OBESITY RELATED ALTERATIONS IN PHARMACOKINETICS AND PHARMACODYNAMICS OF DRUGS: EMERGING CLINICAL IMPLICATIONS IN OBESE PATIENTS – Part I

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Abstract

Obesity is escalating among children and adults all over the world. This non-communicable disorder contributes heavily to severe morbidity and mortality in humans due to the occurrence of diabetes mellitus, cardiovascular diseases, osteoarthritis, and some cancers. Excess deposition of white adipose tissue in obese patients produces hormone like bioactive substances that produce inflammatory cytokines, atherosclerosis and cardiovascular diseases, to name a few. Obesity can also cause pathophysiological changes in liver, kidney, and GI tract that can affect drug disposition, resulting in therapeutic failure or toxic drug reactions. Alterations in drug absorption, distribution, metabolism and excretion (ADME), ie. pharmacokinetics (PK) and pharmacodynamics (PD) have been observed in lean and obese patients. A limited number of studies have shown significant differences in the PK parameters such as V_d , CL, $t_{1/2}$, T_{max} , C_{max} , and AUC of drugs (e.g., antimicrobials, chemotherapeutics, anesthetics, CNS agents) in obese and lean patients. In view of these observations, clinical responses to medications can markedly differ between non-obese and obese patients, and this phenomenon can lead to improper dosing, often leaving obese patients mistreated for their ailments. Morbidly obese patients are more likely to wake up during surgical interventions done under general anesthesia, especially propofol. It is therefore imperative that the loading and maintenance dose of drugs, especially anesthetics and lipophilic agents, should be adjusted in obese patients. Further, obese men, women and children should be enrolled in clinical trials to determine the safety and efficacy of pharmaceuticals. The focus of this review is to highlight the relationship of obesity-related alterations in drug ADME and to provide an updated overview about the PK and PD changes observed for a wide spectrum of drugs in obese and non-obese patients. Literature-based recommendations for rational therapeutic dose-modifications are also provided in the publication.

Adipobiology 2017, 9: 29–38

Keywords: absorption, distribution, metabolism, excretion (ADME), overweight, obesity, pharmacokinetics, pharmacodynamics, drug dose adjustment, obese patients

Received 21 November 2017, revised 5 December 2017, accepted 6 December 2017

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Introduction

The basis for rational pharmacotherapy is that the active pharmacoon should be present at the target site in optimal concentration for the expected time to produce desired clinical response(s). The inter-racial and inter-individual pharmacogenetic differences are well recognised among humans, as some are slow metabolizers while others are fast metabolizers depending upon the genetic expression and composition of cytochrome P-450 drug metabolizing enzymes in the liver. Based on these criteria, clinical responses to medications can differ between patients of same demography (e.g. Caucasians, Afro-Americans, Asians, Hispanics, Aborigines etc.). However, the clinical responses may be further exaggerated among lean and obese patients due to their physiologic differences, adipose tissue deposition and body water as well as capacity for drug metabolism and disposition, especially for lipophilic drugs. Overall, the clinical response may also differ in lean and obese patients receiving weight-based drug regimens, owing to their genetic make up, inter-individual differences, and body compositions. An other important prerequisite in the pharmacological action of medications is the drug binding target sites or receptor molecules that reveal an expected drug response. As drug binding receptors and target sites are usually proteins (enzymes, transporters, nucleic acids) and poly- glycoproteins (pGPs), the inter-individual differences also exist in this prerequisite as well.

Obesity is known to produce metabolic syndrome, fatty liver, renal malfunction (glomerulopathy and glomerulosclerosis), and abnormal changes in the gastrointestinal (GI) tract. When an obese patient suffers from these pathological conditions existing in the liver, kidney and GI tract, the absorption, distribution, metabolism, and excretion (ADME) of drugs, and consequently their PK and PD parameters are expected to be altered in obese individuals. Owing to these pathological conditions, not only the ADME, PK and PD values would be changed in obese patients as opposed to their lean counterparts, but also the clinical responses to medications would differ between lean and obese subjects.

