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

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Introduction

In the first part of the study we demonstrated the epidemiological features and the details of the physiological changes of obesity that serve as background to the pharmacokinetic (PK) and pharmacodynamic (PD) alteration in this illness. In the second part we review the short history of the development of pharmacological trials aimed to discover pharmacological consequences of obesity, and the main data on how overweight and obesity affect dosage of various compounds.

Design and conduct of metabolism and pharmacokinetics studies in obese animal models and patients

Need for drug dosage adjustment in obesity was highlighted around the mid-1970's by Klotz (1), and the first comprehensive reports about the effect of obesity on PK of drugs in humans were published in early eighties (2, 3). During the course of that decade, identification of fat-soluble compounds and white adipose tissue mass were the main targets of these studies (4). By the end of eighties, obese animal models were developed to study drug disposition changes in overfeeding-induced obesity (5). In the early drug kinetic studies, determination of the volume of distribution (V_d) played the primary role in verifying obesity-related alterations in drug metabolism and pharmacokinetics. The PK studies were conducted with different types of drugs (6, 7), the fine tuning of the data obtained is still being done even today.

The findings of a number of PK studies indicate that from practical and clinical point of view, onset of action and elimi-

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nation, PK values like volume of distribution and clearance (CL) are the most important parameters in obese and lean patients. If V_d of a given drug is very high, then the onset of therapeutic action is markedly delayed in obese compared with non-obese subjects. For example, in case of lipophylic diazepam when V_d increases by 2-fold, the onset of action and maximal drug effect is delayed (8). The situation become more complicated if individual's genetics gets modified in the drug disposition process, viz., V_d of diazepam is usually 52% greater in Caucasians than in Chinese people (9).

Since obesity highly correlates with insulin resistance in diabetes mellitus, drug metabolism and disposition process, comparative studies have been done in animal models such as obese Zucker fatty rat and the Zucker diabetic fatty (ZDF) rat for comparing the hepatic metabolism and PK of drugs with Sprague-Dawley rats. The inbred strain of ZDF develops early onset of insulin resistance and displays hyperglycemia and hyperlipidemia. The phenotypic changes resemble human type 2 diabetes associated with obesity. Therefore, ZDF rat is often used as a pharmacological model for type 2 diabetes and for investigating the pharmacokinetics and disposition of anti-diabetic drugs (10). Genetically modified ob/ob and db/db mice, or wide range of knockout-mice (pro-opiomelanocortin, POMC), MC-receptor 3 deficit and others) are also used for doing drug metabolic studies. Furthermore, diet-induced obese (DIO) mice and diet-resistant (DR) rats and the surgically-induced brain lesion and chemical models belong to the recent armamentarium of pharmacokinetic studies in obesity (11).

Body weight references and drug dosage adjustment consideration

Generally, dosages of pharmaceuticals or bioactive substances are calculated on body weight basis. However, ADME and its visualizers: PK and PD of drugs are typically dependent on body fat content, extent of tissue circulation/perfusion and organ function. Thus, both body composition and weight are the major determinative factors for the metabolic disposition and PK and PD features of administered xenobiotics. However, according to the drug/ingredient molecule characteristics and body composition, the body weight alone reference can markedly differ in lean and obese persons. Usually, total body weight (TBW) in kilogram (kg) but not the lean body weight (LBW) is taken into consideration for drug dosage calculations. This practice was first established in 1953 and found clinically useful for administering pharmaceutical agents in humans (12). Subsequently, in 1966, ideal body weight (IBW) in kg was recommended for calculating drug dosages for clinical purposes (13). Later on, Janmahasatian and co-workers (14) proposed adjusted body weight

(ABW) for dosage calculations. Most of the currently used formulas for drug dosage calculations are summarized in Table 1.

