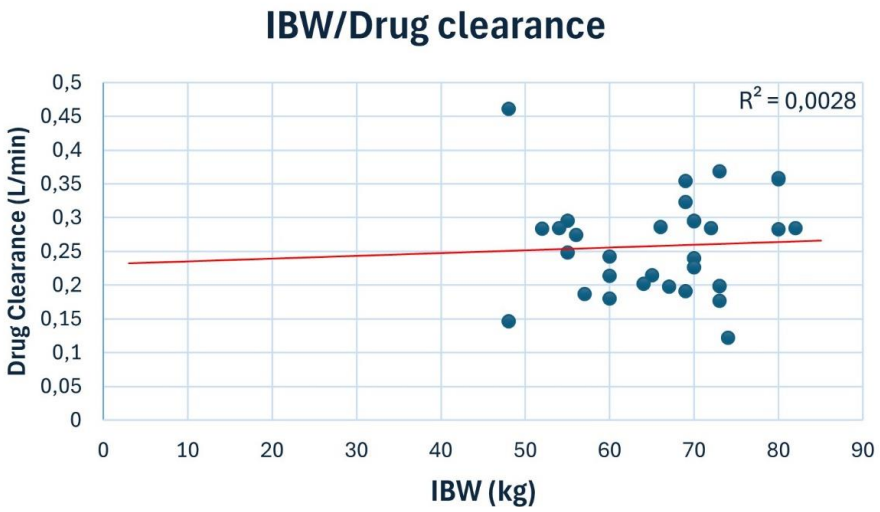

Fig. 5

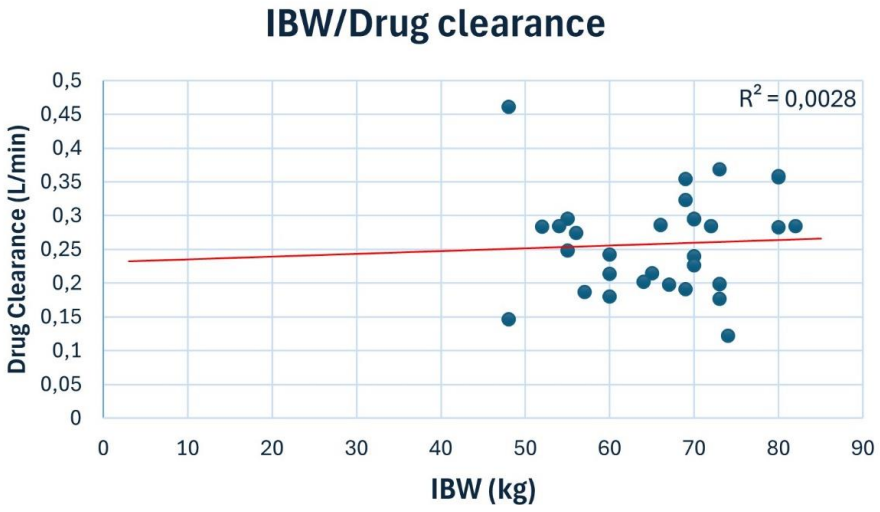

Fig. 6

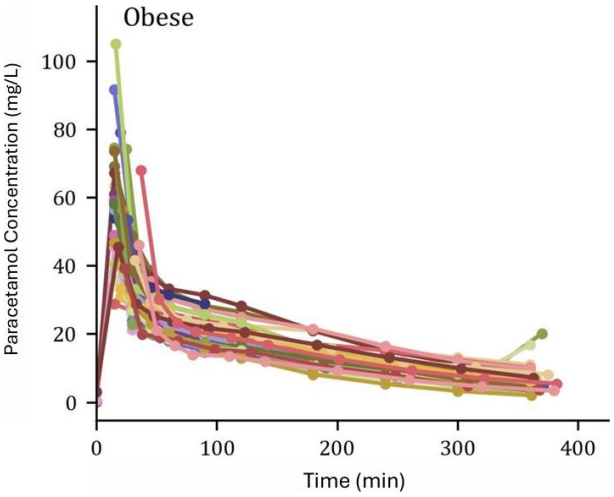

Fig. 7

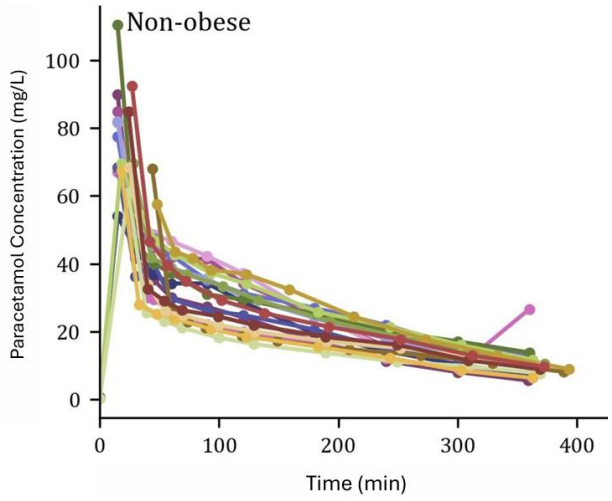

Fig. 8

(R2 =0,003, F= 0,1, p = .774), Fig 5. Only TBW showed a weak, but statistically significant correlation with drug clearance (r(30) = .366, p= .04). With regards to regression, TBW was a weak predictor of drug clearance (R2 =0,134, F= 4,75, p= .04), Fig 6.

