Special Populations: Profiling the Effect of Obesity on Drug Disposition and Pharmacodynamics

Kenneth T. Moore

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Abstract

The health implications of obesity remain a global issue with approximately 13% of the world's population categorized as obese (body mass index [BMI] $\geq$30 kg/m^2) in 2016 (World Health Organization, Obesity and overweight. http://www.who.int/en/news-room/fact-sheets/detail/obesity-and-overweight. Accessed 8 Oct 2018, 2018). Obesity is typically a consequence of either excess food intake, lack of physical activity, genetic predisposition, or a combination thereof. Its impact is multifaceted, not only on the patient's health leading to a myriad of disease states directly related to obesity, but also on the management of these diseases and other common medical conditions that frequently occur. Obesity-related changes in normal physiology, such as alterations in lipid content, plasma proteins, drug metabolizing enzymes, drug transporters, and blood flow, can affect the disposition (absorption, distribution, metabolism, and excretion) and pharmacodynamics of commonly prescribed drugs, thereby altering their pharmacologic profiles. Hence, an understanding of these pharmacologic changes is necessary to ensure proper treatment is exercised. Unfortunately, our understanding of obesity-related changes in drug pharmacology in

K. T. Moore (✉)
Cardiovascular and Metabolism Medical Affairs, Janssen Pharmaceuticals Inc., Titusville, NJ, USA
e-mail: tmoore17@its.jnj.com

F. J. Hock, M. R. Gralinski (eds.), *Drug Discovery and Evaluation: Methods in Clinical Pharmacology*,
https://doi.org/10.1007/978-3-319-56637-5_7-1

addition to the overall safety and efficacy is limited, as clinical trials rarely focus specifically on this population. Therefore, the purpose of this chapter is to provide a review of the available literature assessing the effects of obesity on the disposition and pharmacodynamics of some of the most commonly prescribed drugs. This chapter is a review only; careful clinical decision making should always be used when applying literature from the population to individual patients and scenarios.

Introduction

According to the World Health Organization (WHO), the number of individuals defined as obese has tripled over the last 40 years, and this global trend is expected to continue (World Health Organization 2018). Obesity, defined as a Body Mass Index [BMI = body weight (kg)/height $(m)^2$] $\geq$30 kg/m^2, is considered a consequence of factors, alone or in combination, that include excess food intake, lack of physical activity, and genetic predisposition. Measuring ones BMI is still the most widely used metric for overweight and obesity gradation in adults and is independent of gender (Reflection paper 2018). While obesity is defined as a BMI $\geq$30 kg/m^2, this definition can be further defined by different classes of obesity. Individuals that are categorized as class I (moderately obese) have a BMI of 30 to 34.9 kg/m^2, those within class II (severely obese) have a BMI of 35 to 39.9 kg/m^2, and those assigned to class III (very severely obese/morbid obesity) have a BMI $\geq$40 kg/m^2 (World Health Organization 2018).

Obesity is a major risk factor for several chronic diseases, which includes type 2 diabetes, cardiovascular diseases (i.e., heart disease, coronary artery disease, stroke) osteoarthritis, major depression disorder, obstructive sleep apnea, and cancer (Hanley et al. 2010; Knibbe et al. 2015). It is also considered a proinflammatory state that, among other things, can predispose individuals to arterial and venous thrombosis through prothrombotic mechanisms (Lentz 2016). These risks increase as BMI increases. Considering the prevalence of these disease states associated with obesity, several leading medical associations have taken the step to now classify obesity as an actual disease (Jensen et al. 2014).

Obesity leads to a myriad of physiological and pathophysiological changes that can affect drug disposition. Some physicians may assume that a 100 kg individual is the same as a 70 kg individual, just with an additional 30 kg of adipose; however, this is incorrect (Zuckerman et al. 2015). An increase in weight correlates with more than just an increase in body fat. Lean body mass and organ size also increase with weight and this increase tends to be disproportionate. Changes in gastrointestinal permeability and emptying, changes in cardiac, liver, and renal functions, and changes in endogenous hormones are commonly seen (Knibbe et al. 2015; Smit et al. 2018; Jusko 2017). These changes, both individually and collectively, influence the clinical pharmacology of many drugs. For example, increases in gastrointestinal permeability and gastric emptying may potentially modify a drug's absorption properties, while changes in cardiac output, hepatic, and capillary blood flow may potentially change the metabolism and clearance of a drug (Smit et al. 2018).

Unfortunately, the effects of obesity on the pharmacology of commonly prescribed drugs are lacking. The fact that many drug manufactures do not routinely assess the effects of obesity on either the pharmacokinetics (PK), pharmacodynamics (PD), safety or efficacy of their drugs can be seen as a shortcoming of the drug development process. Perhaps greater direction or influence should be given by the United States Food & Drug Administration (FDA) and the European Medicines Agency (EMA) to help resolve this lack of data. That being said, a recent positive step forward was the development of the EMA's "Reflection Paper" which focuses this topic (Reflection paper 2018).

The following review will address on some of the changes observed in the disposition and pharmacodynamics of commonly prescribed drugs in obese individuals. This review is not intended to encompass all drugs or all the possible changes in the pharmacology of these compounds but to provide a general review in order for the reader to be

better informed on the possible pharmacological changes that can occur when treating obese patients.

Obesity and Drug Disposition

Absorption

Absorption is the process in which a drug is transferred from the site of administration to where it is measured within the body (Rowland and Tozer 1995). The transport of drugs into the systemic circulation where they are typically measured can occur via molecular mechanisms that include passive diffusion, active transport, facilitated transport, endocytosis, exocytosis, ion pair transport, filtration, and bulk flow. Passive diffusion, which is the natural movement of molecules down a concentration gradient, is the most common mechanism for drug transport (Rowland and Tozer 1995). To better understand the process of drug absorption, understanding the different routes of drug administration is needed.

Drug administration can be classified as either intravascular or extravascular. Intravascular drug administration is the process of placing drug directly into the systemic blood circulation via intravenous (i.v.) or intra-arterial routes, while extravascular administration can include oral, sublingual, buccal, intramuscular, subcutaneous, transdermal, pulmonary, vaginal, and rectal routes (Rowland and Tozer 1995). This review will focus on extravascular routes of administration leading to drug absorption.

Oral administration is the most common route for drug absorption. Physiological changes due to obesity that affect this route generally include increases in gastrointestinal blood perfusion, higher cardiac output, increased splanchnic blood flow, changes in enterohepatic recirculation, accelerated gastric emptying, and increased gut permeability, all of which can alter both the rate and extent of drug absorption (Knibbe et al. 2015; Smit et al. 2018; Shank and Zimmerman 2015; Jain et al. 2011). However, there are only a few human-based clinical pharmacology studies that report a change in oral drug absorption in this population. Levothyroxine (a synthetic version of the T4 hormone) as treatment for hypothyroidism is one example (Smit et al. 2018; Cho et al. 2013). In this clinical pharmacology study, it was observed that the corrected area under the curve (AUC) and the maximum T4 concentration (C_{max}) after levothyroxine administration were lower, whereas the time to maximum concentration (T_{max}) and estimated plasma volume was higher in severely obese subjects when compared to the normal weight control group. This led to the conclusion that severely obese individuals may need higher doses than what is administered to normal-weight individuals. The authors suggest that this difference was potentially attributed to higher plasma volume and/or delayed gastrointestinal absorption of the drug in the severely obese (Michalaki et al. 2011). Midazolam, which is a benzodiazepine used as a premedicant/sedative/anesthetic agent, has also shown some PK changes in obese individuals. While drug clearance (CL) does not appear to be impacted, the oral bioavailability and volume of distribution (V_d) increases substantially (Brill et al. 2014a). The increase in bioavailability may be a result of increased splanchnic blood flow or increased paracellular absorption through the gut wall, or a combination of both (Knibbe et al. 2015). Most studies, though, have shown that the rate and extent of oral absorption does not significantly differ between obese and nonobese patients (Smit et al. 2018; Shank and Zimmerman 2015; Cho et al. 2013; Bowman et al. 1986).

While there does not appear to be a significant impact of obesity on oral drug absorption, some other extravascular routes of administration do show some changes. Since obesity is associated with a significant increase in subcutaneous fat, routes of administration that include subcutaneous, transdermal, and intramuscular administration may all be affected by changes in the quantity of fat tissue (Jain et al. 2011). These potential changes in absorption are due to the dependency that these routes have on blood flow to the skin, subcutaneous fat, and muscle (Smit et al. 2018). While cardiac output is generally increased in this population, the blood flow rate per gram of fat tissue is significantly lower when

compared to the nonobese patient (Smit et al. 2018). This is significant, considering that fat tissue typically receives approximately 5% of cardiac output, compared to 73% for viscera and 22% for lean tissues. Drug administration via these routes may ultimately be affected by the percentage of fat tissue present in obese individuals due to alterations in perfusion (Shank and Zimmerman 2015; Cheymol 2000).

One example of this pharmacological change observed in subcutaneous administration is with enoxaparin, a low-molecular-weight heparin. Subcutaneous dosing in obese individuals leads to slower absorption of the drug. This was measured by assessing the maximum PD activity post-injection. Both antifactor X_a and antifactor II_a levels took, on average, 1 h longer to reach maximum activity in obese individuals. However, ultimately the extent of absorption was complete in both the obese and nonobese patients leading the investigators to conclude dose modification in obese patients was unnecessary (Jain et al. 2011).

Human Chorionic Gonadotropin (hCG) is a hormone produced by the placenta after embryo implantation in pregnancy. Injections of hCG are commonly used during in vitro fertilization (IVF) cycles. Depending on the formulation, hCG injections can be either subcutaneous or intramuscular. When assessing the two routes of administration in obese and normal-weight individuals, C_{max}, AUC, and average hCG concentration were higher after intramuscular injection as compared with subcutaneous injection (Shah et al. 2014). When comparing these values between obese versus nonobese individuals, obese women had markedly lower C_{max}, AUC, and average hCG concentration after subcutaneous injection and similar PK values after intramuscular injection when compared with normal-weight women (Shah et al. 2014). An interesting finding in this study was that approximately 1/3 of the obese women studied had an excess of subcutaneous fat that prevented the use of a standard 1.5 in. needle for intramuscular injections (Shah et al. 2014). Therefore, the increased subcutaneous fat associated with obesity leads to inadvertent subcutaneous injection intended to be administered intramuscularly, altering the pharmacokinetics.

Sumatriptan (Imitrex) is a commonly used triptan for treatment of migraines. Following subcutaneous injection, increasing weight was associated with a decrease in sumatriptan systemic exposure. The PK values $AUC_{0–2}$ and C_{max} were approximately 1.2 times and 1.3 times higher, respectively, than those observed in individuals that weighed greater than or equal to the median weight value for the study population (Munjal et al. 2016).

