ORIGINAL ARTICLE

Use of the parenteral antibiotic Ertapenem as short term prophylaxis in bariatric surgery: a pharmacokinetic-pharmacodynamic study in class III obese female patients

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ABSTRACT

Background. The objective of this study was to determine the pharmacokinetics-pharmacodynamics (PK/PD) of Ertapenem in extremely obese female patients (Body Mass Index [BMI] ≥40 kg/m^2) undergoing bariatric surgery.
Methods. Ten patients received 1 g intravenous Ertapenem 0.5 h prior to surgery as short term prophylaxis. Serum Ertapenem concentrations were determined at baseline, at the end of infusion (30 minutes), then at 1, 2, 4, 8, 12 and 24 hours postinfusion. In patients in whom a liver biopsy was necessitated by clinical need, Ertapenem liver concentrations were determined through intraoperative biopsies at 1 and 2 h postadministration. Peritoneal Ertapenem concentrations were determined in drainage fluid samples collected during the 4-8, 8-12, and 12-24 h intervals after Ertapenem administration. A Monte Carlo simulation was performed to estimate the probability of achieving free drug levels above the minimum inhibitory concentration ($fT_{>MIC}$) for at least 20% and 40% of the dosing interval as PK/PD targets.
Results. Peak drug concentration and 24-h area under the concentration-time curve (AUC) were found to be 191.9±37.4 mg/L and 574.3±110.5mg·h/L, respectively. Ertapenem liver/serum concentration ratios were 6% at 1 h and 5% at 2 h. Drug concentrations in peritoneal fluid were 28.2±6.4 mg/L at 4-8h, declined to 15.2±5.9 at 8-12h and fell further to 4.79±0.2 mg/L at 12-24 h post-administration. The probability to reach the desired PK/PD targets were never reached at any MICs >0.25 μg/mL with a 90% probability.
Conclusion. Our data suggest that in extremely obese female patients, the standard dose of 1 g i.v. Ertapenem as short term prophylaxis may not provide optimal clinical levels of free drug for prevention of surgical site infections. *(Minerva Anestesiol 2014;80:1005-11)*

Key words: Ertapenem - Bariatric surgery - Pharmacokinetics - Pharmacology.

The general increase in human Body Mass Index (BMI) has become a public health priority in many countries, with worldwide obesity (defined as BMI≥30 kg/m^2) more than doubling between 1980 and 2008.[1] As a consequence, the number of obese people undergoing both standard and specialized bariatric surgery has dramatically increased over the last few years. Obesity constitutes a major risk factor for postoperative surgical complications, including the development of infections during the first 30 days postsurgery ("surgical site infections", SSIs).[2] The introduction of laparoscopic surgical techniques has been viewed

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as an effective tool for reducing the rate of SSIs, even in obese patients undergoing bariatric surgery (reducing the SSI rate from 1.2% for "open" gastric bypass to 0.4% for laparoscopic bypass).[3] One additional technique to reduce SSIs involves the use of optimal antibiotic prophylaxis,[4] via the administration of an antimicrobial agent with adequate spectrum of activity against the most likely pathogens in doses capable of reaching the pharmacokinetic/pharmacodynamic (PK/PD) target specific for each antibiotic.

Ertapenem is a parenteral carbapenem antibiotic whose indications include the treatment of complicated intra-abdominal infections.[5, 6] Several characteristics may suggest its clinical utility as a prophylactic antimicrobial agent in elective colorectal surgery, including its appropriately wide spectrum, long half-life (not requiring a second administration during most surgical procedures), and safety profile.[7] In a large prospective clinical trial involving patients undergoing elective colorectal surgery, prophylaxis with Ertapenem (1 g) was reported to be superior to that using the antibiotic cefotetan (2 g) in reducing SSIs (modified ITT analysis 17.1% *vs.* 26.2% respectively).[8] However, a post-hoc analysis of those data showed that superficial SSIs were higher in patients with a BMI≥30 kg/m^2 than in non-obese patients, regardless of the prophylactic antibiotic administered.[9] For Ertapenem, this failure may have been due to the fact that in obese patients, the optimal PK/PD target (defined as the time that free drug concentrations are above the MIC ($fT_{>MIC}$) for 20% bacteriostaic and 40% bactericidal activity), might be difficult to achieve using the standard 1 g dose.[10]

This study evaluates whether standard 1 g i.v. administration of Ertapenem dose is sufficient to reach the optimal PK/PD target-based on common MIC distribution for susceptible causative pathogens - for antimicrobial prophylaxis in female Caucasian patients with class III obesity (BMI ≥40 kg/m^2) undergoing bariatric surgery.