Discussion

Our study produced some conflicting data. Most importantly our data showed that there were no significant correlations between drug clearance and body mass descriptors except for TBW. Drug clearance is an important factor in the calculation of a maintenance dose and correlating steady state. TBW might be the body mass descriptor to utilise in calculating the maintenance dose of paracetamol. This finding may come as a surprise since adipose tissue has little metabolic activity. The finding of a moderate positive correlation between LBM and drug clearance, is more in line with physiological mechanisms, where the LBM contains more of the metabolic functions of the body[10]. The increased drug clearance in obese patients can be linked to an increase in hepatic blood flow and increased liver volume. Some studies show an increased glucuronide-conjugation in obese patients with a significant elevation of glucuronide clearance of paracetamol correlated with an increase in LBM[16]. A study by Van Rongen et al. confirmed these results and showed that despite the increased clearance and reaching therapeutic plasma concentrations, one must also consider the similar increase in (possibly) toxic metabolites. Obesity does indeed lead to lower paracetamol plasma concentrations, but with earlier and higher peak concentrations of the metabolites related to NAPQI production. A higher dosing of paracetamol in the obese could therefore be limited by these metabolites[12]. In our study we saw significantly lower peak plasma concentrations in the obese patient group, in line with these findings. Paracetamol dosing should therefore not only be viewed by its (therapeutic) plasma concentrations but also bearing its metabolism in mind. Future research on this topic might therefore be more clinically relevant when considering the PK characteristics of the drug, its associated metabolites and their possible role in toxicity. Related to this finding is the significantly higher Cmax in the non-obese patient group. The clinical relevance of this finding is difficult to interpret without additional pharmacodynamic and toxicological data. A previous study by Juhl et al. has demonstrated increased analgesic effect with longer duration of this analgetic effect in patients receiving 2g of IV paracetamol[14]. The authors did however not measure the plasma concentrations of metabolites, but instead focused on laboratory values of liver enzymes. Further research, incorporating these toxic metabolites might be a more useful way to identify the safety of higher dosing of paracetamol in obese and non-obese individuals.

Vd is most affected by an increase in adipose tissue when lipophilic drugs are considered. We know that hydrophilic drugs such as paracetamol mainly diffuse in LBW and slightly in the water part of the fat tissue[16]. We would therefore expect that LBM would be the body mass descriptor correlating best to the Vd. Our findings indeed show the strongest correlation between LBM and Vd. It is however a weak correlation with little difference compared to the other studied descriptors. This is in line with earlier findings that show that determining the best body mass descriptor in relation to Vd is not clear cut and that the clinical significance of the use of LBM is unclear[10,11]. Important to note is that the Vd does not linearly increase with LBM according to a

study by Van Rongen[12]. More research is needed to best tailor the dosage in morbidly and super obese patients. When considering our findings, we might preferably use LBM for calculating the loading dose of paracetamol in patients.

This study has limitations. Our small sample size, with a vast array of patient characteristics and types of surgery could be considered as one. Secondly, patients undergoing laparoscopic cholecystectomy, might have altered metabolism and liver function, not always detected in preoperative laboratory testing[17]. Thirdly, we might expect more patients with obesity related NAFLD (Non-alcoholic fatty liver disease) in the obese group, influencing liver function and metabolism[16,18]. This makes formulating conclusions on this heterogenous patient group difficult. Further research with a narrower patient selection could resolve this issue. Fourthly, we did not yet reach equal gender and patient group distribution in this preliminary analysis.

Finally, including overweight patients (BMI >25kg/m2 to <30kg/m2) in the non-obese cohort might have influenced our findings since patients in the overweight category might also exhibit the same metabolic changes observed in obese patients, contributing to skewed results. Excluding overweight patients in a non-obese cohort might be preferred in future research.

Conclusion

Earlier literature showed that the Vd of the hydrophilic drug paracetamol correlated best to LBM. We indeed saw the strongest correlation between LBM and Vd in our study. This was however a weak correlation.

When considering drug clearance, we expected a similar strongest correlation with LBM. Our data however, suggested that drug clearance in our patient groups correlated best to TBW. This is in contrast with earlier findings.

Vd and drug clearance were significantly higher in the obese patient group, with the correlating Cmax being significantly higher in the non-obese group, suggesting differences in pharmacokinetics. Further research should be performed on larger patient groups, with less possible confounders (e.g. liver surgery), and specifically with toxic metabolites in mind, in order to improve the clinical relevance of these findings.

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