Cefazolin is a cephalosporin class antibiotic used as a prophylactic for postoperative surgical site infection. Using microdialysis, it was found that unbound cefazolin concentrations were lower in morbidly obese compared with nonobese patients following subcutaneous administration. Cefazolin tissue distribution reduces with increasing body weight and this is believed to be a consequence of altered blood perfusion in obese individuals (Brill et al. 2014b). While these are four examples where obesity may affect the pharmacology of a compound, obesity does not appear to affect either the PK or PD of other agents administered subcutaneously like the insulin Lispro (de la Peña et al. 2015), recombinant follicle-stimulating hormone (rFSH) (Steinkampf et al. 2003), or moxifloxacin (Kees et al. 2011).

Considering that pulmonary function is uniformly altered in obese individuals, primarily due to reduced lung volumes, there is an unfortunate scarcity of published data on the topic (Cheymol 2000). A study conducted in overweight patients with persistent asthma administered inhaled corticosteroids has shown attenuated symptom and fractional exhaled nitric oxide (FeNO) dose responses when compared to normal weight individuals. There were no differences in forced expiratory volume in 1 s (FEV1) or methacholine PC20 between the groups. The investigators hypothesize that attenuated cortisol suppression in the overweight group, secondary to reduced peripheral lung absorption, may be the cause (Anderson and Lipworth 2012).

In summary there is a lack of data concerning drug absorption in obese patients. While the few available published examples seem to indicate orally administered drugs are not likely to show a change in absorption, other routes of

extravascular administration like transdermal, subcutaneous, and intramuscular routes may be affected as weight and fat content increases. Other extravascular routes including sublingual, buccal, rectal, and vaginal routes in obese individuals have not been widely studied and are not mentioned in this review.

Distribution

Distribution is the process of reversible drug transfer to and from the blood and other tissues in the body (Hanley et al. 2010; Rowland and Tozer 1995). Organ size and the extent to which they are perfused with blood, drug binding in both blood and tissues, and its permeability all influence a drug's distribution properties (Rowland and Tozer 1995; Shank and Zimmerman 2015). The rate of drug distribution is determined by the blood flow to the tissues and the ability of the drug to cross the capillary wall and enter the cells of the tissue.

Drug distribution can be quantified by determining the volume of distribution (V_d). This represents the degree to which a drug is distributed into the tissues; therefore, the higher the V_d, the greater a drug is distributed. To properly measure this value, the concentration of the drug needs to be determined. Measurement of this distribution in humans is generally limited to those tissues easily accessible, for example, blood or plasma. Note, once a drug is absorbed, it is delivered simultaneously to all tissues. To calculate V_d, an equilibrium needs to occur in the distribution of the drug between the tissues and plasma (Rowland and Tozer 1995). Once this occurs, the following equation can be used:

$$V_d = A/C$$

where (V_d) is the volume of distribution, (A) represents the total amount of drug in the body, and (C) represents the concentration of the drug in the plasma.

It is important to note that V_d is not a physiologic value but a mathematical concept and it rarely corresponds to a real volume. It is more of a reflection of how a drug will distribute throughout the body, depending on its physiochemical properties (e.g., polarity, molecular size, and degree of ionization) and plasma protein binding (Shank and Zimmerman 2015). An easy way of determining the V_d is with an i.v. bolus of the drug in question. That way the amount of drug in the body is known immediately following the completion of the bolus.

$$V_d = D_{i.v.}/C_0$$

where (V_d) is the volume of distribution, ($D_{i.v.}$) represents the amount of drug administered via i.v., and (C_0) represents the concentration of the drug in the plasma at time 0.

Different disease states may influence the V_d of a drug and obesity is one such example. These changes can be a result from both physiological changes observed with increased body weight (i.e., increases in adipose tissue, changes in protein binding, and reduced tissue perfusion) and the intrinsic physiochemical properties of the drug, described previously (Knibbe et al. 2015).

When considering the physiological changes, alterations in either the concentrations of plasma binding proteins or in their binding affinity could ultimately affect the movement of drugs into the tissues and affect its distribution. Obesity has been associated with changes in both characteristics. Research has shown that serum albumin tends to be unaltered in obesity (Jain et al. 2011). Therefore, those compounds that primarily bind to albumin (most acidic drugs) do not appear to be affected and thus the V_d remains unaltered. For example, both thiopental (used for the induction of general anesthesia) and phenytoin (an antiepileptic) bind primarily to albumin and are generally unaltered by increases in weight (Jain et al. 2011). However, those compounds binding to α_1-acid glycoprotein (most basic drugs) appear at times, to be affected. That is, the degree of protein-binding increases, reducing the free plasma concentrations and decreasing their V_d (Leykin et al. 2011). Yet, this affect when assessed across basic drugs is inconsistent (Jain et al. 2011).

Physiological changes to the microvascular system due to obesity may ultimately impact

tissue blood flow and perfusion, therefore altering drug distribution (Levy et al. 2008). This impairment may be due to the increased levels of oxidative stress and/or inflammatory cytokines generally associated with this disease state (Levy et al. 2008). Proper tissue penetration is particularly important for antibiotics used for localized infections or perioperative prophylaxis, where certain tissue concentrations need to be achieved (Smit et al. 2018). Microdialysis studies with cefuroxime (a cephalosporin antibiotic) and ciprofloxacin (a fluoroquinolone antimicrobial) have shown that tissue penetration in obese patients was significantly reduced (Smit et al. 2018).

Lipophilicity (a molecule's affinity to bind to adipose tissue) is one example of a physiochemical property that may influence the distribution of a drug in these patients, as there is a marked increase in the ratio of adipose tissue to lean body mass (Shank and Zimmerman 2015). Therefore, intuitively, highly lipophilic molecules may accumulate more in fat stores and display a larger V_d in these individuals. For example, Diazepam (Valium), a benzodiazepine derivative commonly used for anxiety, is a highly lipophilic drug and shows a dramatic increase in V_d when studied in obese patients (Knibbe et al. 2015). However, the literature is not always consistent in this regard, and it should be noted that the size of V_d does not always correlate with the degree of lipophilicity, nor can it be predicted based on lipophilicity alone (Knibbe et al. 2015; Cheymol 2000). Propofol, an i.v. sedative-hypnotic commonly used for initiation and maintenance of monitored anesthesia care, is a classic example of this dichotomy as it is also highly lipophilic but does not show an increase in V_d when dosed in obese patients. Another physiochemical property that may affect drug distribution is the polarity of the molecule. Polar molecules have more difficulty passing into cells and are not likely to deposit into fat (Shank and Zimmerman 2015).

In summary, changes in drug distribution (V_d) are highly influenced by the intrinsic physiochemical properties of a drug and the physiological changes typically associated with obesity. Understanding these changes is critical in drug therapy, particularly when determining the proper loading dose for antimicrobial agents or treatment with sedatives. Unfortunately, our current understanding of these changes is limited.

Metabolism

Metabolism is a biochemical mechanism in which drugs are altered and eliminated from the body (Rowland and Tozer 1995). These mechanisms (or pathways) consist of chemical reactions which include oxidation, reduction, hydrolysis, and conjugation (Rowland and Tozer 1995). Most drug metabolism occurs in the liver; however, the kidneys, skin, lungs, blood, and gastrointestinal wall may also play a role (Rowland and Tozer 1995). These biotransformation pathways convert drugs into products termed metabolites, which are generally polar molecules that can be easily excreted by the body. Oxidation, reduction, and hydrolysis pathways are typically referred to as Phase I pathways. Oxidation-based reactions primarily rely on the superfamily of enzymes called cytochrome (CYP) P450 monooxygenases (most common enzymes include: CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4) (Morrish et al. 2011; Atkinson et al. 2007). Reduction-based reactions rely on reductase enzymes found in intestinal anaerobic bacteria and hydrolysis-based reactions rely on esterases, amidases, and proteases (Atkinson et al. 2007). Once completing this type of metabolism, the original drug and its metabolites can become either completely pharmacologically inactive; the original drug becomes inactive, but one or more of the metabolites are active (however to a lesser degree) or the original drug, which was inactive to start, produces one or more active metabolites (Atkinson et al. 2007). For the last scenario, the original inactive drug substance is called a prodrug.

Phase II metabolism refers to chemical reactions through the covalent bonding of an endogenous molecule to the drug (Atkinson et al. 2007). This type of reaction is termed conjugation and can come in the form of glucuronidation, sulfation, acetylation, methylation, and amino acid conjugation (Atkinson et al. 2007). These

reactions bond a hydrophilic molecule (e.g., glucuronic acid, sulfate, or glycine) to either the parent drug or the metabolite of the parent drug to form a water-soluble compound that can be excreted. The metabolites (or conjugates in this case) produced from this reaction are unlikely to be pharmacologically active. Glucuronidation is the most common type of phase II reactions. The products, glucuronides, are formed by uridine diphosphate (UDP)-glucuronosyltransferases (UGTs) enzymes located in the liver, kidneys, and brain (Atkinson et al. 2007). While some drugs undergo either phase of metabolism, most undergo phase I followed by phase II metabolism.

While these reactions can occur in a few different tissues, the liver is the main organ of metabolism. This enzyme activity determines what is called the intrinsic liver clearance (CL_{int}) of the drug. This intrinsic clearance of a drug is a theoretical value of CL in the absence of any dependence on blood flow or protein binding. CL_{int} together with hepatic blood flow (Q_H) and fraction of unbound drug (f_u) determines the hepatic clearance (CL_H) of the drug (Smit et al. 2018). The following equation can be applied (well-stirred model):

$$CL_H = Q_H \cdot (f_u \cdot CL_{int})/(Q_H + f_u \cdot CL_{int})$$

Changes in these parameters in addition to the hepatic extraction ratio (E_H) (i.e., the efficiency of the liver to clear the drug from the blood) can therefore alter the hepatic clearance (Smit et al. 2018).

$$CL_H = Q_H \cdot E_H$$

A drug's extraction ratio can be either high or low (Range from 0 to 1). High extraction drugs ($E_H > 0.7$) are primarily dependent on Q_H and less on enzyme capacity or f_u as it is nonrestrictively cleared (High CL_{int}). Low extraction drugs ($E_H < 0.3$) are primarily dependent on hepatic enzyme capacity, therefore restrictively cleared (Low CL_{int}) (Smit et al. 2018).