Materials and methods

Between September and December 2012, we conducted a prospective, uncontrolled, open-label, single-center PK/PD study in class III obese female patients undergoing bariatric surgery at a University Hospital (Azienda Ospedaliera Universitaria Careggi, Florence, Italy, Ethical committee approval number 114/1-2012). Because bariatric surgery is much more frequent in female than in male patients,[11] we decided to enroll in the study all the consecutive female patients who met the inclusion criteria and agreed to participate to the study. Inclusion criteria, in addition to female gender, were: Caucasian ethnicity, BMI≥40 kg/m^2, age between 18-65 yrs, American Society of Anesthesiology (ASA) physical status classification system class I and II undergoing elective videolaparoscopy gastric bypass or biliopancreatic diversion. Exclusion criteria were: renal failure (defined as estimated glomerular filtration rate (GFR) of less than 60 mL/min/1.73 m^2 calculated using the MDRD formula), hepatic failure (Child-Pugh B and C), history of heart failure (New York Heart Association [NYHA] functional classification class III and IV), hypersensivity to beta-lactam agents, pregnancy, history of alcohol or illicit drug abuse. All patients included in the study gave their written informed consent.

Patients received 1 g of Ertapenem as a 30-minute i.v. infusion 30 min prior to the commencement of surgical procedures as short term prophylaxis. A general balanced anesthesia regimen was employed. During all surgical procedures, crystalloids were infused at a rate of 6-8 ml/kg/h to maintain an euvolemic state. In order to compare the degree of fluid administration among patients, blood hematocrit was measured prior to (baseline) and at the end of Ertapenem administration and expressed as percent variation compared to baseline. To assess Ertapenem serum levels, 5 mL of venous blood were collected in 5 mL ammonium lithium tubes cooled (4 °C) and centrifuged for 5 min at 5000×g, and then transferred into appropriate sample tubes and stored at -80°C until high-performance liquid chromatography (HPLC) analysis. In each patient, the Ertapenem concentration was evaluated at baseline and at the end of infusion (30 min, Cmax), then at 1, 2, 4, 8, 12 and 24 hours. In patients in whom a liver biopsy was necessitated by clinical need (such as stadiation of liver steatosis), liver samples were obtained to

determine Ertapenem concentrations in hepatic tissue at 1 or 2 h following the start of infusion. Samples were rinsed with sterile saline solution to remove excess blood, dried and frozen in glass tubes at -80 °C until assayed. Liver biopsies were then weighed, diluted in sterile normal saline (1:1 w:v ratio), homogenized at 4 °C (Polytron PT 10-35 Homogenizer, Kinematica, Lucerne, Switzerland), centrifuged at 1200 g for 10 minutes for HPLC analysis. Peritoneal drainage fluid was collected between 4 and 8, 8 and 12, 12 and 24 hours after the start of Ertapenem infusion and stored at -80 °C until HPLC evaluation of Ertapenem concentrations. Plasma, liver and peritoneal fluid concentrations of Ertapenem were determined using a validated HPLC assay with ultraviolet detection set at a wavelength of 305 nm.[6] The mobile phase consisted of 10 mM phosphate buffer adjusted to pH 6.5 with concentrated orthophosphoric acid (phase A) and mixed with acetonitrile (phase B). The flow rate was set at 1 mL/min. The analytical column was a HyperClone C18 (Phenomenex, Torrance, CA) 4.6×100 mm, ODS 5 µm. The assay was linear over the concentration range 0.1-50 mg/L in plasma and peritoneal fluid. Precision validation data were between 2.7% and 9.5% and intraday accuracy ranged from 99.9-105.5%.

Individual PK analysis

A two-compartmental i.v. infusion model with first-order elimination was selected to fit concentration versus time data for Ertapenem. The following PK parameters were estimated for each patient: volume of the central compartment (V_1), volume of distribution (Vd) at steady state, total clearance (Cl), area under the curve from zero to infinity (AUC 0-∞), and mean residence time. Individual PK analyses were performed in WinNonlin Professional (Version 5.2.1; Pharsight Corporation, Mountain View, CA, USA).