Table 1. The frequently used formulas to estimate Lean Body Mass

Green-Duffull formula (15)

$$\begin{aligned} \text{LBW}_{\text{male}} &= 1.1 \times \text{TBW} - 0.0128 \times \text{BMI} \times \text{TBW} \\ \text{LBW}_{\text{female}} &= 1.07 \times \text{TBW} - 0.0148 \times \text{BMI} \times \text{TBW} \end{aligned}$$

James formula (16)

$$\begin{aligned} \text{LBW}_{\text{male}} &= (1.1 \times \text{TBW}) - 128 \times (\text{TBW}/\text{H})^2 \\ \text{LBW}_{\text{female}} &= (1.07 \times \text{TBW}) - 1.48 \times (\text{TBW}/\text{H})^2 \end{aligned}$$

Janmahasatian-Duffull formula (14)

$$\begin{aligned} \text{LBW}_{\text{men}} &= (9270 \times \text{TBW})/[6680 (216 \times \text{BMI})] \\ \text{LBW}_{\text{female}} &= (9270 \times \text{TBW})/[8780 + (244 \times \text{BMI})] \end{aligned}$$

$$\text{ABW} = \text{LBW} + (f^* \times (\text{TBW} - \text{LBW}))$$

$$\text{IBW}_{\text{male}} = 49.9 + 0.89 \times (100\text{H} - 152.4)$$

$$\text{IBW}_{\text{female}} = 45.4 + 0.89 \times (100\text{H} - 152.4)$$

All these sophisticated equations/formulas are based on anthropometric data [height (H) in meters] and body weight [BW in kg], but do not offer easy and practically convenient methods for drug dosage calculations. While several methods have been developed to calculate drug dosages, their accuracy still remains a matter of debate, confirmation and/or corrections (17). It should be mentioned that even in case of reliable correlation of specific adult body weight and therapeutic effect, there exist fundamental differences and flaws between estimation and calculation of dosage reference weights under specific conditions. Namely newborn/infant and children (18), critically ill and cancer patients (19), HIV patients (20) as well as frail and elderly persons may differ in many respects regarding pharmacotherapy. Therefore, awareness and education of physicians and surgeons, pharmacists and nurses is critically important for safe prescribing of medicines and adjusting dosages in sensitive patient populations depending upon their metabolizing capacity, renal function, PK and PD properties of drugs. An other concern that should also be kept in mind while prescribing medications is about drug-drug, drug-herbal/food interactions, because combined oral administration can alter the ADME and bioavailability

Therapeutic consequences of pathophysiological changes in obesity

In obese men and women the excessive increase of white adipose

tissue mass not only means overweight where the fat per kg of total body weight is markedly increased, but also a significant reduction in lean tissue mass. As eluded to earlier, obesity is often associated with several health complications, including gastroesophageal reflux disease (GERD), arthritis, diabetes mellitus, cardiovascular diseases, renal problems and some cancers. It is well recognized that obesity-related alterations occur in hemodynamics such as increased cardiac output and blood volume mainly due to the increased left ventricular mass (21). Several important obesity-related changes such as tissue blood flow, function of drug binding plasma proteins and glycoproteins as well as alterations in liver and kidney function and activity of hepatic CYP isoenzymes can play a pivotal role to alter the PK and PD of drugs in obese individuals (22-25). When administering drugs to obese patients, health professionals should pay special attention to the adjustment of initial doses of several classes of drug, mainly in case of general anesthetics, opioids, analgesics, anticoagulants, antidiabetics, oral contraceptives, neuromuscular blockers, β -blockers, antibacterials, anticancer agents, psychotropics, and anticonvulsants. This suggestion is based on

the lipophilic properties of drugs which after absorption can be easily sequestered by the white adipose tissue of obese patients. Overall, the main PK parameters such as drug clearance, the volume of distribution and elimination half-life are the primary determinants to be considered for designing the loading and maintenance dose regimens of drugs in obese patients. The PK values reported for some antimicrobial, CNS and anaesthetic drugs are summarized in Tables 2 and 3.

Another way of adjusting the dosage regimen is by monitoring plasma concentrations of drugs after the first (loading) dose in obese men, women and children. Even by this method, the precise calculation of starting dose is essential to avoid any harm. 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 narrow therapeutic index drugs. Inclusion of obese men, women and children in clinical trials is needed for better understanding the ADME and to determine PK and PD profiles of old and new drugs in obese patients.