Since $CL_H = Q_H \cdot E_H$, the extraction ratio can be determined with the following equation:

$$Q_H \cdot (f_u \cdot CL_{int})/(Q_H + f_u \cdot CL_{int}) = Q_H \cdot E_H$$

$$E_H = (f_u \cdot CL_{int})/(Q_H + f_u \cdot CL_{int})$$

In obese individuals, liver pathologies are common. Fat deposition and inflammation in the liver can result in hepatic steatosis (fatty infiltration), changes in Phase I or II enzyme systems, and hepatic blood flow (Jain et al. 2011). It is hypothesized that chronic low-grade inflammation in the liver can result in decreased enzyme expression of certain CYP enzymes (Smit et al. 2018). For example, obesity has been found to correlate to a decrease in CYP3A4-mediated metabolism for low E_H drugs (Jusko 2017). A good example of this can be seen with the corticosteroid methylprednisolone, in which the absolute clearance was decreased by approximately 40% in the obese individuals (Jusko 2017; Dunn et al. 1991). Another example of decreased CYP3A4 metabolism in obese individuals can be seen with the use of triazolam, a benzodiazepine class drug. In a small clinical pharmacology study with 12 obese patients and 12 pair-matched normal weight subjects, the administration of triazolam was found to result in a much lower CL in the obese subjects (340 mL/min) compared to the matched controls (531 mL/min) (Abernethy et al. 1984). A final example of decreased CL in this phase I CYP3A4 mediated pathway is alfentanil, an opioid antagonist. The CL of alfentanil was shown to decrease approximately 46% from 321 mL/min in nonobese subjects to 179 mL/min in obese subjects (Brill et al. 2012).

Alternatively, the activity of CYP2E1 enzymes has been observed to increase in obese individuals thereby increasing drug clearance. This can be seen with the use of acetaminophen (Fig. 1) in morbidly obese patients. When administered in this population, the median AUC of acetaminophen was significantly smaller, while the AUCs of the glucuronide, sulfate, and cysteine metabolites were significantly higher (van Rongen et al. 2016).

Additionally, the muscle relaxant chlorzoxazone was found to have an unbound CL values that was ~3-times higher (CL_{obese} = 27.5 L/min vs.

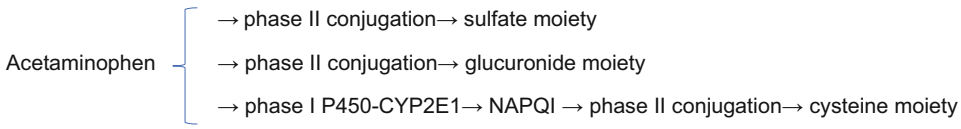

Fig. 1

$CL_{non\text{-}obese}$ = 9.9 L/min) in morbidly obese subjects indicating a significant induction of the CYP2E1 enzyme system (Brill et al. 2012). With the exception of the changes reported for the CYP3A and CYP2E1 enzymes, and a possible trend toward higher clearance of CYP1A2, CYP2C9, CYP2C19, and CYP2D6 substrates, phase I pathway enzymes do not appear to be highly impacted by obesity (Knibbe et al. 2015) (Fig. 1).

The phase II pathway, specifically conjugation reactions, seems to be consistently elevated in morbidly obese individuals, leading to an increase in drug CL (Knibbe et al. 2015). This was observed with acetaminophen, oxazepam, and lorazepam, the last two being benzodiazepines, and notably, all three are examples of low-to-medium extraction ratio drugs (Smit et al. 2018; Jain et al. 2011). Mean acetaminophen CL values were CL_{obese} = 484 mL/min and $CL_{non\text{-}obese}$ = 323 mL/min; mean oxazepam CL values were CL_{obese} = 156.8 mL/min and $CL_{non\text{-}obese}$ = 50.4 mL/min; and mean lorazepam CL values were CL_{obese} = 102 mL/min and $CL_{non\text{-}obese}$ 62.9 mL/min for obese and nonobese subjects, respectively (Brill et al. 2012).

Interestingly, recent studies with morphine, also mainly glucuronidated, show somewhat conflicting results. While these studies have demonstrated higher morphine glucuronide concentrations in obese and nonalcoholic steatohepatitis (NASH), patients compared to nonobese individuals, a couple of these studies have also shown similar morphine concentrations together with increased glucuronide concentrations (Smit et al. 2018). This then suggests that there was not a significant increase in glucuronidation, but likely a decrease in glucuronide clearance (Smit et al. 2018). A possible explanation for this difference may be attributed to the fact that morphine is actually a medium-to-high extraction ratio drug. Assuming hepatic blood flow is unchanged in this population, that may explain the difference observed between drugs that have high versus low extraction ratios and are primarily glucuronidated (Smit et al. 2018). As previously mentioned drugs with high extraction ratios depend almost entirely on hepatic blood flow, rather than intrinsic metabolic clearance.

Whether hepatic blood flow changes in obese individuals remains unclear. Some have reported that obesity and NASH lead to an increase in fat accumulation in the liver, in turn causing sinusoidal narrowing and ultimately a reduction in hepatic blood flow (Knibbe et al. 2015; Cho et al. 2013; Farrell et al. 2008). While others argue that hepatic blood flow is not necessarily reduced in these patients because of the increased blood volume and cardiac output observed with an increase in body mass (Cho et al. 2013; Casati and Putzu 2005).

Interestingly, when assessing Propofol, which is extensively metabolized by phase II UGT enzymes and considered a high hepatic extraction ratio drug (having a CL that is limited only by Q_H), drug CL was significantly increased (~10.0 L/min) in morbidly obese subjects compared to nonobese subjects (4.1 L/min) (Wu 2016; van Kralingen et al. 2011). The authors suggest that this increase in CL is likely a result of increase in Q_H secondary to the typical increase in cardiac output generally observed in obese patients. While the literature remains sparse, there have been other reports of higher CL values observed for a small number of high-extraction-ratio drugs, again suggesting an increase in Q_H in obese patients (Knibbe et al. 2015).

In summary, changes in drug clearance via phase I metabolism are dependent on the specific enzymatic pathway. In the current published literature, CYP3A4 mediated clearance was found to be consistently lower in obese subjects, while CYP2E1 mediated clearance tends to show higher

activity in this population. Other pathways, including CYP2C9, CYP2C19, and CYP2D6, show a trend for higher clearance in obese subjects; however, in most cases these changes were not statistically significant. In contrast, the phase II pathways, specifically conjugation reactions, appear to be elevated in morbidly obese individuals and hence an observed increase in CL. Lastly, there appears to be a trend for higher CL values for drugs considered to have high hepatic extraction ratios. While the exact reason for these higher CL values may not yet known, many have speculated that higher Q_H with increasing body mass may explain these observations.

Excretion

Excretion is the process of eliminating a drug from the body. Drugs can be excreted unchanged as the parent moiety or following metabolism as active and/or inactive metabolites. There are several physiological routes in which a drug can be eliminated from the body; however, most drugs are eliminated via the kidneys or liver. In some cases, drug excretion can occur through the lungs, breast milk, sweat, tears, skin, hair, or saliva, though these are considered secondary pathways.

Renal excretion plays a critical role in elimination of both unchanged drugs and metabolites from the body. Although the ability to eliminate these compounds by renal processes would require them to be polarized and water-soluble first. Therefore, normally highly lipid soluble drugs generally require them to first go through hepatic metabolism (phase I/II) to increase their water solubility before they can be excreted. It is important to note that drugs entering the hepatic circulation may also be excreted into the bile. For these compounds, the drug re-enters the intestinal tract and can be eliminated via the feces or re-absorbed back into the systemic circulation, which is termed enterohepatic recycling.

For the purposes of this review, we will focus on renal elimination. The basic functional unit of the kidney is the nephron. Collectively these units are responsible for the removal of metabolic waste and the maintenance of water and electrolyte balance. The nephron can be broken down into five basic anatomic units: the glomerulus, proximal tubule, loop of Henle, distal tubule, and collecting tubule (Rowland and Tozer 1995). Blood is first filtered through the glomerulus with a rate of approximately 120 mL/min. The resulting filtrate is passed down the proximal tubule then through the loop of Henle, the distal tubule and finally whatever filtrate is left is passed into the collection tubules and eliminated from the body (Rowland and Tozer 1995). There are four processes involved in drug elimination via these nephrons, they include glomerular filtration, tubular secretion, tubular reabsorption, and renal metabolism with glomerular filtration playing a primary role (Morrish et al. 2011; Brill et al. 2012; Fan and de Lannoy 2014).

Clearance by glomerular filtration (CL_{FILT}) is a passive process that relies on normal physiologic hydrostatic pressure in the glomerulus and can only filter unbound drug into the urine. It can be represented as the following equation:

$$CL_{FILT} = f_u \cdot GFR$$

where f_u is the fraction of unbound drug and GFR is the glomerular filtration rate (GFR is approximately 125 mL/min in an average adult)

Tubular secretion of drugs is an active transport process that occurs in the proximal tubule of the nephron. Since this is a carrier mediated system, its capacity is limited and can become saturated. Clearance by tubular secretion (CL_{SEC}) relies on renal blood flow (Q_R), the unbound fraction (f_u), and the intrinsic clearance (CL_{INT}) of the drug and is similar to hepatic clearance. It is represented by the following equation: (Tucker 1981)

$$CL_{SEC} = (Q_R \cdot f_u \cdot CL_{INT})/(Q_R + f_u \cdot CL_{INT})$$

Tubular reabsorption (F_{REAB}) of drugs occurs in the distal tubule after the drug is filtered through the glomerulus and passes the proximal tubule and loop of Henle. Reabsorption can be either a passive or active process and is dependent on the f_u, urine flow and pH.

Renal clearance (CL_R) is therefore the sum of these four processes and can be represented by the equation below: (Fan and de Lannoy 2014)

$$CL_R = (f_u \cdot GFR + CL_{SEC}) \cdot (1 - F_{REAB}) + CL_{MET}$$

where GFR is the glomerular filtration rate, f_u is the fraction unbound in plasma, CL_{SEC} is clearance by tubular secretion, F_{REAB} is the fraction reabsorbed, and CL_{MET} is clearance by renal metabolism.

The influence of obesity on renal function and drug excretion is not straight forward nor clear. There is some evidence that obesity is related to a state of glomerular hyperfiltration and estimated GFRs have been seen to increase up to 62% (Cho et al. 2013). This type of increase mimics those observed in early stage diabetic nephropathy or end-stage renal disease, both of which are commonly observed in obese individuals (Cho et al. 2013; Brill et al. 2012). However, less is known about the effect of obesity on renal tubular secretion and tubular reabsorption. Ultimately an increase in drug CL has been observed in obese individuals who have normal kidney function. This increase is likely secondary to increased kidney size and renal blood flow generally associated with obesity (Knibbe et al. 2015; Atkinson et al. 2007; Brill et al. 2012).