Monte Carlo simulation

We used an $fT_{>MIC}$ for at least 20% and 40% of the dosing interval as PK/PD targets. An $fT_{>MIC}$ of 40% is the target for near maximal bactericidal activity of Ertapenem, and an $fT_{>MIC}$ of 20% and 40%were the target for bacteriostasis and bactericidal activity respectively. We used the patient-specific PK parameter estimates and the variance-covariance matrix representing the two-compartmental model estimated by WinNonlin. We also assumed that the dose, duration of infusion, and timing of infusion had no variability. We used the "micro constants notation" of our PK models during both estimation and Monte Carlo simulation and assumed a normal distribution of the PK parameters on a log scale. An unbound drug fraction of 5% was used in all PD analyses.[12] For each patient a total of 100,000 simulations were conducted to determine plasma concentration curves of unbound Ertapenem during the dosing interval. We estimated the probability of obtaining free drug target values using empirical distribution $fT_{>MIC}$ generated through simulation. Monte Carlo simulation was implemented in R 2.13.0.

Results

Ten consecutive female patients who met the study entry criteria and agreed to participate to the study were enrolled and included in the analysis. Clinical and demographic data are presented in Table I. The patients' mean age was 47.9 years (min 32-max 61) and BMI ranged

Table I.—*Clinical and demographic data.*

	Mean	SD	Min	Max	Median
Age (years)	47.9	9.4	32.0	61.0	48.5
Weight (kg)	124.2	12.6	106.0	150.0	122.5
Height (cm)	162.8	8.2	152.0	178.0	165.0
BMI (kg/m^2)	47.0	5.3	42.5	58.5	45.4
Total proteins (g/100 mL)	7.2	0.3	6.8	7.6	7.1
Bilirubin (mg/dL)	0.4	0.3	0.1	1.1	0.3
GFR value (mL/min/1.73 m^2)	76.4	25	71	83	78.5
Urea (g/L)	0.22	0.09	0.13	0.41	0.21

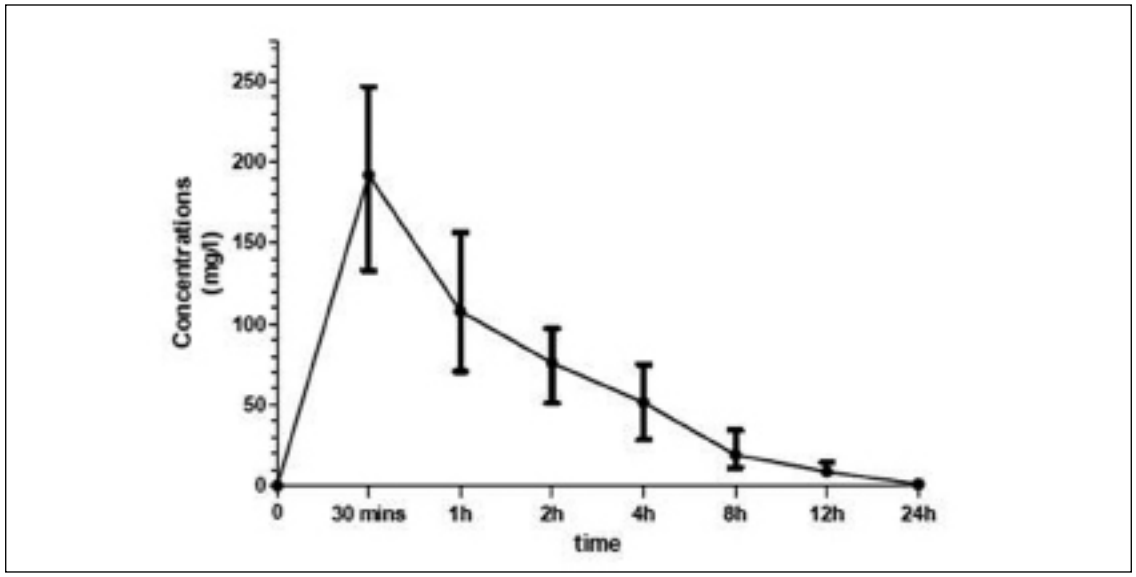

Figure 1.—The total plasma Ertapenem concentration observed in our patients was 191.9±37.4 mg/L at the end of infusion, which then decreased to 107.9±23.4 by 1 h, decreasing further to 75.8±14.8 mg/L by 2 h and to 1.0±0.1 mg/L by 24h postadministration.