Most of the Summary Product Characteristics (SPC) in UK and Europe and Product Monographs (PMs) in the USA and Canada do not contain any information for physicians and patients about the adjustment of drug dosage regimens in obese patients. At present, there are no clearcut rules or guidelines to indicate how the physicians, pharmacists or nurses should take into account fat surplus for calculation of drug dosages in highly obese subjects (BMI > 35-40). Since this kind of information about many drugs/ingredients is lacking and needs to be searched and incorporated on a product-to-product basis. In view of all these factors, inclusion of obese men, women, and

adolescents in clinical trials is warranted for enhancing our understanding about the PK and PD profiles of old and new drugs in very obese patients. Such clinical approach would not only ensure the dose adjustment but also the safety and efficacy of lipid soluble pharmaceuticals and anesthetics in obese individuals.

In the past, the influence of obesity on ADME, PK and PD properties of a number of drugs has been studied and reported in the literature (1-5). Several investigations revealed that it seems no longer sufficient to base drug doses on size metrics such as body weight alone. In the present review, information from several sources was collected in order to provide health professionals with knowledge of ADME, PK and PD profiles of a wide variety of drugs and formulas that can help in dose adjustment and improve the safety and effectiveness of drug therapy in obese men, women and children.

Obesity-related physiologic and pathologic health impact

According to the World Health Organization (WHO) overweight and obesity are defined as abnormal or excessive accumulation of fat that presents a risk to health in men, women and children (6). Obesity has alarmingly increased worldwide, and its pandemic has been noticed during the last 50 years. By the estimates of WHO, the prevalence of obesity has more than doubled between 1980 and 2014 on the global level. In 2014, about 39 % adults aged >18 years were overweight and 13% were obese around the world. Furthermore, 41 million children under the age of 5 were overweight or obese in 2014 (7). In most European countries and North America, the prevalence of obesity has escalated by 10-40% over the last 20 years. Similar trends are being noticed in the developing countries during the last 10-15 years. In Germany, the recently registered population data revealed that 29% women and 43-45% men can be considered overweight, and nearly 13-24% adult females and 16-23% males fall in the category of being obese (8). In the 2011/2012 school year, around 23% of children in reception and 34% in year 6 were either overweight or obese. Around 9.5% and 19%, respectively, were considered to be obese (9). In the USA, some 10 years ago, nearly 33% of adults (>20 yrs) and 17% of teenagers (12-19 yrs) were found to fall in obese category (10). Body composition in obesity develops asymmetrically. Blood volume remains nearly unchanged, overall lean body mass increases slightly, whereas the fat mass increases markedly. It means that the fat-proportion in a person with BMI = 25 is approx. 25% but with BMI = 40 is about 45% (11).

From physiologic aspects, white adipose tissue (WAT) is mainly composed of visceral and subcutaneous as well as inter-

nal organ-associated adipose tissue. These are sources of fatty acids (FFAs), and serve as endo- and paracrine organs. FFAs represent important energy source and signaling molecules, that indirectly inhibit insulin signaling. WAT exerts oxidative stress, promotes sympathetic hyperactivity and endothelial dysfunction as well as hyperinsulinemia, hyperaldosteroidemia, and hypertension (12). WAT also produces hormones and other biologically active molecules, collectively termed adipokines. In addition, WAT produces adipokines that influence appetite, energy metabolism of peripheral tissues, and the central steering by sympathetic nervous system. Obesity and related diseases are associated with low-grade chronic inflammation, which is mediated via an increased secretion of proinflammatory adipokines. The interaction between drugs and WAT-released compounds are not yet fully understood (13, 14), and requires further investigations. Morbid obesity correlates with fatty infiltration of the liver (15), and this pathological phenomenon influences endogenous and exogenous metabolic processes as well.

Some investigators have determined the influence of various gastrointestinal and renal factors that can alter the intestinal absorption and renal excretion of drugs in humans. For instance, Levitt (16) has reported data of 90 acidic and basic drugs or charged solutes whose rate of absorption is influenced by different factors such as intestinal pH, pKa, and drug's physical and chemical properties. He estimated that in normal humans, the intestinal absorption of 90 acidic and basic drugs ranged from 1% to 99%. Recently Hall *et al* (17) reported that partial kidney impairment and malfunction occurs because of obesity-induced compression of kidneys by the adipose mass and the sympathetic nervous system activation. These renal effects are produced from inside (e.g., interstitial adipose infiltration) as well as from outside (e.g., adipose accumulation around the kidney). It is anticipated that pathophysiological factors associated with obesity may alter ADME processes and PK of drugs administered by different routes.