There is a controversy whether or not the first-phase metab-

Table 2. Pharmacokinetic parameters of antimicrobials in obese and lean patients

Drug	$t_{1/2}$		Vd (L/kg)		Cl		Reference
	obese	control	obese	control	obese	control	
Vancomycin	3.2 h ^t	4.8h ^t	0.26±0.03	0.39±0.06	1.112±0.160 mL/min/kg	1.085	(26)
Daptomycin	7.34 h	6.83 h	0.092	0.11	10.07 mL/h/kg	11.89 mL/h/kg	(27)
Cefepime	1.92±0.42 h	NR	24.59±6.79	NR	9.09±2.58 L/h/kg	NR	(28)
Ertapenem	NR	NR	0.063± ?	5.15±0.5	0.019±0.003 (I-II)* L/h/kg	0.024±0.004	(29)
			(I-II)*	0.078±0.08	0.015±0.002 (III)* L/h/kg	L/h/kg	
			0.057±0.009 (III)*				
Ciprofloxacin	NR	NR	2.46-0.4	3.1-0.3	897.7-159.6	744.4-120.5	(30)
Levofloxacin	8.2±1.8	8.1±1.0	1.3±0.7	NR	163.3±70.5 mL/min	186±5 mL/min	(31)
Cefoxitin	1.2±0.4* h	0.9±0.2 h	0.29±0.08	0.25±0.09	1.6±0.5* mL/min/kg	4.1±1.0 mL/min/kg	(32)
Cefazolin	1.4 h	1.6 h	11.9±5.1 h 13.0±3.1	12.6±2.9 h	5.1±1.5 h 4.2±1.0 L/h/kg	5.0±1.1 h	(31,33)

Abbreviations: $t_{1/2}$ = elimination half-life; **kg** = kg TBW; h^t = terminal elimination half-life; (I-II) = class I-II obesity group; (III) = class III obesity group; *p<0.05.

Table 3. Pharmacokinetic parameters of CNS drugs and anesthetics in obese and lean patients.

Drug	$t_{1/2}$		Vd		CL		Reference
	obese	control	obese	control	obese	control	
Midazolam	8.40±0.84* h	2.73±0.34 h	2.66±16* L/kg	1.74±0.11 L/kg	4.21±0.35 mL/min/kg	8.06±0.46 mL/min/kg	(34)
Vecuronium	119±43 min	133±57 min	473±142* mL/kg	993±401 mL/kg	2.83±0.54* mL/min/kg	5.36±1.14 mL/min/kg	(35)
Thiopental	27.85 h	6.33 h	4.72±2.73 L/kg	1.40±0.46 L/kg	0.18±0.08 L/h/kg	0.21±0.06 L/h/kg	(36)
Remifentanyl	-	-	68.3±29.3 mL/kg	101.9±37.3 mL/kg	27.9±7.1 mL/min/kg	42.3±7.4 mL/min/kg	(37)
Sufentanil	208±82 min	135±42 min	5818±1745 mL/kg	4818±1515 mL/kg	20.8±7.3 mL/min/kg	25.2±5.7 mL/min/kg	(38)
Diazepam	82.0 h*	32.0 h	228.0* L/kg	70.0 L/kg	32.0 mL/min/kg	26.0 mL/min	(8)
Propofol	-	-	1.63±0.541 L/kg	-	25.4±6.5 mL/min/kg	-	(39)

Abbreviations: $t_{1/2}$ = elimination half-life; **kg** = kg TBW; * $p < 0.05$

olism of drugs carried out by the hepatic metabolizing CYP isoenzymes can be increased or decreased in obese subjects. Initial studies support the hypothesis that the activity of CYP isoenzymes in the liver increases in proportion to the total body mass, whereas their activity decreases with increase in liver fat content (40). Some studies with chlorzoxazone showed significant increase in oral clearance (41), but decrease in N-methylation of erythromycin (42). Recent findings also supported the variable effect of obesity on drug metabolizing enzyme system. This is in concert with the observations of Kotlyar and Carson (43), who described the separate isoenzyme-dependent change of CYP activity: e.g. CYP3A4 decreasing and CYP2E1 increasing in obesity. To understand the metabolic variability, we refer to Flockhart (44), who pointed out the large difference of CYP2D9 and CYP2D19 isoenzyme activity on genetic polymorphism basis. From practical point of view, the example of warfarin-bleeding can be cited here (45). However data collected by Hart et al. (46) suggest that obese patients show significantly lower risk for major bleeding than non-obese patients. They also investigated the significant interaction between CYP4F2*3 genetic status and obesity. The underlying mechanism is not yet elucidated. Kinoshita et al. (47) have reported that besides other isozymes, the WAT also contains CYP17 and CYP19, and both of these isozymes are capable of producing sex steroid hormones like the