between 42.5 and 58.5 kg/m^2. Ertapenem was well tolerated and no significant adverse event related to its infusion was reported. No patients were observed to develop SSIs up to 30 days after surgery. Mean fluid-therapy in the first hour was 13.64±5.81 mL/kg and mean hematocrit measured at the beginning of surgery was 37.7%, representing a 4.57% reduction as a consequence of fluid therapy.

The total plasma Ertapenem concentration observed in our patients are presented in Figure 1 and the main PK parameters in Table II. The mean concentration of Ertapenem in liver tissue was found to be 6.5±3.3 mg/kg at 1 h (N.=5) and 4.2±0.5 mg/kg at 2h postinfusion (N.=3). Drug concentrations in peritoneal fluid were 28.2±6.4 mg/L at 4-8 h postinfusion, 15.2±5.9 mg/L at 8-12 h postinfusion and 4.8±0.2 mg/L at 12-24 postinfusion.

For MIC=0.25 mg/L, the target of bacteriostasis ($fT_{>MIC}$ of 20%) was predicted for 80% of patients and that of maximal bactericidal activity ($fT_{>MIC}$ of 40%) for approximately 70% of patients. For MIC=0.5 mg/L the target for bacteriostasis was reached in 75% of patients and that of bactericidal activity in 35% of patients only (Figure 2).

Discussion

Obese patients remain at risk for several types of post-surgical complications. SSIs alone can harm surgical patients since they are often associated not only with local damage (*e.g.*, dehiscence, hernia), but also with a higher risk (up to 60%) of requiring intensive care unit stay and a 2 to 3 times higher risk of death.[13] SSIs can be considered a potentially preventable complication,

Table II.—*Total plasma Ertapenem concentration.*

	Mean	SD	Min	Max	Median
AUC from 0 to infinity (mg·h/L)	574.3	110.5	382.9	741.5	623.3
Clearance (L/h/kg)	0.0148	0.0038	0.0106	0.0223	0.0138
Volume of central compartment (L/kg)	0.0242	0.0092	0.0110	0.0372	0.0256
Volume of distribution at steady state (L/kg)	0.0630	0.0157	0.0460	0.0947	0.0601
Mean residence time (h)	4.4	1.1	3.1	6.5	4.0
T ½ beta (h)	3.7	0.6	2.2	5.2	3.7