With drugs that are primarily excreted through the kidneys via filtration, for example, vancomycin and low molecular-weight heparins (LMWH), they generally display an overall increase in CL with an increase in weight. This can be seen with the use of vancomycin, having a greater than 50% increase in CL in obese versus nonobese patients ($CL_{obese} = 197$ mL/min vs. $CL_{non\text{-}obese} = 77$ mL/min) (Brill et al. 2012). A similar trend is observed with Dalteparin ($CL_{obese} = 1.30$ L/h vs. $CL_{non\text{-}obese} = 1.11$ L/h) (Cho et al. 2013; Brill et al. 2012). In both cases, the increase in CL is likely related to an increase in GFR.

There are several drugs that are at least partly eliminated by tubular secretion, procainamide, ciprofloxacin, and digoxin to name a few (Blouin and Warren 1999). In general, a trend towards higher CL has been observed with these compounds. Procainamide, an antiarrhythmic drug, is eliminated unchanged through a combination of glomerular filtration and tubular secretion. The approximate 50% increase in CL observed ($CL_{obese} = 4.19$ mL/min vs. $CL_{non\text{-}obese} = 2.68$ mL/min) is likely a result of increased tubular secretion as there was no difference in observed in creatinine clearance (Brill et al. 2012). Studies with oseltamivir, an antiviral medication used to treat and prevent influenza A and B, that undergoes both renal tubular secretion and filtration, have shown a consistent increase in renal excretion, suggesting renal secretion may be augmented in these patients (Smit et al. 2018).

In a similar fashion, the renal CL of lithium, a compound used for bi-polar and major depression disorders, primarily involves glomerular filtration and tubular reabsorption. When dosed in obese individuals, renal CL increased without a change in glomerular filtration, supporting the premise that tubular reabsorption was decreased in obese individuals (Blouin and Warren 1999).

In summary, obesity has a significant impact on kidney function and renally eliminated compounds. Changes include compensatory hyperfiltration to meet increased metabolic demands, alterations in tubular secretion and reabsorption, and potential changes in some of the metabolic pathways of the kidney. In general, studies have shown that clearance of renally eliminated drugs is higher in obese patients. This increase in CL is likely due to increased glomerular filtration and tubular secretion. There is less published evidence on the changes to tubular reabsorption and renal metabolism with obesity and hence, just briefly mentioned in this review. It should be noted that though renal clearance is initially enhanced by compensatory hyperfiltration and hyperperfusion in obese individuals, this effect is believed to eventually decrease over-time or with a continued increase in weight, as a result of persistently elevated intraglomerular pressure.

Obesity and Pharmacodynamic Changes

Obesity and morbid obesity is more than just excess weight gain; it is associated with both an altered anatomy and physiological state. Many of the pathophysiological manifestations of obesity can be characterized by a low-level chronic inflammation leading to dysregulation of metabolic homeostasis, dyslipidemia, altered blood pressure, diabetes, cardiovascular disease, chronic kidney disease, cancer, and thrombosis (Lentz 2016). This low level of chronic inflammation is reflective of the over expression of cytokines like TNF-α, interleukin-6, and interleukin-1b secreted by adipose tissue, leading to an increase in the concentration of macrophages (Lentz 2016; Gandhi et al. 2012). Additionally, nutritional and genetic changes related to obesity can affect receptor expression and/or receptor affinity to many drugs (Shank and Zimmerman 2015; Jain et al. 2011). For example, cytokine tumor necrosis factor alpha is produced in excessive amounts in obese patients; this in turn perpetuates insulin resistance (Shank and Zimmerman 2015). This is compounded by the fact that adipose tissue also has greater intrinsic insulin cleaving activity, hence the need for more insulin to produce the same pharmacodynamic (PD) response (Shank and Zimmerman 2015).

Other receptor changes observed in obese patients include a decreased sensitivity to acetylcholine and increased sensitivity to benzodiazapines (e.g., triazolam), thereby increasing the psychomotor response (Shank and Zimmerman 2015; Jain et al. 2011; Blouin and Warren 1999). Polymorphisms in the μ-opioid receptor gene, the P-glycoprotein gene (ABCB1), and the catechol-O-methyltransferase gene (COMT) seem to be responsible for the variability observed in morphine PD and PK, as previously discussed (Jain et al. 2011). Additionally, adipocytes secrete leptin, which reduces macrophage and T-cell differentiation and activity, in turn affecting the immune system (Smit et al. 2018). In fact, when obese patient contract infectious diseases, they are generally associated with worse outcomes compared to the normal weight patients (Smit et al. 2018).

Whole organ systems are also affected. The cardiovascular system is significantly impacted in obese individuals. Increasing weight leads to an increase in blood volume and a subsequent increase in cardiac output, and an increase in baseline heart rate (Zuckerman et al. 2015). Some of the anatomical changes observed in obese individuals include the development of cardiomyopathies (left ventricular hypertrophy), atherosclerosis, and endothelial dysfunction (decrease in nitric oxide production) leading to hypertension (Zuckerman et al. 2015). While obesity causes an initial hyperdynamic change leading to increased cardiac output and blood volume, the long-term effects of obesity lead to increases in vascular resistance and to structural changes in the heart and ultimately heart failure (Martin et al. 2012). While serum albumin and total protein concentrations do not appear to be altered, concentrations of alpha-1-acid glycoprotein are generally increased (Hanley et al. 2010; Knibbe et al. 2015; Smit et al. 2018).

Obesity impacts respiratory function as well. Changes in large airway anatomy lead to changes in lung volumes, compliance, reserve capacity, airway resistance, ventilatory drive, and the work of breathing (Zuckerman et al. 2015; Smit et al. 2018). Obese patients are also at increased risk for obstructive sleep apnea and asthma and may also suffer from obesity-hypoventilation syndrome (Zuckerman et al. 2015; Smit et al. 2018).

Physiologic changes to the gastrointestinal track typically include accelerated gastric emptying and increases in gut permeability, blood perfusion, and splanchnic blood flow (Zuckerman et al. 2015; Smit et al. 2018). Intestinal motility is increased in the upper intestinal tract and decreased in the lower intestinal tract and colon (Zuckerman et al. 2015). Changes in enterohepatic recirculation commonly occur along with changes in the expression of metabolic enzymes and transporters (Zuckerman et al. 2015). Other changes include an increased risk for a hiatal hernia and increased intra-abdominal pressure which increases the risk for aspiration (Zuckerman et al. 2015).

Excessive accumulation of fat in the liver can cause functional changes in morphology (Knibbe et al. 2015). Nonalcoholic fatty liver disease (NAFLD) resulting in steatosis or steatohepatitis (NASH) commonly occurs (Knibbe et al. 2015). Together with the increased rate of sinusoidal narrowing, it may cause liver blood flow to decline over time (Smit et al. 2018). Liver volume in obese and morbidly obese individuals is generally increased and alterations in some enzyme systems (e.g., CPY3A and CYP2E) have been observed (Knibbe et al. 2015).

Changes in renal function have also been observed in obese and morbidly obese individuals. These changes can include alterations in glomerular filtration, tubular secretion, and tubular reabsorption. Similar to the trend in hepatic changes observed over time, it is generally believed that renal clearance, though initially enhanced via hyperfiltration and hyperperfusion, eventually declines as a result of constantly elevated intra-glomerular pressure (Smit et al. 2018).

Obesity is also associated with mood disorders, specifically depression, and changes in dopamine-mediated reward mechanisms (which regulate both substance abuse behaviors and binge eating behaviors) (Zuckerman et al. 2015).

The following are some selected examples of compounds from different classes of therapeutics where the effects of obesity on the PK and/or PD were assessed.

Obesity and Pharmacokinetic and Pharmacodynamic Changes

Cardiovascular System

Antihypertensive Drugs

Obesity is an underlying cause of hypertension, with approximately 75% of obese individuals ultimately diagnosed with the condition (Landsberg et al. 2013). Together they are recognized as a significant risk factor for cardiovascular disease. The relationship between increasing body weight and blood pressure (BP) was demonstrated in the 1960s with the Framingham Heart Study (Landsberg et al. 2013). While the exact cause is not known, insulin-mediated sympathetic nervous system (SNS) stimulation appears to be a significant factor. Hypertension in lean patients appear to be a result of peripheral vasoconstriction, while obesity-related hypertension seems to depend on SNS hyperactivation, with downstream effects that include increases in cardiac output and renin and aldosterone release (Cataldi et al. 2016). The mechanism behind this SNS stimulation appears to be related to the release of adipokines, inflammatory cytokines, and free fatty acids from adipose tissue. The release of these substances then affects insulin sensitivity and in turn SNS stimulation (Cataldi et al. 2016). This mechanism is supported by clinical studies that demonstrated the concomitant decrease in BP and SNS activity when insulin was lowered by low energy diets in obese patients (Landsberg et al. 2013).

As far as treatment of hypertension is concerned, some of the more popular antihypertensive medications include the β-adrenergic receptor antagonists due to their efficacy in the treatment of hypertension, ischemic heart disease, congestive heart failure, and certain arrhythmias. Propranolol is an example of a nonselective β-blocker, as it has equal infinity for β_1 and β_2 adrenergic receptors. Other β-blockers like metoprolol, atenolol, acebutolol, nebivolol, bisprolol, metoprolol, and esmolol have a greater affinity for β_1 receptors than β_2 (Brunton et al. 2006). While several studies have been conducted, assessing the PK and PD in obese patients taking propranolol, results have not been consistent across these studies. A study conducted by *Cheymol* et al. that assessed a 8 mg i.v. dose of propranolol in obese and nonobese subjects reported a significant increases in AUC ($AUC_{obese} = 161.0\ h \cdot \mu g/L$ vs. $AUC_{non\text{-}obese} = 109.6\ h \cdot \mu g/L$) and lower V_d ($V_{d\text{-}obese} = 208.9$ L vs. $V_{d\text{-}non\text{-}obese} = 318.6$ L) and CL ($CL_{obese} = 57.5$ L/h vs. $CL_{non\text{-}obese} = 75.9$ L/h) values for obese subjects compared to nonobese subjects (Cheymol et al. 1987).