testes and ovary. The sex steroid hormones originating from the WAT may cause induction/inhibition of major drug metabolizing enzymes in the liver (CYP3A4, CYP2D6), and consequently modify drug metabolism/disposition in obese subjects. It has been reported that xenobiotic-metabolizing cytochromes are also expressed in the WAT, especially CYP1A1 and CYP1B1 that can activate carcinogenic polycyclic aromatic hydrocarbons and exogenous estrogens (48).

In obese subjects, kidney function is generally compromised and reduced clearance of creatinine and drug metabolites would be expected (49). Even in metabolically-healthy obese the incidence of chronic kidney disease is higher than in their normal-weight counterparts (50). The glomerular filtration rate is reported to be greater in obese than in normal-weight patients (51, 52). In obese patients, endothelial dysfunction, tubular atrophy, interstitial fibrosis, glomerulosclerosis can develop with an outcome of chronic kidney malfunction. Obesity-related concomitant diseases like hypertension, diabetes mellitus and low-grade inflammation can also impair the kidney function. Consequently, these pathological changes, sooner or later, are expected to decrease renal function.

Earlier studies with ciprofloxacin, lithium and gentamycin demonstrated no obesity-related change in clearance (25). Similarly, no adverse effect of obesity on drug clearance was noticed

by several other investigators (53-55). While early clinical studies did not show the renal compromised feature, relatively recent reports have shown marked weight-dependent changes in the systemic clearance of some drugs. For instance, in cases of cisplatin, paclitaxel and troxacitabin but not for carboplatin, docetaxel and irinotecan significant increase of absolute CL were observed in morbidly obese patients. Moreover for doxorubicin the systemic clearance decreased for obese women but not for obese men (56). In an another study with levofloxacin, the drug clearance was strongly co-related with creatinine clearance but not with weight (57). Since these CL studies have provided differing data on systemic clearance, incl. the kidney function and renal clearance of drugs in obese patients, further well designed studies are warranted to fill the gaps of our knowledge.

Schröder and his colleagues (105) are of the opinion that some of the differing results of renal clearance observed in various studies cited above may partly be explained on inter-individual differences in drug ADME and polymorphism involved in the genetic expression of hepatic CYP isozymes and other factors such as fat accumulation in kidney responsible for kidney malfunction. It should be pointed out that this ADME genes study was performed with the human surgical liver samples obtained from Caucasian donors. Further studies are needed from different ethnic/racial populations to develop data base and to enhance our understanding regarding ADME associated pharmacogenomics and the renal clearance of wide variety of drugs administered to obese patients.

It was mentioned in Part I of the present review that WAT cells secrete a wide range of signaling proteins collectively designated adipokines, the term being introduced by (59). The involvement of the hypothalamic-pituitary-adrenocortical axis activity in abnormally obese patients was suggested (60). It has been observed that the circulating level of anorexigenic hormone leptin is increased, while the level of orexigenic hormone ghrelin is decreased in obese subjects. Ghrelin stimulates appetite, whereas leptin suppresses food intake and causes weight loss. But some obese patients become leptin-resistant. The precise underlying mechanisms by which ghrelin and leptin influence energy balance and contribute to the development and/or maintenance of obesity is not clear as yet (61). Leptin produces profibrinogenic effect in the liver that may affect hepatic drug metabolism, and other PK profiles (40).