The aforementioned pathophysiological conditions associated with obesity can markedly alter the ADME and PK parameters and PD responses of drugs administered orally or by other routes. As a result, one may find therapeutic insufficiency and drug-induced adverse reactions (ADRs) in obese patients, mainly with lipophilic drugs, anesthetics or compounds with narrow therapeutic margin (theophylline, aminoglycosides, cytostatics, etc). For example, Longo *et al* (18) have reported antibiotic treatment failure and increased occurrence of ADRs in obese patients.

While the total body composition of lean adult men or women consists of about 20 % WAT, the latter can increase up to > 40% in obese humans and secrete a wide variety of biologically

active compounds. Today, an increased endo- and paracrine secretion of adipokines is increasingly implicated in the pathogenesis of obesity-related diseases. White adipocytes secrete a wide range of adipokines with anti-inflammatory (e.g., adiponectin) and pro-inflammatory (e.g., IL-1, IL-1 β , IL-8, TNF- α) action, also the neurotrophins and metabotropic nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF) (reviewed in 19). Adipokines are signaling proteins, which regulate various cellular functions and processes such as appetite, insulin sensitivity, inflammation, immunity, angiogenesis, and blood pressure. Obesity-induced up-regulation of pro-inflammatory adipokines is linked with the pathogenesis of cardiometabolic diseases (CMD) such as atherosclerosis, hypertension, obesity, type 2 diabetes mellitus, and metabolic syndrome), also neurodegenerative diseases, including Alzheimer's disease, the latter viewed recently as type 3 diabetes (19).

Influence of obesity on ADME and PK parameters

At first, it should be mentioned that human body rarely depicts a fixed thermodynamic model, whereby consequent equilibrium within certain body compartments can be seen. Thus during the research phase, we should learn about the basic chemical behaviour and cellular movement of given bioactive molecules and measure their biodegradation and primary PK parameters (V_d , CL, $t_{1/2}$). Such garnered information would give us the framework for predicting the probability of therapeutic effectiveness and nontoxic dose regimens in lean and obese patients. However, these PK parameters could be influenced by the individual's age, gender, race and genetics, pathophysiology and comorbid conditions. The typical steps involved in ADME in obese humans are described in the following sections.

Absorption

In case of orally administered drugs, the rate and extent of absorption (often referred to as bioavailability) is determined by the passage through the gastrointestinal tract and entry into the systemic circulation. Intestinal lumen intima consists of enterocytes totaling up to 250 m² surface area. Majority of the gut area for food and xenobiotic absorption is lined by cell membranes which is composed of double lipid layer. Mechanisms of absorption can be endocytosis, paracellular diffusion, passive transmembrane diffusion, active transport and facilitated diffusion. Often different mechanisms are simultaneously present for a given absorption mix. Endocytosis (mainly pinocytosis and phagocytosis) is an usual process by the gut wall cells that bind and internalize substances, mainly proteins and fatty substances. However, drug absorption rarely happens through this mode. Paracellular diffusion is the absorption mode for small

molecules (water, electrolytes), because the gap between the cells is very small in size. Passive absorption is an entirely physical process that can be described by Fick's 1st law of diffusion. Vast majority of drugs are absorbed by this manner. Some drug molecules are absorbed by active transport, that is an energy dependent mechanism and works against the concentration gradient and the size of pores. In this process, the cell surface proteins and the transmembrane proteins (GLUT, SGLT, aquaporins) play significant carrier role. This process can be influenced by several factors like structural characteristics of transmembrane protein, polyglycoprotein carriers/transporters, and the physico-chemical characteristics of the gastrointestinal tract (e.g. pH). Therefore, this variable process cannot be described by one fixed equation. Similarly, description of the facilitated diffusion process is also very difficult to predict, because it involves non-peptide transporters (carnitine, malate etc.) that transport substrates from one side of the membrane to the other.