A slightly older study conducted by *Bowman* et al. assessed both an i.v. dose (10 mg) and oral dose (40 mg) of propranolol in obese and nonobese subjects. Following i.v. administration

propranolol CL was unchanged, however the V_d was greater ($V_{d\text{-obese}}$ = 3391 vs. $V_{d\text{-non-obese}}$ = 1981 L). Similarly, following oral administration, there was no difference observed in CL, while V_d was higher in the obese subjects and there was a trend towards higher systemic availability in the obese group (35% vs. 27%) however this was not statistically significant (Bowman et al. 1986). Both propranolol (80 mg) and atenolol (100 mg), β_1 selective blockers, were assessed in lean normolipaemic, obese normolipaemic, and obese hyperlipidaemic patients. After completion of this crossover study, there was no statistically significant difference in propranolol serum concentrations across the three groups, while the concentrations of atenolol were significantly lower in both normolipaemic obese and hyperlipidaemic obese subjects. Propranolol displayed a trend towards increases in both V_d and CL in the obese patients with hyperlipidaemia. In comparison, Atenolol displayed a significantly lower systemic exposure (AUC), C_{max} and CL in both normolipaemic and hyperlipidaemic obese patients. Changes in the PD effects (heart rate and systolic blood pressure) for both compounds were similar across patient groups (Wójcicki et al. 2003). Studies with other β_1 selective blockers (nebivolol and metoprolol) have shown higher V_d and CL values in obese subjects when compared to nonobese subjects however with similar reductions in HR and BP (Galletti et al. 1989; Cheymol et al. 1997).

While there was some diversity in changes observed in the PK of these β-blockers, the PD effects were generally the same across the different weight groups assessed. That being said, there is a lack of data on the simultaneous administration of multiple antihypertensive drugs when treating patients that display poor responsiveness to single drug therapy. Important to note is that β-blockers have been linked to insulin resistance and associated weight gain as well as decreased diet-induced thermogenesis and fat oxidation. Therefore, many have suggested that this class of antihypertensives should be limited to obese patients with specific cardiovascular indications, like postmyocardial infarction and heart failure (Landsberg et al. 2013). Based on this rationale, many physicians have suggested the use of ACE inhibitors that antagonize the renin-angiotensin-aldosterone system (RAAS) as first-line agents (Landsberg et al. 2013).

Antiarrhythmic Drugs

Antiarrhythmic drug therapy can have two goals: (1) the termination of an ongoing arrhythmia or (2) the prevention of an arrhythmia. Since antiarrhythmic drugs can have various mechanisms of action, the Vaughan-Williams classification system was developed to better organize these compounds. Most antiarrhythmic drugs are grouped into 4 main classes based on their dominant cellular electrophysiologic effect. Class I drugs are sodium channel blockers, which can be broken down into three subclasses (a, b, c,) based on their kinetic effects of the sodium channel; Class II drugs are beta-blockers; Class III drugs are primarily potassium channel blockers; and Class IV drugs are the nondihydropyridine calcium channel blockers (Brunton et al. 2006).

Amiodarone is a Class III antiarrhythmic but noted to have properties of the other classes (Shank and Zimmerman 2015). It is a preferred antiarrhythmic for patients with structural heart disease. Following a literature search, only one study was identified that assessed the effects of weight on the pharmacology of this compound. A study conducted by *Fukuchi* et al. evaluated the influence of obesity on pharmacology of amiodarone using PK Modelling in Japanese patients treated with oral therapy. The model indicated that the total clearance of amiodarone was influenced by BMI and age, specifically the clearance decreased by approximately 22.3% with a BMI >25 kg/m (Fukuchi et al. 2009).

Procainamide is a Class Ia antiarrhythmic. The PK of i.v. procainamide was studied in a small clinical pharmacology study in obese and normal-weight subjects. The V_d was similar between both groups, while CL, corrected for body surface area, was greater in obese subjects. While metabolic clearance was similar between the groups, renal clearance was found to be significantly increased, which is likely due to increased tubular secretion of PA in the obese group (Christoff et al. 1983).

Verapamil is a Class IV antiarrhythmic. Verapamil (0.15 mg/kg) was administered by 10-min i.v. infusion to 12 obese (127 +/− 8 kg) and 11 normal weight (74 +/− 4 kg) hypertensive patients. Pharmacodynamic measures which included electrocardiographic P-R interval, mean BP, and HR were recorded with simultaneous PK blood sampling. Elimination half-life ($t_{1/2}$) was prolonged in obese patients ($t_{1/2obese}$ = 10.1 h vs. $t_{1/2non\text{-}obese}$ = 3.6 h) and a marked increase in V_d ($V_{d\text{-}obese}$ = 713 L vs. $V_{d\text{-}non\text{-}obese}$ = 301 L) was observed with no change in total CL (CL_{obese} = 1339 mL/min vs. $CL_{non\text{-}obese}$ = 1250 mL/min). Additionally, verapamil plasma protein binding was similar between groups (percent unbound, 4.8% obese vs. 5.1% nonobese). Through PD modeling, the E_{max} (maximal prolongation in the P-R interval) was unchanged with obesity ($E_{max\text{-}obese}$ = 53.7 ms vs. $E_{max\text{-}non\text{-}obese}$ = 45.9 ms). However, the EC_{50} (verapamil concentration required to achieve 50% of E_{max} prolongation in the P-R interval) was greater in obese patients ($EC_{50\text{-}obese}$ = 45.9 ng/mL vs. $EC_{50\ -\ non\text{-}obese}$ = 22.6 ng/mL) (Abernethy and Schwartz 1988).

Digoxin is a cardiac glycoside, typically used for the treatment of heart failure and arrhythmias. Digoxin PK was studied in obese (mean weight = 100.2 kg) and nonobese (mean weight = 64.6 kg) subjects. After administration of 0.75 mg digoxin via i.v., serial plasma samples were obtained. Elimination $t_{1/2}$ was similar between groups ($t_{1/2\text{-}obese}$ = 36 h vs. $t_{1/2\text{-}non\text{-}obese}$ = 41 h), along with the V_d ($V_{d\text{-}obese}$ = 981 L vs. $V_{d\text{-}non\text{-}obese}$ = 937 L), and total CL (CL_{obese} = 328 mL/min vs. $CL_{non\text{-}obese}$ = 278 mL/min) of digoxin (Abernethy et al. 1981).

Anticoagulants/Antiplatelets

Obesity isa risk factor for both arterial and venous thrombosis, along with ischemic stroke, deep vein thrombosis (DVT), and pulmonary embolism (PE) (Shank and Zimmerman 2015; Lentz 2016). The obesity-related mechanisms that appear to be associated with this risk of thrombosis are chronic inflammation, impaired fibrinolysis, immobility, obstructive sleep apnea, heart failure, and venous stasis (Lentz 2016). Additionally, obese patients appear to have a greater risk of recurrent VTE compared with normal-weight patients (Alquwaizani et al. 2013).

Unfractionated heparin (UFH) is one of several options for VTE prophylaxis in medical patients with known risk factors or for both general and bariatric surgery (Shank and Zimmerman 2015). Heparin reversibly binds to antithrombin, which in turn inhibits activated coagulation factors in both the intrinsic and common coagulation pathways, including thrombin (factor IIa), factor Xa, and factor IXa (Brunton et al. 2006). Both i.v. and subcutaneous (s.c.) injections are routes for UFH administration. When administered subcutaneously, doses need to be large enough (>30,000 U/day) to overcome UFH's low bioavailability; therefore, i.v. administration is generally preferred, as therapeutic plasma concentrations can be quickly achieved and effectively monitored (Alquwaizani et al. 2013). Several clinical trials have been published suggesting that modified dosing regimens in obese patients may be necessary to rapidly achieve the desired PD effect. This is done by measuring the activated partial thromboplastin time (aPTT) when administering UFH (Shank and Zimmerman 2015). Several studies suggest that larger than normal standard dosing of UFH may be warranted in these cases to provide the desired therapeutic aPTT levels (Freeman et al. 2010). Many of these same studies have also suggested that this can be done without risking excessive anticoagulation leading to bleeding. However, while this may allow the target aPTT level to be reached quicker, administering a higher dose of UFH to obese patients may not lead to additional efficacy in reducing the incidence of VTE, and the potential increase in the risk for bleeding should not be ignored (Joy et al. 2016).

Because of the unpredictable bioavailability and inconsistent anticoagulant effects of UFH, low molecular weight heparins (LMWHs) with their predictable dose response (peak anti-Xa activity occurring 3–5 h after injection) have replaced UFH in many treatment paradigms. LMWHs are derived by depolymerization of UFH, with isolation and extraction of low

molecular weight fragments. The most consistent and widely used laboratory test for LMWH has been the anti-FXa activity assay, although monitoring is typically not used, it remains an option for high-risk patients (renal insufficiency, obesity, pregnancy, noncompliance) where dosing adjustments may be required. In these cases, anti-Xa plasma levels are typically drawn 4 h after administration, and subsequent dosing adjusted to target levels (Alquwaizani et al. 2013).

The enoxaparin package insert recommends a 1 mg/kg dose; however, many times obese patients receive an arbitrary lower dose in practice. This seems to be out of a concern that if the recommended dose is followed in obese patients, there is an increased likelihood of supratherapeutic anti-Xa levels and therefore an increased risk of bleeding. However, it is important to note that anti-Xa levels have not been prospectively correlated with any clinical outcomes (Thompson-Moore et al. 2015). That said, a recent study assessed the i.v. administration of enoxaparin sodium (1.5 mg/kg Total Body Weight) as a 6-h infusion and resulted in higher observed maximum PD activity (E_{max}) and overall systemic PD activity (effect)-time curve from time zero to infinity ($AUEC_1$) values for both anti-Xa and anti-IIa levels in the obese patients. The absolute CL and V_d for anti-Xa activity were significantly increased in obese subjects (0.99 L/h vs. 0.74 L/h and 5.77 L vs. 4.37 L, respectively) (Hanley et al. 2010).

Another study conducted by *Thompson-Moore* et al. prospectively assessed enoxaparin dosing in hospitalized morbidly obese patients (Thompson-Moore et al. 2015). The dosing practices observed in the hospital setting seemed to be reflective of other studies reported in the literature. Approximately 53% of patients received less than the recommended 1.0 mg/kg dose of enoxaparin. While 15 patients weighed >150 kg, only 1 patient was dosed with 1.0 mg/kg, again, reflective of an arbitrary dosing limit for these types of patients. Interestingly, despite this under-dosing, greater than 50% of the patients still had supratherapeutic anti-Xa levels. The actual median dose that produced a therapeutic anti-Xa level was 0.83 mg/kg actual body weight) (Thompson-Moore et al. 2015). The increased PD activity observed in this study is likely reflective of the drug's poor distribution into adipose tissue and corresponding increased V_d (Thompson-Moore et al. 2015). While no recommendations are provided in the enoxaparin package insert for dosing in obese patients, considering this increase in PD activity, it is generally recommended that initiation of

therapy should occur at a lower initial dose and anti-Xa levels should be monitored and used for dose adjustments as needed (Thompson-Moore et al. 2015).

