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Evaluation of total body weight and body mass index cut-offs for increased cefazolin dose for surgical prophylaxis

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ABSTRACT

French and American guidelines recommend increased dosage regimens of cefazolin (CFZ) for surgical prophylaxis in patients with a body mass index (BMI) ≥ 35 kg/m^2 or with a total body weight (TBW) ≥ 120 kg. The objective of this study was to evaluate the accuracy of these cut-offs in identifying patients who require CFZ dose adjustment. A pharmacokinetic study was conducted in patients of varying TBW and BMI who received 2 g of CFZ intravenously for prophylaxis prior to digestive surgery. Adequacy of therapy, defined as a serum concentration of unbound CFZ (*f*CFZ) ≥ 4 mg/L, was evaluated 180 min (T_{180}) and 240 min (T_{240}) after the start of CFZ infusion. Possible factors associated with insufficient *f*CFZ levels were also assessed. A *P*-value of <0.05 was considered statistically significant. A total of 63 patients were included in the study, categorised according to BMI (<35 kg/m^2, 20 patients; and ≥35 kg/m^2, 43 patients) and TBW (<120 kg, 41 patients; and ≥120 kg, 22 patients). All patients had adequate drug levels at T_{180} but only 40/63 patients (63%) had adequate levels at T_{240}. At T_{240}, therapy was adequate in 15/20 patients (75%) and 25/43 patients (58%) with BMI <35 kg/m^2 and ≥35 kg/m^2, respectively ($P = 0.20$), and in 28/41 patients (68%) and 12/22 patients (55%) with TBW <120 kg and ≥120 kg, respectively ($P = 0.28$). No factor associated with insufficient *f*CFZ was identified. In conclusion, current BMI and TBW cut-offs are poor indicators of which patients could benefit from increased CFZ dosage regimens.

1. Introduction

A recent survey in the USA reported that surgical site infections (SSIs) are among the most frequent type (22%) of healthcare-associated infections [1]. Such infections are associated with increased healthcare costs, increased risk of hospital re-admission and increased mortality in the 30-day period following surgery [2]. Obesity, defined as a body mass index (BMI) ≥ 30 kg/m^2, is one of the risk factors for developing these post-operative infections [3–6].

Insufficient serum and tissue concentrations of antibiotics used for surgical prophylaxis are one of the explanations given for the increased risk of infection observed in obese individuals. Cefazolin (CFZ), a hydrophilic, strongly protein-bound (80%), first-generation cephalosporin eliminated primarily by the kidneys is most often the drug of choice for prophylaxis [7]. Despite an estimated 600 million obese adults worldwide [8] and a significant increase in the number of obese surgical patients over the past 20 years [9,10], the optimal prophylactic dose of CFZ for obese individuals has not yet been established.

Recent guidelines on antibiotic use for surgical prophylaxis provide some recommendations on CFZ dosage regimens for obese individuals. However, these recommendations are based on expert opinion and are supported by limited data showing that the pharmacokinetics of CFZ is altered in obese patients. Serum and/or tissue concentrations of CFZ are lower in obese compared with non-obese patients after administering the same antibiotic dose [11–14]. The French Infectious Diseases Society (SPILF) and the French Society of Anaesthesia and Resuscitation (SFAR) have, since 2010, recommended an increased dosage regimen of CFZ in heavier patients: 2 g for patients with a BMI < 35 kg/m^2 and 4 g for those with a

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BMI ≥ 35 kg/m² [15]. Since 2013, the Infectious Diseases Society of America (IDSA) has recommended giving 2 g of CFZ to patients with a total body weight (TBW) of <120 kg and 3 g to those weighing ≥120 kg. The dose is to be repeated after 4 h if surgery is ongoing and the patient does not have renal insufficiency [7].

Since the publication of these guidelines, only two studies have evaluated the clinical relevance of these recommendations in non-pregnant adults. One retrospective clinical study performed in a cohort of 198 surgical patients concluded that there was little evidence for increasing CFZ dosage regimens in obese patients because SSI rates were similar in obese and non-obese patients. However, the study was underpowered to show any differences and the cohorts were not stratified by the recommended cut-offs, as the mean TBW and BMI values for the two groups were 90 kg vs. 110 kg and 27 kg/m² vs. 35 kg/m², respectively [16]. Another pharmacokinetic (PK) study on CFZ in eight morbidly obese and seven non-obese individuals confirmed significant PK changes in morbidly obese patients, attributed to changes in TBW; the authors recommended using 3 g of CFZ for prophylaxis in morbidly obese patients [17]. However, the optimal BMI or TBW cut-off at which the CFZ dosage regimen should be increased was not identified.

The objective of this study was therefore to evaluate whether the proposed BMI and/or TBW cut-offs could accurately identify which patients require CFZ dose adjustment for surgical prophylaxis.