Studies performed in overweight or obese patients have demonstrated that total intestinal absorption for many drugs remain unchanged. For instance, Cho and colleagues (19a) reported that the rate and extent of absorption does not change for compounds of different solubility such as midazolam, dexfluramine and propranolol. However, physiologic studies showed that intestinal blood perfusion may be greater in obese than their normal-weight counterparts. Therefore, theoretically speaking, higher rate of absorption could be expected from the GI tract in obese subjects. On the contrary, Lamielle *et al* (20) reported a 3.5-fold difference in absorption lag-time in the orally administered dexamethasone in obese versus non-obese subjects. Similar results were obtained in a study done with orally administered paracetamol or acetaminophen (21). Maximum plasma concentrations of acetaminophen were reached at a significantly later time and were markedly lower in the obese patients as compared to subjects of normal weight. However, the half-life was almost similar in the obese patients (2.6 $\pm$ 0.85 hrs) and normal subjects (2.6 $\pm$ 0.12 hrs). Since total body weight may exceed 200% of the ideal weight in obese patients, dosing administered according to total weight rather than ideal weight could lead to toxic or lethal effects when using the recommended 10 mg/kg dosing in morbidly obese patients.

Brill *et al* (22) reported that oral bioavailability of midazolam is markedly increased in morbidly obese patients (60%) as opposed to normal weight healthy volunteers (28%). Both central and peripheral volumes of distribution were substantially increased in obese patients (mean body weight 144 kg, range 112-186 kg), while absorption rate was lower in the obese group. Considering the large increase in volumes of distribution, dose adaptations for intravenous midazolam should be considered

in the obese. The pathophysiological changes at the intestinal absorption and hepatic metabolism levels that are responsible for modifying midazolam pharmacokinetics in obese patients remain unknown.

The situation with parenterally administered drugs (transdermal, intradermal, subcutaneous, or in eye/nose/lung) is quite different. As is to be expected, the first three modes of administration would be influenced by the amount of subcutaneous fat. It is known that vascularization of adipose tissue is generally good, but does not meet the demand of increased oxygen consumption of adipocytes and the microcirculation dysfunction occurs (23). Therefore, it is not surprising that bioavailability of subcutaneously administered gentamicin is just 83% in animal models (24). In humans, the absorption rate of low molecular weight heparin (LMWH) is slower in obese than lean subjects, and after subcutaneous administration of LMWH one should expect a delay in T_{max} by approx. one hour (19). However, total bioavailability of LMWH does not show any change. The maintenance dose of LMWH should be calculated on weight-basis and not according to the BMI (25). In contrast, absorption from transdermal fentanyl patch did not change in obese and lean dogs (26). In case of other substances, like lidocaine, nicotine, glyceryltrinitrate and estrogen showed normal anatomically determined differences in absorption after dermal application [27]. To the best of our knowledge, no comparative absorption studies in obese and normal weight subjects have been done with drugs intended to be given by the sublingual, buccal, rectal, and vaginal routes.

Distribution

Systemically absorbed drugs in blood, and sometimes in lymph, are carried to different body compartments. There are four main factors those affect drug distribution: lipid solubility, degree of ionization, molecular size, and tissue blood flow. Distributed amount of absorbed drugs and the effective local concentration of substances in circulation are primarily influenced by first-pass effect and biodegradation in the liver and renal excretion, and secondly influenced by deposition in lean and adipose tissues. All these factors play an important role for keeping therapeutic drug level in plasma. In this respect, data obtained from distinct group of strongly fat soluble drugs used in anesthesiology along with their recommended reference weight for calculating the initial dose are displayed in Table 1.

The binding of drugs to transport proteins (albumin, alpha-acidic glycoproteins, lipoproteins) influence the distribution process, but in practice albumin does not seem to be altered in obesity (28), but alpha-acidic glycoproteins and lipoproteins may be slightly increased in morbidly obese patients. These

Table 1. Some frequently used anaesthesiology drugs and their references for dosage adjustment.