Warfarin is still the most commonly prescribed anticoagulant globally. Warfarin's mechanism of action involves the inhibition of the vitamin K epoxide reductase complex in the liver thereby depleting the body's vitamin K dependent coagulation Factors II, VII, IX, and X and anticoagulant proteins C and S (Brunton et al. 2006). Warfarin is dosed to a therapeutic PD effect by measuring the international normalized ratio (INR), a value derived from the patient's prothrombin time (PT) laboratory value. Compared to normal weight patients, obese and morbidly obese patients have been found to take a significantly longer median time to achieve therapeutic INR (8 and 10 days vs. 6 days) values and higher average daily doses (6.6 ± 0.3 and 7.6 ± 0.5 vs. 5 ± 0.3 mg) and mean discharge doses (6.7 ± 0.5 and 6.7 ± 0.7 vs. 4.4 ± 0.5 mg). In summary, compared to normal weight patients, obese and morbidly obese patients had a lower initial response to warfarin (Wallace et al. 2013).

Rivaroxaban is an oral, direct Factor Xa inhibitor that targets free and clot-bound Factor Xa and Factor Xa in the prothrombinase complex. Rivaroxaban is the first of a new class of compounds termed direct oral anticoagulants that specifically target a single coagulation factor (such as Factor Xa or thrombin). These compounds were developed in recent years to overcome the limitations of established anticoagulants, particularly warfarin. Factor Xa plays a central role in blood coagulation as it is activated by both the intrinsic and common coagulation pathways. Factor Xa directly converts prothrombin to thrombin via the prothrombinase complex, leading to fibrin

clot formation and activation of platelets by thrombin (Mueck et al. 2014). Rivaroxaban does not require routine PD monitoring; however, there is a linear relationship between PT and rivaroxaban concentrations when using a sensitive PT reagent (e.g., Neoplastin+). Additionally, antifactor Xa values derived from an assay using rivaroxaban calibrators can be used to indirectly measure rivaroxaban concentrations.

In a clinical pharmacology study conducted during drug development, there was no clinically significant difference between rivaroxaban PK and PD observed when assessed in obese vs. nonobese individuals. The C_{max} and AUC values were unaffected in subjects weighing >120 kg. Additionally, rivaroxaban inhibited FXa activity to a similar extent in obese and nonobese individuals. FXa maximum values (E_{max}) occurred 3 to 4 h after rivaroxaban administration for both groups. However, the E_{max} for prolongation of PT decreased significantly (P <0.001) with increasing body weight and was observed 2 to 3 h after administration of rivaroxaban (Kubitza et al. 2007).

As previously mentioned, obesity is a risk factor for cardiovascular disease (CVD), many times caused by hyperlidemia and platelet hyperactivity that leads to atherosclerosis. Excess adipose tissue promotes a prothrombotic and inflammatory state and in turn increases plaque formation. Antiplatelets are commonly used in this CVD. However, observations from several clinical trials have shown that obese individuals have higher platelet reactivity and ultimately display a blunted response to antiplatelet agents (Beavers et al. 2015). Aspirin reduces prostaglandin biosynthesis and irreversibly inhibits cyclooxygenase-1 & -2 (COX) enzyme activity (Brunton et al. 2006). Aspirin exerts its antiplatelet effects through its inhibition of COX-1, which in turn decreases the downstream production of platelet activation by thromboxane A2, a potent platelet activator (Shank and Zimmerman 2015). In a study conducted by *Bordeaux* et al., obese patients consistently showed greater platelet reactivity both before and after administration of low-dose aspirin (81 mg daily). Increasing the dose of aspirin did not appear to increase platelet activity suppression (Bordeaux et al. 2010). These results suggest that obese individuals have an innate hyperaggregable state, which have been suggested in other studies (Bordeaux et al. 2010).

Clopidogrel is an irreversible $P2Y_{12}$ receptor antagonist. Due to its improved tolerability, reduced incidence of hematological side effects, more rapid onset of action, and a convenient dosing regimen, this second-generation thienopyridine has largely replaced ticlopidine (a first-generation thienopyridine with similar efficacy). Clopidogrel asserts its PD effects by specifically and irreversibly binding to $P2Y_{12}$, a subtype of the adenosine diphosphate (ADP) receptor, on the surface of platelets (Jiang et al. 2015). This PD effect is measured by ADP-induced platelet aggregation in platelet-rich plasma which has been the gold standard for assessing platelet function in relation to the clinical outcome (Jiang et al. 2015). Obesity has been shown to significantly affect clopidogrel response. Several studies have reported that BMI or body weight is associated with high platelet reactivity (HPR) in both patients and healthy subjects.

Measurement of platelet aggregation utilizing the VerifyNow $P2Y_{12}$ assay is a fast, standardized point-of-care method that determines platelet-induced aggregation in whole blood by using ADP and prostaglandin E1. A recent clinical pharmacokinetic study reported that, compared with patients with lower body weight, patients with higher body weight had approximately 30% lower AUC values for the pharmacologically active metabolite R-130964 (clop-AM), which ultimately led to higher on treatment platelet reactivity in these obese patients. This can be seen when assessing the VerifyNow $P2Y_{12}$ reaction reading in patients, which was 207 $P2Y_{12}$ reaction units (PRU) for those considered obese and 152 PRU for those considered of normal weight (Jiang et al. 2015). The increased platelet reactivity observed in obese patients is likely a result of the inflammatory state created by obesity. This state may set in motion a number of mechanisms that lead to increased reactivity, suppression of some CYP-P450 activity, and platelet turnover, that all

contribute to this poor clopidogrel response (Jiang et al. 2015).

Endocrine System

Estrogens/Progestins/Contraceptives

Obesity adds to the overall risk of pregnancy. Those females of reproductive age who are obese have an increased risk of spontaneous abortion, preeclampsia, gestational diabetes, shoulder dystocia, and cesarean section (Robinson and Burke 2013). While obese females have the same potential risks for altered drug PK as any other obese individual (i.e., the potential for changes in drug absorption, distribution, metabolism, and excretion), there are also potential PD changes in the outcomes of contraceptive therapy (Robinson and Burke 2013). For example, the suppression of ovarian follicular development, alterations in cervical mucus characteristics, higher serum estrogen concentrations, lower progesterone concentrations, decreased luteinizing hormone concentrations, and altered rhythmic patterns of some of these during the menstrual cycle (Robinson and Burke 2013).

There are various forms of contraceptives, pill forms, intrauterine devices, subdermal implants, and injectables. Additionally, there are single hormonal and combined hormonal formulations. Progestin-only contraceptives can be found in each of these forms. The two intrauterine systems (IUS) available, release progestin levonorgestrel (LNG) come in both 3- and 5-year LNG-IUS formulations (Robinson and Burke 2013). The main mechanism of action of the LNG-IUS is that it delivers hormone directly to the endometrium where it leads to endometrial thinning and decidualization. Considering that the mechanism of action occurs locally on the uterus, there is no reason to think that these systems would be less effective in obese versus nonobese women (Robinson and Burke 2013). While some authors have noted that insertion of the IUS in obese individuals may be problematic, the efficacy that is preserved across BMIs makes these systems ideal for obese women wishing to delay or avoid pregnancy.

Currently marketed contraceptive subdermal implants include etonogestrel (ENG) and levonorgestrel (LNG). A study by *Mornar* et al. assessed the PK of ENG implants in obese (BMI $\geq$30 kg/m^2) women and nonobese women that were consistent with historical controls (Mornar et al. 2012). The researchers observed that the obese women had approximately 50% lower ENG AUC values than the nonobese women. Additionally, this lower systemic exposure led to an estimated 40% lower ENG exposure over the life of the implant; however, none of these women were projected to have an ENG level below the estimated cut-off concentration for reliable ovulation suppression (90 pg/mL) (Mornar et al. 2012).

Depot medroxyprogesterone acetate (DMPA-i.m.) is an intramuscular injectable contraceptive that is widely used around the world at a dose of 150 mg and provides highly effective contraception for approximately 3 months. The subcutaneous formulation (DMPA-s.c.) delivers a lower dose of DMPA (104 mg) and also provides comparable contraceptive effect. Neither the efficacy of the i.m. nor s.c. formulations are known to be decreased in obese women. While one study that evaluated the PK and PD of DMPA-s.c. did observe lower serum concentrations in obese subjects, levels remained above the threshold needed for ovulation suppression (Robinson and Burke 2013).

The most frequently used agents are the combination oral contraceptives containing both an estrogen and a progestin. The theoretical efficacy of this combination is approximately 99.9%. Both ethinyl estradiol (EE) and mestranol are the two estrogens used in the various formulations, while there is a greater variety of progestins that are included (Brunton et al. 2006). The estrogen component contributes to ovulation suppression and control of irregular bleeding, while the inclusion of a progestin suppresses the hypothalamic–pituitary–ovarian axis leading to inhibition of ovulation. The transdermal patch and vaginal ring also contain a combination of estrogen and progestin, and their mechanism of action is the same as the oral formulations (Robinson and Burke 2013).

In previous studies that assessed the various PK parameters in obese women taking the

combination oral contraceptive, 20-mg EE/100-mg levonorgestrel (LNG), the $t_{1/2}$ was prolonged, systemic exposure measured by AUC values were larger and CL was lower. At the same time, it was observed that obese women had higher levels of ovarian hormone production (estradiol and progesterone), suggesting greater ovarian activity and the potential for decreased contraceptive efficacy (Robinson and Burke 2013; Simmons and Edelman 2016). These PK changes led to longer times to reach steady-state concentrations and therefore a longer time to reach levels sufficient for ovulatory suppression. In one study, steady state concentrations in one obese individual was not achieved even after the full 21-day pill cycle (Robinson and Burke 2013; Simmons and Edelman 2016).

However, other studies have demonstrated very different results. For example, one study assessing the use of a 30 μg EE/150 μg LNG combined oral contraceptive in nonobese and obese women found obese individuals had lower AUC, C_{max} and T_{max} values as well as a prolonged t½ for both hormones, compared with nonobese women. Results are somewhat contradictory to the previously mentioned studies. Furthermore, PD assessments indicated that there was no significant difference in ovarian follicular activity across BMI, supporting the conclusion that despite the PK changes observed, conceptive efficacy was maintained in obese individuals. When considering the limited data available on the use of oral contraceptives in obese women, most studies tend to demonstrate that there is not a significant difference in effectiveness across weight or BMI. However, it is important to note that these studies rarely included women that were morbidly obese, and the total amount of data is insufficient.