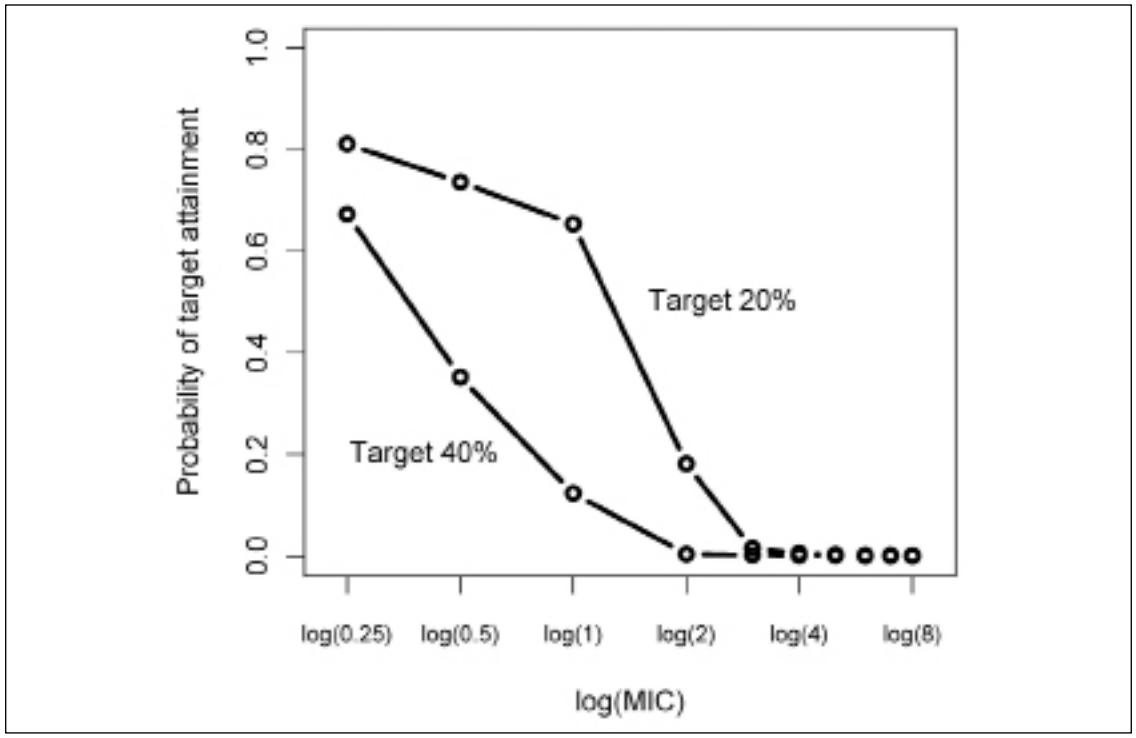

Figure 2.—Monte Carlo simulation. Probability (%) of attaining free drug target values of $fT_{>MIC}$ for bacteriostatic (20% of the dosing interval, *i.e.* 4.8 hours) and bactericidal activity (40% of the dosing interval, *i.e.* 9.6 hours).

and optimization of preoperative antimicrobial prophylaxis is instrumental in achieving this goal.[4] However, few studies to date have evaluated whether antimicrobials used for surgical prophylaxis are administered at doses sufficient to reach the optimal PK/PD target pertaining to each molecule, and fewer have explored this topic in the obese patient. In fact, the obese patient often presents with specific alterations in terms of PK (due to BMI and variable composition of body mass itself).[14, 15] Bowel bacterial flora is also different from that found in non-obese patients and this should deserve special consideration in selecting the appropriate antimicrobial for prophylaxis according to the spectrum of activity.[16]

Our data show that Ertapenem PK has both similarities and differences when compared to data reported in both healthy volunteers and non-obese patients. Plasma concentrations in female obese were higher during the first 4 h after administration than those reported in healthy, normal weight volunteers.[17] On the contrary, the $AUC_{0-\infty}$ measured in our population was comparable to that reported previously [18] in normal-weight healthy individuals (574.3+110.5 mg·h/L *vs.* 586±50.4 mg·h/mL) but higher than the values obtained for class III obese individuals (486+64.9 mg·h/mL). The higher $AUC_{0-\infty}$ in our study may be related to the higher values observed at the end of infusion (30 min) and at 1h. Irrespective of the explanation, an elevated AUC relative to a higher Cmax does not normally impact the T>MIC, which represents the major PK/PD parameter for time-dependent antimicrobials. Finally, even though the values of Ertapenem clearance (expressed as L/h·Kg) were found to be similar between those previously reported for normal weight patients [18] and our obese study population, a lower Vd in the central compartment was observed in our patients. These differences might be related to the different characteristics of the two study groups, (healthy volunteers *vs.* morbidly obese patients undergoing surgical procedures with general anesthesia), since surgery and anesthesia are both known to impact a drug's PK.[15]

Levels in peritoneal fluid were comparable to those previously reported in peritonitic patients undergoing surgery,[6] thus suggesting that an Ertapenem peritoneal fluid/serum ratio of approximately 80% (in the 4-8 h interval) and 100% (in the 8-12 and 12-24h intervals) can be obtained even in obese patients irrespective of the grade of peritoneal inflammation. Some studies have suggested a reduced tissue penetration of antimicrobials in obese patients as a consequence of lower blood flow/tissue ratio.[13] Our data do not support such a view, since liver tissue penetration in our patients was similar to that described for septic patients undergoing abdominal surgery (liver/serum ratio 0.06 -0.05 *vs.* 0.088), thus suggesting that tissue penetration is not affected by body weight at least when inflammation is present.[19]