Active ingredient	Body mass basis
Alfentanyl	IBW
Atracurium	IBW
Dexmedetomidine	TBW
Etomidate	IBW
Fentanyl	FFBW
Propofol	ABW(60)
Remifentanyl	LBW
Rocuronium	IBW
Succinylcholine	TBW
Sufentanyl	TBW
Tiopental	FFBW
Vecuronium	IBW

Abbreviations: FFBW = fat free body weight,

TBW = total body weight

IBW = ideal body weight LBW = lean body weight

ABW(60) = adjusted body weight (factor: 60)

deviations, however, do not induce alterations in distribution. Changes with age seem to cause much higher impact in the protein-binding of drugs than body weight as was observed for the distribution of naproxen by Upton and co-workers (29). In this study, 50% higher free plasma level of naproxen was found in healthy-old persons than in young subjects with similar body weight after the oral administration of a single dose of 375 mg naproxen.

Because several factors influence drug distribution in body, the calculation of actual tissue levels of drugs in advance is rather impossible (30). In general, it can be stated that lipid soluble compounds which easily pass through cell membranes their volume of distribution is markedly higher (e.g. diazepam, dilantin) than compounds that bind strongly to albumin (e.g., phenylbutazon, warfarin) or that cross cell membranes not easily (e.g., amikacin) they possess markedly low V_d .

Keeping in view the body fat composition, and based on earlier studies (31) and relatively recent reports (4), one can say that V_d of lipophilic molecules (amfotericin B, thiopental, diazepam, bisoprolol) is greater in obese persons than in lean per-

sons. The other examples are of fat soluble vitamins (A, D, E, K) that get deposited in white adipose tissue and are slowly released in systemic circulation. Therefore, there exists a strong correlation between adipose tissue and serum vitamin concentrations. In contrast, vitamin E concentration in serum can be modified over a few days, but a year-long supplementation can significantly influence vitamin E level in fat tissue (32). In case of intermediate hydrophilic drugs, studies show slight increase in V_d of aminoglycosides, ampicillin, paracetamol, methyxanthines, cefamandole and ciprofloxacin in the obese, while for some other drugs (e.g. ranitidine) V_d remains unchanged. It's noteworthy that a number of investigations show limited distribution of beta-blockers in fatty tissue, even if they are more or less lipid soluble drugs, and neither protein binding nor haemodynamics can explain why their diffusion into lean body mass is higher than into adipose tissue (33). Hydrophilic molecules like digoxin, cyclosporine and procainamide do not show increase in V_d .

Based on the above cited examples, we can hypothesize that: (i) lipophilicity of a molecule is only one factor among others that can affect V_d , and (ii) lipophilicity can increase V_d , but does not decrease it.

For lipid soluble drugs, generally increase in V_d and half-life can be expected for obese patients. In case of benzodiazepines, carbamazepine, trazodone, verapamil and sufentanyl this hypothesis seems to work. In other cases, e.g., cyclosporine or propranolol this hypothesis is not applicable. In a recent study authors also did not demonstrate any general association between drug lipophilicity and changes in V_d or clearance due to obesity (34). When we look at water soluble compounds, we can make some additional observations. For instance, antipyrine (phenazone) is a fairly water soluble material, that can be used for determination of water-compartments and liver-metabolism of phase-I biotransformations, thus it is often regarded as a test compound for such purpose. Distribution studies with antipyrine show that in obese patients, V_d is smaller than in normal weight patients (35). From such observations, one can conclude that water soluble molecules are distributed in extracellular fluid-space. This means that with water soluble compounds, we should expect lower relative V_d in case of obesity in comparison to normal weight patients. This fact was verified by Jones' experiment where 0.4 g/kg ethanol was injected intravenously to normal-BMI subjects and obese patients, and the V_d s were based on the serum ethanol levels, viz., 0.7 vs. 0.45 L/kg, respectively (36). With the beta-blockers we see great solubility-dependent differences too. The water soluble atenolol or sotalol pharmacokinetics is not influenced by adiposity at all, but fat soluble metoprolol, which is extensively metabolized by the liver, PK is markedly altered in kinetic behaviour by obesity (37). On the

other hand, for highly fat soluble nebivolol, half-life did not change in obese, while $t_{1/2}$ was prolonged in patients with poor metabolic hydroxylation processes (38).