Again, there is limited data on the PK, PD, or efficacy of transdermal contraceptive patches. A study by *Westhoff* et al. stratified participants according to three BMI groups (Group 1 $\leq$30 kg/m^2; Group 2, n >30 kg/m^2 and $\leq$35 kg/m^2; and Group 3 >35 kg/m^2) (Westhoff et al. 2014). Each participant received a transdermal patch containing 0.55-mg EE and 2.1-mg gestodene (GSD). Each patch was used weekly for three 28-day cycles and its PD effect was measured by the Hoogland score, which is a composite score that comprises of transvaginal ultrasound and estradiol (E_2) and progesterone levels every 3 days in Cycles 2 and 3. Additionally, PK and EE, GSD, and sex hormone-binding globulin were assessed (Westhoff et al. 2014).

Study results reported that only six ovulations occurred during the study, and no participant ovulated in both study cycles. The ovulations observed occurred across the different weight groups and was unaffected by differences in BMI. A majority of participants had Hoogland scores of 1 or 2 regardless of BMI grouping. Follicle-like structures <13 mm were reported in ~80% (Cycle 2) and ~86% (Cycle 3) in Group 1; ~61% (Cycle 2) and ~75% (Cycle 3) in Group 2; and ~78% (Cycle 2) and ~73% (Cycle 3) in Group 3. Hormone levels (follicle-stimulating hormone (FSH), luteinizing hormone (LH), E2, and progesterone) were similar across BMI groups. The authors concluded that the EE/GSD patch provided effective ovulation inhibition across BMI strata (Westhoff et al. 2014).

Emergency contraceptive pills (ECPs) are effective at reducing the risk of pregnancy up to 5 days after unprotected intercourse. Their mechanism of action involves the inhibition of delaying of ovulation and is most effective if taken soon after unprotected intercourse. The LNG-based regimens are provided as either a single dose of 1.5 mg LNG or two doses of 0.75 mg LNG taken 12 h apart and are effective in reducing the risk of pregnancy up to 72 h after unprotected intercourse, while the ulipristal acetate (UPA) ECP, which is a progesterone agonist/antagonist, is a one-time 30 mg dose that is effective up to 5 days after unprotected intercourse (Glasier 2013).

Similar to the other contraceptives discussed, there are limited data on the effects of obesity on these treatments. A meta-analysis performed by *Glasier* et al. looked at the combined results from two randomized clinical trials comparing LNG and UPA ECPs (Glasier et al. 2011). The authors reported that the risk of pregnancy was >3-fold for obese women compared to nonobese women whichever ECP was taken. However, this risk was greater for those taking LNG than for those taking UPA. Interestingly, women who had unprotected

intercourse after using ECP were more likely to get pregnant than those who did not, regardless of type used (Glasier et al. 2011). Consistent with Glasier et al., a small clinical pharmacology study conducted by *Edelman* et al. assessed the PK parameters of nonobese (median 22.8 kg/m^2) and obese women (median 39.5 kg/m^2) dosed with both a single and double dose of LNG ECP. The single dose of LNG ECP in obese women resulted in a significantly lower C_{max} ($C_{max\text{-}obese}$ = 5.57 ng/mL) than that observed in normal weight women ($C_{max\text{-}non\text{-}obese}$ = 10.30 ng/mL), approximately 50% lower. Doubling the dose of LNG ECP increased the C_{max} significantly ($C_{max\text{-}obese}$ = 10.52 ng/mL) essentially normalizing the C_{max} level to that of the normal BMI subjects receiving a single ECP dose (Edelman et al. 2016).

Invading Organisms

Antimicrobials

Antimicrobial agents are classified based on chemical structure and proposed mechanism of action. There are those agents that: (1) inhibit synthesis of bacterial cell walls; (2) act directly on the cell membrane, increasing permeability and compromising the structure of the microorganism; (3) disrupt ribosomal function to inhibit protein synthesis and are bacteriostatic; (4) disrupt ribosomal function to alter protein synthesis and are bactericidal; (5) affect bacterial nucleic acid metabolism; and (6) are antimetabolites that block essential enzymes of folate metabolism (Brunton et al. 2006).

Additionally, these mechanisms of action can be further divided into time-dependent or concentration-dependent effects and each antimicrobial class has a unique PK/PD target. For example, β-lactam antibiotics are time-dependent, they produce the most effective PD response when the concentration of the free drug remains above the minimum inhibitory concentration (MIC). Aminoglycosides are concentration-dependent, with the most effective PD response occurring when the C_{max} of the drug is over the MIC (C_{max}/MIC) (3). Then there are those compounds that are both time- and concentration-dependent, therefore when the AUC of the antimicrobial from 0–24 h is over the MIC (AUC_{0-24}/MIC) thereby drives bacterial killing (Alobaid et al. 2016).

The β-lactam antibiotics fall into the first class of agents described that inhibit the synthesis of bacterial cell walls. They include the penicillins, cephalosporins, β-Lactamase inhibitors, and Carbapenems (Brunton et al. 2006). A prospective study conducted by *Hites* et al. assessed the PK and PD parameters of infected obese patients (BMI $\geq$30 $kg{\cdot}m^{-2}$) who received either meropenem (MEM), piperacillin-tazobactam (TZP), or cefepime/ceftazidime (CEF) β-lactam antibiotics. The primary PD parameter in this study was defined as the "clinical breakpoint" of the microorganisms assessed for different antimicrobial therapies (Hites et al. 2014).

These breakpoints, as defined by the European Committee on Antimicrobial Susceptibility Testing (EUCAST), have been fixed to ensure a good probability of therapeutic success. The breakpoint for β-lactams used by EUCAST is defined as the drug's free fraction (fT) >1× MIC [fT>MIC] during 40–50%, 50–60%, and 60–70% of the dosage interval for MEM, TZP, and CEF, respectively. It should be noted that a higher PD target is frequently used when clinical situations arise where patients are suffering from conditions like septic shock or are neutropenic due to oncological treatment. These situations may justify the use of a total fraction (T)>4×MIC [T>4MIC] for 40%, 50%, and 70% of the dosage interval for MEM, TZP, and CEF, respectively (Hites et al. 2014).

Different pathogens have different PD targets. For example, for infections caused by *Enterobacteriaceae* spp. and *P. aeruginosa*, the EUCAST's clinical breakpoints for these pathogens are: 2 mg/L for MEM, 8 mg/L and 16 mg/L for TZP, and 1 mg/L and 8 mg/L for CEF, respectively. Total serum concentrations and fT at 40%, 50%, and 70% of the dosage intervals for MEM, TZP, and CEF, respectively, were as follows: 6.2 mg/L and 6.1 mg/L for MEM, 36.7 mg/L and 25.7 mg/L for TZP, and 16.1 mg/L and 12.5 mg/L for CEF (Hites et al. 2014).

When evaluating the fT>MIC for *Enterobacteriacae* spp., adequate serum concentrations

were obtained in 93% of patients receiving MEM, 84% of patients receiving TZP, and 91% of patients receiving CEF. For infections due to *P. aeruginosa*, adequate *f*T>MIC were obtained in 93% of patients receiving MEM, 68% of patients receiving TZP, and 73% of patients receiving CEF. According to the EUCAST criteria, any percentage of PD target that is <90% was considered insufficient therapeutic coverage (Hites et al. 2014).

Therefore, when standard doses of these antibiotics were administered to obese, noncritically ill patients, infected with *Enterobacteriaceae* spp., only MEM and CEF reached therapeutic serum concentrations. Additionally, when the same antibiotics were administered to obese, noncritically ill patients infected with *P. aeruginosa*, only MEM reached therapeutic serum concentrations (Hites et al. 2014).

When the investigators assessed the higher PD target (T>4MIC) for infections from *Enterobacteriacae* spp. and *P. aeruginosa*, much fewer patients reached the PD target. Adequate serum concentrations were only reached for 21% for MEM, 55% for TZP, and 91% for CEF with *Enterobacteriacae* spp. infections and for 21% for MEM, 19% for TZP, and 18% for CEF *P. aeruginosa* infections. Therefore, only CEF with 91% of patients infected with *Enterobacteriacae* spp. met the EUCAST criteria (Hites et al. 2014).

The decreased serum concentrations observed in this study is likely caused from an increase in V_d and CL for all three study drugs, when compared to non-obese individuals. A CrCL of >150 mL/min was observed in approximately 25% of those in the obese cohort. This augmented renal CL appears to be the major risk factor for failure to reach therapeutic concentrations. Together, these data suggest that standard dosage regimens, particularly for TZP, are insufficient in obese, noncritically ill patients (Hites et al. 2014).

Increased drug CL has been described in critically ill patients and has been termed augmented renal clearance (ARC), a condition where renal elimination of circulating solutes is increased. ARC is defined as a CrCL of ≥130 mL/min/1.73 m^2. ARC is associated with subtherapeutic antimicrobial concentrations and worse clinical outcomes in critically ill patients receiving standard doses of antimicrobial therapy.

An increase in renal CL has been observed in obese individuals who have normal kidney function, most likely due to the increased kidney size and renal blood flow associated with obesity. While this altered physiology may result in lower antimicrobial concentrations, higher concentrations may be observed in obese patients with co-morbidities such as diabetic nephropathy. Obese individuals are more likely to have pathologies that cause hepatic dysfunction, such as hepatic steatosis, possibly resulting in decreased drug metabolism. Obesity may also have an impact on different hepatic enzyme systems causing increased (e.g., CYP2E1) or decreased (e.g., CYP3A4) activity.

In another study conducted by *Sturm* et al., the use of piperacillin/tazobactam was examined in critically ill morbidly obese patients (BMI >40 kg/m^2). All patients achieved the PK/PD target of 100% *f*T>MIC for pathogens with an MIC of 16 mg/L using a piperacillin/tazobactam dose of 4.5 g i.v. every 6 h. Morbidly obese patients had a higher piperacillin V_d (31.0 L vs. 22.4 L) and lower CL (6.0 L/h vs. 13.7 L/h) compared with nonobese patients (Atkinson et al. 2007). The net result was a $t_{1/2}$ of 3.7 h compared with 1 h reported in other populations. This longer $t_{1/2}$ likely contributed to an extended % *f*T>MIC for susceptible pathogens. Based on these results, it would appear that the tested 4.5 g i.v. dose every 6 h would be sufficient to attain the desired PK/PD target of %fT>MIC (Sturm et al. 2014).

While the effects of obesity on penicillin PK and PD parameters are sparse to nonexistent in the literature, compounds like ampicillin, penicillin, ticarcillin would likely exhibit similar changes in their PK and PD to that of piperacillin.