For Ertapenem, as for all β-lactams, the PK/PD parameter that best correlates with maximal activity is T>MIC. Specifically for carbapenems, $fT_{>MICs}$ of 20% and 40% of the dosing interval are commonly employed clinical PD targets for bacteriostatic and maximal bactericidal effect, respectively.[20] If we assume that the PK/PD target should be reached in 90% of patients, the Monte Carlo simulation reveals that this PK/PD goal was not possible for any of the tested MICs for either bacteriostatic activity ($fT_{>MIC}$ of 20%) or maximal kill activity ($fT_{>MIC}$ of 40%). Therefore, our results demonstrate that pre-surgical prophylactic treatment with 1 g Ertapenem in obese patients does not provide optimal drug exposure even for pathogens which are well within the susceptibility breakpoint recognized by EUCAST (0.5 mg/L) (www.eucast.org). Accordingly, Frei and coworkers, using a Monte Carlo simulation on PK/PD models of different antibiotics to evaluate antimicrobial breakpoints for Gram-negative aerobic bacteria, suggested a tentative breakpoint for Ertapenem of 0.25 mg/L.[21]

The major limitation of our study is the lack of a prospective, concurrent control group and for this reason we have compared our data with those reported in the literature. Moreover, our study was restricted to Caucasian female patients and it is well-recognized that fat tissue distribution can vary significantly in males and in individuals from different ethnic groups.[15] Therefore, our data on drug exposure should not be directly extended to other obese populations. However, the restriction of our study to Caucasian female patients only, although it represents a potential limitation of the study, guarantees a more homogenous collection of data and reduces biases due to the effects of gender and ethnicity on fat distribution and therefore on PK/PD.[22, 23] Another potential limitation of our study is that it focuses on PK/PD and therefore does not allow us to ascribe clinical relevance from our data analysis. Moreover, we did not measure creatinine clearance but we calculated it with a predetermined formula. Whatever formula is chosen, it does not guarantee to accurately reflect renal function as direct measurement should have done. Finally, Ertapenem is not normally indicated for surgical prophylaxis using current guidelines. The fact that the spectrum of activity of Ertapenem is similar to that of the II generation cephalosporin cefotetan, a drug previously suggested in published guidelines for surgical prophylaxis,[24] and which is presently unavailable in many countries, together with lack of activity against *Pseudomonas* spp. and enterococci could provide this antimicrobial a reduced ecological impact.[25] Therefore its use for prophylaxis might be suggested in postsurgical units with a high percentage of multidrug-resistant *Pseudomonas aeruginosa* infections. Indeed, Ertapenem has also been shown at least as effective as cefalosporins in abdominal infections.[8, 26] However, because of this and of the concern about the use of carbapenems and selective pressure on *Klebsiella pneumoniae* producing carbapenemase strands, the cost/effectiveness of Ertapenem as prophylaxis remains to be established.

Conclusions

In summary, we have found that when Ertapenem is given to extremely obese Caucasian female patients for surgical prophylaxis, the currently proposed dose might be insufficient. The results of the present study have direct clinical relevance to healthcare personnel caring for obese patients and support the continuing need to further investigate more extensively the PK/PD of antimicrobials in a surgical population often ignored in clinical research and care.

Key messages

— The pharmacokinetics of Ertapenem in obese female patients has both similarities and differences to those found in both non-obese patients and healthy volunteers.

— Ertapenem tissue penetration is similar to that found in non obese patients with inflammation.

— In extremely obese female patients, the optimal PK/PD target cannot be reached at the currently proposed dose (1 g) even for MICs within the susceptibility breakpoints.