Keeping in view the above mentioned scenarios and based on drug disposition experiences, it may be stated that for obese patients, one should calculate decreased dose per kg body weight mostly for water soluble compounds, and if the patient's body weight is more than 30% above the ideal body weight then drug doses should be adjusted accordingly (4).

Another ideal way of adjusting the dosage regimen is by using therapeutic plasma concentrations of drugs in obese men and women. Unfortunately, drug monitoring facilities may not be available in all hospitals. Studies in obese patients or obese volunteers using clinically relevant end-points or surrogate markers would help in risk identification, risk reduction or minimize ADRs associated with polypharmacy, especially for narrow therapeutic index drugs (39).

Biotransformation

Biotransformation of xenobiotics is carried out by two consecutive processes: type-I and type II- metabolic reactions. The first step is usually referred to as bio-degradation and mainly caused by hepatic metabolizing enzymes, cytochrome P₄₅₀ isoenzymes (eg. CYP 3A4, CYP 2D6), and to a lesser extent by dehydrogenases, esterases, epoxide hydrolases, etc. Afterwards, the chemical composition of unchanged drug and/or its metabolites is changed by conjugation with endogenous substrates like glucuronic acid, sulphate, cystine, glycine, glutathione etc.

Type-I reactions include:

- a) Oxidative reactions: generally catalyzed by either microsomal or non-microsomal enzymes. The first-step reactions in majority of cases are catalyzed through hepatic cytochrome P₄₅₀ (further on: CYP) isoenzymes (N-dealkylation for diazepam, morphine, theophylline, O-dealkylation for codeine and indomethacin). The non-microsomal or cytoplasmic enzymes include alcohol-dehydrogenase and monoamine oxidase-mediated reactions. In humans and laboratory animals, approximately 90% of oxidation reactions of drugs are catalyzed by six CYP isoenzymes: 1A2, 3A4, 2C9, 2C19, 2D6, 2E1 (40).
- b) Reduction processes are mainly catalysed by aldo-keto reductases, and CYP-reductases.
- c) Other metabolic reactions like hydrolysis and isomerization are mediated by esterases, glycosylases, aldolases etc.

Nearly 50% of modern drugs are metabolized by CYP 3A4. This isoenzyme is responsible for 30% of liver CYP activity and 70% of intestinal CYP activity. The main CYP3A4 activities are

hydroxylation, dealkylation and demethylation. Many compounds need multiple biotransformations, and these reactions are done by different enzymes, e.g., N-demethylation of tamoxifen is done by CYP3A4, but aromatic hydroxylation of the same compound is processed by CYP2D6. Oxidative reactions of antipyrine result in a higher V_d and prolonged half-life in obesity, providing increased metabolic process in obese patients. However, after dose-correction to TBW, the extent of metabolism was just slightly changed. In case of clopidogrel, similar correlation with CYP2C19 polymorphism (poor metabolizers) was detected (41). To forecast the rate and extent of metabolic processes in individual patients, especially obese subjects, is very difficult. However, there are now pharmacogenetic techniques available by which genetic polymorphism and metabolizing enzyme activities can be determined for slow and fast metabolizers (42). In general, metabolic transformation of drugs with type-I reactions either increases or remains unchanged in obesity (43).

Type II reactions are synthetic processes in the metabolic pathway of drugs. During this phase of biotransformation, metabolites of type-I conversion bind with other molecules (usually to endogenous compounds, like glucuronic acid, glycine, cystine, sulphate, glutathione etc.). Type-II reaction enzymes are mainly expressed in the liver, the gastrointestinal tract, the adipose tissue and the kidney. Primary step in phase-II metabolic processes is glucuronidation accounting nearly 50% of the biotransformations. Conjugated end-products are usually inactive and are more water-soluble, ready for renal or biliary excretion. Both metabolic steps are mainly dependent on liver's metabolic capacity and the set of hepatic enzymes. Some type-II reactions (single- or double-glucuronidation) are affected to a lesser extent in obesity than type-I reactions mediated via CYP isoenzymes (61). However, some authors have reported that type-II metabolism of drugs increases in obesity (43), and also support increase in absolute clearance (45).