2. Patients and methods

2.1. Study design and patient selection

This prospective study was performed at Erasme Hospital, the academic hospital of the Université Libre de Bruxelles in Brussels, Belgium. All consecutive, consenting patients undergoing gastric bypass surgery, partial hepatectomy, duodenopancreatectomy or colectomy between October 2011 and October 2013 were included. These surgical procedures were selected because only patients who would need central lines during surgery could be included in the study and, in our institution, central venous catheters are not inserted for uncomplicated routine surgical interventions. At 30–60 min prior to surgery, all patients receive a 2 g intravenous (i.v.) dose of CFZ over 30 min for surgical prophylaxis. Patients were excluded from the study if they were pregnant or lactating, were <18 years old, had a known allergy to β-lactams, had a serum creatinine level >1.3 mg/dL, had peripheral oedema and/or had pre-operative signs of hepatic dysfunction (total bilirubin levels > 2.5 mg/dL, altered coagulation and/or albuminaemia < 32 g/L). Patients were excluded from the analysis if blood loss was >1 L during the sampling period of the study because significant blood loss has been associated with antibiotic PK changes [7,18].

To ensure a similar distribution of patients of different sizes, patients were stratified into different groups of BMI as they were enrolled: <30 kg/m², 30–39 kg/m² and ≥40 kg/m². Patient enrolment for each group was stopped when a minimum of 10 patients and a maximum of 30 patients had been included, or when the 2-year study period came to an end. For data analysis, patients were then categorised into both a BMI group (<35 kg/m² or ≥35 kg/m²) and a TBW group (<120 kg or ≥120 kg).

2.2. Data collection

Demographic data and co-morbidities were recorded. Patients were weighed on the day prior to surgery and their height and abdominal circumference were measured. The BMI was calculated using the following equation: weight (kg)/height (m²) [19]. Blood loss and volume of fluid administered during the 180 min after the start of the CFZ infusion were recorded. The occurrence of a SSI (as defined by the IDSA) [7] in the 30 days following the surgical procedure was recorded.

2.3. Serum samples during the surgical procedure

A central venous line was placed in all patients after induction of anaesthesia for surgery. Two blood samples (3 mL) were collected from the central line into polypropylene Venosafe® VF-054SAS serum tubes (Terumo, Leuven, Belgium) immediately prior to the CFZ infusion (T_0). One serum sample was collected at each of the following time points after the start of the CFZ infusion: 30 min (T_{30}); 60 min (T_{60}); 120 min (T_{120}); and 180 min (T_{180}). A final serum sample was taken at the end of the surgical procedure, except in patients undergoing partial hepatectomy. In these patients, sampling was stopped at T_{180}, before portal triad clamping and resection of the liver, to limit any potential PK changes associated with this type of surgery [20].

After each serum sampling, the catheter was purged with 10 mL of physiological serum. Exact sampling times were recorded. Samples were kept on ice and were sent directly to the clinical chemistry laboratory where they were centrifuged at 3000 rpm at 4 °C for 10 min before the supernatant was removed and then frozen at –80 °C to be analysed at a later date.

2.4. Measurement of cefazolin serum concentrations

A modified liquid chromatography–ultraviolet spectrophotometry technique was used to measure CFZ levels [21]. Analyses were conducted using an ACQUITY UPLC® (ultra performance liquid chromatography) system (Waters, Zellik, Belgium). The UPLC separation was carried out at 50 °C. The mobile phase consisting of acetonitrile and phosphate buffer (0.3% phosphate buffer/acetonitrile 98:2 v/v) (pH 5.0) was delivered at a flow rate of 0.6 mL/min. Six-level aqueous calibrators with concentrations of CFZ ranging from 1 mg/L to 150 mg/L were employed for quantification of total CFZ (*t*CFZ) and unbound (free) CFZ (*f*CFZ) serum concentrations. For *t*CFZ, 50 μL of the internal standard solution (cefoperazone 200 mg/L) was added to 200 μL of thawed sample, precipitation of serum proteins was performed by adding 800 μL of methanol, and the mixture was then vortex-mixed. Following evaporation under nitrogen, the residue was reconstituted with 300 μL of phosphate buffer and was vortex-mixed for UPLC analysis. For *f*CFZ, 500 μL of sample was subjected to filtration using a Centrifree® device (Merck Millipore, Overijse, Belgium) by centrifugation (two times at 4000 rpm) for 10 min at 4 °C. The filtrate was mixed with 25 μL of the internal standard solution and was used as such for UPLC analysis. The coefficients of variation for CFZ were <6.7% for mean concentrations varying from 19.8 mg/L to 102 mg/L.

2.5. Measurement of renal function

Pre-operative serum creatinine levels were recorded. Serum and urinary creatinine were measured using a Hitachi Modular P analyser based on the Jaffé method [22] on a serum and urine sample (from a 24-h collect) taken on the day following the surgical intervention. Creatinine clearance (CL_{Cr}) was calculated using the following equation: $CL_{Cr,24h}$ (mL/min) = [urine creatinine (mg/dL) × volume (mL)]/[plasma creatinine concentration on the day of the urine collect (mg/dL) × 1440 min].

2.6. Free fatty acid and plasma protein determination

Serum albumin, α-1-acid glycoprotein, total proteins and free fatty acids were measured on the T_0 serum sample using a Hitachi Modular analyser (Roche Diagnostics, Vilvoorde, Belgium) according to the manufacturer's instructions.