References

1. World Health Organization. Global Health observatory, obesity and overweight [Internet]. http://wwwwhoint/mediacentre/factsheets/fs311/en/.
2. Wick EC, Hirose K, Shore AD, Clark JM, Gearhart SL, Efron J et al. Surgical site infections and cost in obese patients undergoing colorectal surgery. Arch Surg 2011;146:1068-72.
3. Varela JE, Wilson SE, Nguyen NT. Laparoscopic surgery significantly reduces surgical-site infections compared with open surgery. Surg Endosc 2010;24:270-6.
4. Mangram AJ, Horan TC, Pearson ML, Silver LC, Jarvis WR. Guideline for prevention of surgical site infection, 1999. Hospital Infection Control Practices Advisory Committee. Infect Control Hosp Epidemiol 1999;20:250-80.
5. Yellin AE, Hassett JM, Fernandez A, Geib J, Adeyi B, Woods GL *et al.* Ertapenem monotherapy versus combination therapy with ceftriaxone plus metronidazole for treatment of complicated intra-abdominal infections in adults. Int J Antimicrob Agents 2002;20:165-73.
6. Arrigucci S, Garcea A, Fallani S, Cassetta MI, Canonico G, Tonelli F *et al.* Ertapenem peritoneal fluid concentrations in adult surgical patients. Int J Antimicrob Agents 2009;33:371-3.
7. Curran MP, Simpson D, Perry CM. Ertapenem: A review of its use in the management of bacterial infections. Drugs 2003;63:1855-78.
8. Itani KMF, Wilson SE, Awad SS, Jensen EH, Finn TS, Abramson M a. Ertapenem versus cefotetan prophylaxis in elective colorectal surgery. N Engl J Med 2006;355:2640-51.
9. Itani KMF, Jensen EH, Finn TS, Tomassini JE, Abramson MA. Effect of body mass index and ertapenem versus cefotetan prophylaxis on surgical site infection in elective colorectal surgery. Surg Infect (Larchmt) 2008;9:131-7.
10. Drusano GL. Antimicrobial pharmacodynamics: critical interactions of "bug and drug". Nat Rev Microbiol 2004;2:289-300.
11. Santry HP, Gillen DL, Lauderdale DS. Trends in bariatric surgical procedures. JAMA 2005;294:1909-17.
12. Odenholt I. Ertapenem: a new carbapenem. Expert Opin Investig Drugs 2001;10:1157-66.
13. Anaya DA, Dellinger EP. The obese surgical patient: a susceptible host for infection. Surg Infect (Larchmt) 2006;7:473-80.
14. Falagas ME, Kompoti M. Obesity and infection. Lancet Infect Dis 2006;6:438-46.
15. Leykin Y, Miotto L, Pellis T. Pharmacokinetic considerations in the obese. Best Pract Res Clin Anaesthesiol 2011;25:27-36.
16. Le Chatelier E, Nielsen T, Qin J, Prifti E, Hildebrand F, Falony G *et al.* Richness of human gut microbiome correlates with metabolic markers. Nature 2013;500:541-6.
17. Majumdar AK, Musson DG, Birk KL, Kitchen CJ, Holland S, McCrea J *et al.* Pharmacokinetics of ertapenem in healthy young volunteers. Antimicrob Agents Chemother 2002;46:3506-11.
18. Chen M, Nafziger AN, Drusano GL, Ma L, Bertino JS. Comparative pharmacokinetics and pharmacodynamic target attainment of ertapenem in normal-weight, obese, and extremely obese adults. Clin Pharmacol Ther 2006;50:1222-7.
19. Wittau M, Wagner E, Kaever V, Koal T, Henne-Bruns D, Isenmann R. Intraabdominal tissue concentration of ertapenem. J Antimicrob Chemother 2006;57:312-6.
20. Livermore DM, Sefton AM, Scott GM. Properties and potential of ertapenem. J Antimicrob Chemother 2003;52:331-44.
21. Frei CR, Wiederhold NP, Burgess DS. Antimicrobial breakpoints for gram-negative aerobic bacteria based on pharmacokinetic-pharmacodynamic models with Monte Carlo simulation. J Antimicrob Chemother 2008;61:621-8.
22. Katzmarzyk PT, Bray GA, Greenway FL, Johnson WD, Newton RL Jr, Ravussin E *et al.* Racial differences in abdominal depot – specific adiposity in white and African American adults. Am J Clin Nutr 2010;91:7-15.
23. Sumner AE, Farmer NM, Tulloch-Reid MK, Sebring NG, Yanovski JA, Reynolds JC *et al.* Sex differences in visceral adipose tissue volume among African Americans. Am J Clin Nutr 2002;76:975-9.
24. Bratzler DW, Houck PM. Antimicrobial prophylaxis for surgery: an advisory statement from the National Surgical Infection Prevention Project. Am J Surg 2005;189:395-404.
25. Goldstein EJC. Beyond the target pathogen: ecological effects of the hospital formulary. Curr Opin Infect Dis 2011;24(Suppl 1):S21-S31.
26. De Werra C, Di Micco R, Pilone V, Formato A, Montella E, Lambiase A *et al.* Serum in vivo and in vitro activity of single dose of ertapenem in surgical obese patients for prevention of SSIs. Obes Surg 2013;23:911–9.

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