Considering the influence of body composition on pharmacokinetics, we can conclude that low and moderate lipid accumulation of drugs in the body does not seem to influence the above mentioned metabolic processes. But high fat content in the obese body may cause lipotoxicity, oxidative stress, and mitochondrial dysfunction. It is well known that high BMI is often accompanied by NAFLD, which may influence microsomal metabolism of drugs through different genetic expression of enzymes mentioned above. Furthermore, adipokines secreted by the white fatty tissue activate Kupfer-cells in the liver, so the secretion of cytokines increases which suppress metabolizing enzymes. For instance, concentration of CYP2B that plays an important role in insulin-metabolism and CYP2C11 participating in the biotransformation of glutathione (GSH) diminish due

to this indirect action. In contrast, CYP3A4 isoenzymes that take part in metabolism of midazolam, shows no quantitative or qualitative difference in obese or normal weight adults, and similar is the situation with CYP1A2 too, as tested using xanthines (46).

According to these observations, enzyme induction and increase in protein-expression that influence the fate of drug molecules can also be seen in adiposity, in a moderate manner. For example, CYP2A5 and CYP2E1 are more active in obese, than in non-obese, as well as CYP2C and CYP2D are more active also, but to a lesser extent.

It is well recognized that biotransformation of xenobiotics does not only take place in the liver, but also in the intestinal tract, lungs and kidneys. Drug metabolizing enzymes have even been detected in the adipose tissue. The retinal-dehydrogenase (RALDH) enzyme, which basically participate in vitamin E synthesis as it catalyze the formation of active compound retinoic acid, also belongs to them. The expression of this enzyme also occurs in white adipose tissue (WAT). Increased expression of hepcidine-gene was observed in overweight animals (32), too. This protein helps in iron metabolism and its accumulation in liver and spleen.

Overall, these examples indicate that wide range of metabolic and drug biotransformation changes occur in obesity, and in case of many drugs we can take them into account. Hence, it is not easy to precisely predict the influence of obesity on the metabolic disposition and other PK parameters of drugs used in obese patients.

Elimination

Primarily, elimination of unchanged drugs and/or their metabolites takes place via the kidneys and to a lesser extent through liver/bile and feces. Small amounts of metabolites may be excreted through lungs, saliva, sweat, tears, and milk, etc. For inhalation anaesthetics, the main elimination occurs through the lungs. The physiological condition of metabolizing and excretory organs always determines the biotransformation of administered drugs as well as elimination of metabolic products, and PK parameters. It should be stated that besides the above mentioned drug metabolizing organs, the renal elimination and biotransformation are also influenced by the extent of tissue perfusion or blood flow (47). For instance, liver blood flow seems to be increased in obesity and this significantly increases the hepatic clearance of busulfan and fentanyl in obese patients (2,48). Impairment of liver and kidney can cause reduction in hepatic metabolism and renal clearance, and consequently lead to drug-induced adverse reactions.

Elimination rate of unchanged drug and/or its metabolites

can be estimated by clearance (CL). Total or cumulative CL is referred to as overall elimination that consists of the sum of individual clearances, predominantly by liver (e.g. bile, feces), kidney and lung (eg. inhalation anesthetics). Disappearance of xenobiotics from blood stream is often determined by the first-pass effect in the liver, and subsequent excretion of water soluble products through kidney, bile and GI tract. Drugs which are extensively filtered by the liver's first-pass effect following oral administration (e.g. morphine, isoprenaline, meperidine) should be given through other routes (iv, sublingual, rectal). Such practice will not only be economical to save the amount of administered drug but also ensure its high therapeutic concentration at the target site. It has been observed that hepatic clearance is greater in obese patients than lean subjects. The physicians, surgeons, dentists, nurses, and pharmacists should calculate effective doses carefully for obese patients (49). Unfortunately, there is no general rule of thumb for estimating drug doses in obese patients. For example, Cheymol (50) reported increased clearance of some drugs (prednisolone, halothane, enflurane), whereas decreased clearance for others (methylprednisolone, propranolol) in obese patients.