Cefoxitin is a second-generation cephamycin antibiotic and classified as a semisynthetic, broad-spectrum, cephalosporin. Cefoxitin is commonly used for perioperative parenteral surgical prophylaxis. *Moine* et al. studied the PK and PD of a 40 mg/kg i.v. dose in morbidly obese individuals (Moine et al. 2016). Although the dose used in this study was substantially higher than the standard

cefoxitin doses typically used, the C_{max} observed in this study was similar to those previously reported for nonobese populations receiving a much lower weight-based dose. This lower than expected C_{max} along with a prolonged $t_{1/2}$ is consistent with the approximate twofold higher V_d values observed in this study compared to nonobese populations. Additionally, despite the use of these higher doses, tissue concentrations were poor, with an average tissue/serum ratio of 8%, and below the Clinical and Laboratory Standards Institute (CLSI) breakpoint for anaerobes targeted by this antibiotic. As with the other β-lactams, the time during which unbound drug concentrations are greater than the pathogen MICs ($fT>MIC$) is the PD parameter best correlated with clinical efficacy (Moine et al. 2016).

The authors noted that the PD target for surgical prophylaxis is largely undefined. Considering that surgical contamination may occur at any point during the procedure, a *f*TMIC of 100% was suggested as an ideal target for cefoxitin and β-lactam antibiotics in general, during surgery. Even though the authors calculated a more conservative *f*TMIC of 70%, tissue concentrations failed to reach the needed level for efficacy. Concentrations were below the susceptibility breakpoint for *S. aureus* and *E. coli*, suggesting inadequate coverage if an intraoperative contamination would have occurred. The authors suggest that although the weight-based dose at 40 mg/kg performed better than a standard 2-g dose, it would likely be inadequate to prevent infection (Moine et al. 2016).

Aminoglycosides are primarily used to treat infections caused by aerobic gram-negative bacteria. They are considered bactericidal as they disrupt ribosomal function to alter protein synthesis. This class of antibiotic includes gentamicin, tobramycin, amikacin, kanamycin, netilmicin, streptomycin, and neomycin (Brunton et al. 2006). The aminoglycoside antimicrobials are hydrophilic weak bases and have a corresponding low V_d (closer to blood volume). These compounds have optimal bactericidal activity when achieving peak concentrations that are 8x to 10x the MIC of the targeted pathogen (Hanley et al. 2010). A study conducted by *Bauer* et al. assessed the steady-state PK of three aminoglycosides – gentamicin, tobramycin, and amikacin – in morbidly obese subjects (Bauer et al. 1983). The investigators observed that the mean V_d values were substantially larger for the morbidly obese subjects compared to the nonobese subjects: gentamicin ($V_{d\text{-obese}} = 23.31$ L vs. $V_{d\text{-non-obese}} = 17.01$ L), tobramycin ($V_{d\text{-obese}} = 29.01$ L vs. $V_{d\text{-non-obese}} = 18.31$ L), and amikacin ($V_{d\text{-obese}} = 26.81$ L vs. $V_{d\text{-non-obese}} = 18.61$ L). Similarly, CL values were larger in the morbidly obese subjects compared to the nonobese subjects: gentamicin ($CL_{obese} = 135.8$ mL/min vs. $CL_{non\text{-}obese} = 95.9$ mL/min), tobramycin ($CL_{obese} = 162.4$ mL/min vs. $CL_{non\text{-}obese} = 101.3$ mL/min), and amikacin ($CL_{obese} = 157.3$ mL/min vs. $CL_{non\text{-}obese} = 99.2$ mL/min). Albeit the significant increases in V_d and CL, there was no significant difference between predicted and measured steady-state concentrations as determined by C_{max} and C_{min} values. This is likely attributed to the larger creatinine clearance values secondary to hyperfiltration commonly observed in obese individuals (Bauer et al. 1983).

Daptomycin is a lipopeptide antibiotic used in the treatment of systemic and life-threatening infections caused by gram-positive organisms (i.e., enterococci, staphylococci, streptococci). The MIC of daptomycin (MIC_{90}) is typically ≤ 1 μg/mL for staphylococci and streptococci and 2 to 4 μg/mL for enterococcal species. This compound is both time- and concentration-dependent, in which bacterial eradication is dependent upon the ratio of $AUC_{0\text{–}24h}$ to the MIC ($AUC_{0\text{–}24h}$/MIC). *Dvorchik* and *Damphousse* conducted a study assessing the PK of daptomycin in moderately obese (BMI between 25 and 39.9 kg/m^2) or morbidly obese (BMI ≥ 40 kg/m^2) compared to matched nonobese (BMI between 18.5 and 24.9 kg/m^2) subjects (Dvorchik and Damphousse 2005).

After administration of a 4-mg/kg total body weight dose, the C_{max} and AUC values for both obese groups were higher compared to their respective matched nonobese controls: Moderately Obese [$C_{max\text{-}obese} = 57.75$ μg/mL vs. $C_{max\text{-}non\text{-}obese} = 46.28$ μg/mL and $AUC_{(0\text{-}\infty)obese} = 420.53$ μg·h/mL vs. $AUC_{(0\text{-}\infty)non\text{-}obese}$

= 322.37 μg·h/mL] and Morbidly obese [$C_{max\text{-}obese}$ = 67.00 μg/mL vs. $C_{max\text{-}non\text{-}obese}$ = 53.22 μg/mL and $AUC_{(0\text{-}\infty)obese}$ = 547.78 μg·h/mL vs. $AUC_{(0\text{-}\infty)non\text{-}obese}$ = 418.76 μg·h/mL]. These differences equate to mean C_{max} values that were ~25% higher in the obese groups than in their matched controls and AUC values were ~30% to 35% greater in the obese groups compared to their matched controls.

Additionally, significant differences in daptomycin V_d were observed between obese and nonobese groups. The obese group saw increases in absolute V_d that were ~25% larger in the moderately obese subjects and ~55% in the morbidly obese subjects compared to the respective controls. In a similar trend, CL values were also increased in obese vs. nonobese subjects: moderately obese CL_{obese} = 855.80 mL/h vs. $CL_{non\text{-}obese}$ = 732.80 mL/h and morbidly obese CL_{obese} = 1015.83 mL/h vs. $CL_{non\text{-}obese}$ = 696.41 mL/h. Interestingly, renal CL was not substantially different between obese and nonobese subjects. The authors speculate that this may be a consequence of all subjects having an estimated creatinine clearance ≥70 mL/min, however did not provide any information on whether obese subjects had CrCL values representative of abnormally high glomerular filtration rate (GFR) or hyperfiltration (Dvorchik and Damphousse 2005).

Vancomycin is a tricyclic glycopeptide antibiotic that is commonly used to treat Gram positive pathogens, for example, severe staphylococcal and enterococcal infections. Vancomycin exerts a time-dependent antibacterial effect, and its clinical response is a function of the $AUC_{0–24h}$ and MIC ($AUC_{0–24h}$/MIC). Current guidelines recommend maintaining vancomycin trough concentrations >10 μg/mL to avoid *Staphylococcus aureus* resistance and between 15 and 20 μg/mL in complicated infections such as bacteremia, endocarditis, and osteomyelitis. Guidance is also provided for treatment of *methicillin-resistant staphylococcus aureus* (MRSA) in which a dosage of 15–20 mg/kg every 8–12 h without exceeding 2000 mg of vancomycin/dose. This in turn creates a challenge since obese patients would, however, typically require doses that would exceed 2000 mg/dose due to the initial weight-based dosing paradigm.

A study conducted by *Adane* et al. assessed the PK of vancomycin in obese subjects. For the treatment of *S.aureus*-associated lower respiratory tract infections, clinical success was found with an $AUC_{0–24h}$/MIC >315, whereas a successful microbiologic response required a $AUC_{0–24h}$/MIC >866. Clinical practice guidelines state that an $AUC_{0–24h}$/MIC ≥400 is needed for clinical effectiveness. At this level, the likelihood of *S. aureus* resistance is low and ensures adequate penetration in tissues such as the lung with minimizing potential nephrotoxicity. Those enrolled into the study had a median weight of 147.9 kg, BMI of 49.5 kg/m^2 a Cl_{Cr} of 124.8 mL/min/1.73m^2 and received a median vancomycin dose of 4000 mg/day, resulting in median $AUC_{0–24h}$ that was 582.9 mg·h/L. The mean V_d was 0.51 L/kg, and CL was 6.54 L/h. Simulations indicated that 4000–5000 mg/day of vancomycin in this population provided ≥93% probability of a $AUC_{0–24h}$ /MIC ratio of ≥400 leading to an MIC of 1 μg/mL and therapeutic effectiveness (Adane et al. 2015).

Ciprofloxacin is a broad-spectrum fluoroquinolone antibiotic. Quinolones function by inhibiting DNA gyrase and topoisomerase ultimately inhibiting cell division. Its PD effect is both concentration-dependent and time-dependent, with clinical efficacy best described using an $AUC_{0–24}$/MIC ratio. Ciprofloxacin is active against both gram-positive and gram-negative bacteria. A study conducted by *Allard* et al. assessed the PK of ciprofloxacin and its primary metabolite (desethyleneciprofloxacin) in both obese subjects (mean weight = 110.7 kg; mean BMI = 36.4 kg/m^2) and normal weight subjects (mean weight = 71.8 kg; mean BMI = 23.3 kg/m^2) (Allard et al. 1993). After receiving a single 400 mg iv dose of ciprofloxacin infused over 1 h, ciprofloxacin CL was significantly increased in obese subjects (897.44 mL/min) compared with nonobese subjects (744.44 mL/min), additionally CL_{renal} in obese subjects was 29% higher than in nonobese subjects. Lastly, ciprofloxacin V_d was

larger in obese subjects ($V_{d\text{-obese}} = 269.17$ L) than nonobese subjects ($V_{d\text{-non-obese}} = 219.03$ L) (Allard et al. 1993).

Antifungals

The azole antifungals include the imidazole and triazole classes, which share the same antifungal spectrum and mechanism of action. Azoles inhibit the fungal cytochrome P450 enzyme 14α-sterol demethylase thereby inhibiting fungal growth (Brunton et al. 2006). Fluconazole is active against a variety of *Candida* spp., with a PK/PD target of $AUC_{0-24h}/MIC > 25$. There is scarcity of literature that addresses the effects of obesity on the PK and PD of fluconazole. Of the few publications available, most report data from case studies.

Lopez and Phillips described a case report of a critically ill morbidly obese patient (BMI = 84 kg/m^2) receiving renal replacement therapy and who was being treated with fluconazole at a dose of 600 mg (Atkinson et al. 2007). The investigators calculated a $V_d = 163.3$ L and CL = 3.25 L/h, for this patient, which was significantly larger than those previously reported for critically ill nonobese patients with acute renal failure ($V_d = 65.6$ L and CL = 1.9 L/h) (Atkinson et al. 2007).

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