Generally speaking, the pharmacological activity of conventional drugs is reduced following biodegradation reactions, but in case of pro-drugs eg. loratadine, ifosfamide, dacarbazine, losartan etc. (51) metabolic processes are needed to activate pro-drugs to make them therapeutically effective in the body.

Excretory function of kidneys depends on perfusion pressure, filtration rate and membrane pore size as well as reabsorption capacity. In obesity, hyperfiltration and increased glomerular capillary wall tension occurs (52). Chronic kidney disease cause excretion difficulties and build up of unchanged drug and its metabolites as well as transport impairments in both obese and lean patients (53). It has been observed that adipocyte-mediated production of cytokines trigger renal inflammation which consequently cause reduction in renal function among obese patients (54). The adipocyte-derived leptin hormone also impairs renal architecture and function (55). In addition, adiponectin secreted by WAT impairs the function of glomerular cells (56). Following renal impairment, the filtration ability of kidney diminishes and results in lesser excretion of parent drugs and their metabolites into the urine. The high filtration pressure in hypertensive patients also causes similar detrimental effects in the kidney. Since obese persons are highly susceptible and prone to pathological injury and damage to the kidney, the resultant reduction in renal clearance of drugs is to be expected in these individuals.

Influence of obesity on pharmacodynamics

The pharmacologically mediated actions of drugs are produced through biochemical or physiological changes in body organs. In general, dose-dependent therapeutic responses are not very different in different humans therefore dose recommendations of pharmaceuticals are well-founded and the actions may be predicted. However, on the individual level, pharmacological response is always a little bit different due to the individual's genetic make-up, gender and race, nutritional status, young and old as well as acute or chronic illness conditions. Besides these differences, pharmacodynamics (PD) to drugs may differ between lean and obese patients (57). The impact of adipose tissue in PK and PD, especially the influence of adipokines on drug-receptors and their behaviour is a hot topic in the field of pharmaceutical research, and more and more information is being discovered by applied and basic researchers.

It is well recognized that obesity is accompanied by chronic inflammation in the body. The adipocytes-activated macrophages increase the secretion of proinflammatory cytokines and interleukines (e.g., IL-6, IL-1b and TNF- α) that propagate inflammation in the majority of organs, like liver, vascular endothelium and blood platelets. The endothelial inflammation not only causes atherosclerosis but also leads to the upregulation of pro-coagulant and the downregulation of anti-coagulant factors. The problematic anticoagulation effect in obese patients is another example that modifies efficacy of well known drug unfractionated heparin (58,59). The distortion of hemostasis in obesity increases the risk of thrombosis (60). This example also highlights the treatment difficulties involved in thromboprophylaxis in obese patients. Metoprolol's pharmacodynamics is strongly influenced in obese patients, where systolic efficacy is 23% and diastolic efficacy is 30% higher than in lean hypertensives (61). Detailed discussion of this topic is outside the scope of this review, but several studies suggesting alterations in PD have been reported.

Adipocyte glucocorticoid receptors are able to inhibit psychogenic and metabolic stress response (62). Adipokine secretion and lipid profile is influenced by PPAR γ that is under the control of WAT (63). Adiponectin exerts multiple biological effects through activation of AMP-activated protein kinase and PPAR α pathways (64). Diet-induced obesity produced alterations in vascular adrenergic and angiotensin II receptor dynamics (65). Neuroendocrine secretion that control the inflammatory process has been observed in the obese (66). Adipokines regulate glucose homeostasis, insulin sensitivity, lipids metabolism, reproduction, as well as endothelial and platelets function (67). Glucocorticoid receptors (GRs) play an important role in adipocyte physiology by affecting lipolysis and mediate at least

some of the adverse effects of exogenous steroids on metabolic functions (68). Several polymorphisms in the GR gene have been described (69). Practical aspects for these new findings are subjects of future pharmacological and clinical research.

Closing remarks

The physiological and pathophysiological changes during the weight gain result in pharmacotherapeutic consequences. The therapeutic impact of this alteration is translated into modifications in drug administration, mainly in dosing of drugs. Details are presented in the second part of the article.

Conflict of interest statement

The authors certify that they have no affiliations with or involvement in any organization with any financial interest in the subject matter discussed in this review article.

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