The regulation, expression, and activity of CYP group of isoenzymes in the liver that metabolize drugs to more water-soluble forms for renal excretion, are influenced by hormones, neurogenic amines, cytokines, interleukins, and eicosanoids. Nearly 50% of all synthetic medications currently on the market are metabolized by the enzyme CYP3A4, while metabolism

of other 35-40% occurs through enzymes CYP1A2, CYP2C19, CYP2D6, CYP3A5 CYP3A6, and CYP3A7 (62). Collectively, the adipokines and hormones produced by the adipocytes as well as hypoxia and acidic environment due to increased production of lactate in the adipose tissue may modify biotransformation processes of xenobiotics. The cross-talk between adipose tissue, kidney and liver may play a pivotal role in the development of signals and factors involved in PK and PD changes in obesity.

For any age group, overweight and obesity are strong risk factors and signals of red flag for the development of cardiometabolic diseases (atherosclerosis, hypertension, type 2 diabetes, and metabolic syndrome). The co-morbid conditions associated with obesity often require multiple drug therapy or surgical interventions. The polypharmacy is likely to cause drug-drug, and drug-disease interactions, and consequently produce changes in the metabolic disposition of drugs. Obesity-related changes in PD parameters of drugs, especially lipid soluble agents, may be profoundly altered in morbidly obese patients, thereby requiring drug dose adjustment. One good and relevant example of this review is shown by Diepstraten and co-workers (63), who have discussed age and weight-dependent clearance of propofol in morbidly obese and non-obese adults, adolescents and children (Fig. 1). Formula used to determine amount of propofol anesthesia can lead to insufficient doses, as morbidly obese patients are more likely to wake up during surgical interventions

Figure 1. Age and weight-dependent clearance of propofol in morbidly obese and nonobese adults, adolescents and children. Based on data from (63).

(e.g. bariatric or stomach-shrinking surgery) done under propofol general anesthesia.

It is well known that age-related factors profoundly influence ADME process, ie. PD of drugs, and should be mentioned too. The infants and elderly constitute two important populations those require extra care for prescribing medications as is done in obese patients. However, the age-related concerns that require drug dosage adjustment are usually not addressed in detail for the guidance of health care professionals. For example, a newborn or infant cannot be considered as 'miniature adult'. In newborn, elderly and frail individuals, the intestinal absorption, hepatic metabolism and renal elimination of drugs are far slower than their adult counterparts. Adverse drug reactions are often observed in the pediatric and elderly subjects. These two sensitive groups of humans, viz, infants and seniors over 75 years, are most important populations in which drug dose adjustments are highly recommended (64).

For physicians, surgeons and dentists the main challenge and crucial step is the estimation of loading dose and later on the adjustment of maintenance dose regimen in obese patients. The maintenance dose could be determined by monitoring the steady therapeutic plasma levels as well as the tolerance reactions after the administration of initial dose. Most important issue for dose adjustment pertains to narrow therapeutic index medicines (warfarin, digoxin, quinidine, disopyramide, theophylline).

Some phenolic chemicals (bisphenol-A, triclosan, n-nonylphenol) have an intrinsic bioaccumulation potential in human adipose tissues. After absorption, they are rapidly converted to their glucuronides and sulphate conjugates to promote urinary excretion. These compounds have rapid turnover rate in humans with a half-life ($t_{1/2}$) shorter than 24 hours (65). Their excessive presence in the liver, kidney and adipose tissues may alter the metabolism of endogenous and exogenous substrates in the body. These phenolic compounds also possess endocrine disruptive properties. The endocrine disrupters are known to interfere with the physiological functions of estrogen and androgen hormones and cause reproductive disorders and infertility in men and women. Overall, in the above sections we have attempted to provide an updated overview about the PD changes of a wide spectrum of drugs in obese and non-obese patients. Some theoretical considerations and practical examples for PD has been demonstrated.

Some specific consideration on pharmacokinetics and pharmacodynamics of drugs in obese patients

The PK parameters describe drug's ADME processes, bioavailability, plasma levels and proportion of drug that reaches its site of action, biodegradation, and ultimate elimination through

different routes. On the other hand, PD depicts drug's actions (exposure-effect relationship) on various organ systems of a patient. Mainly PK influences drug's dosing, and adverse reactions. However, pharmacological actions of different drugs can differ in different individuals depending on their body make up (lean and obese), and pharmacogenomic profile (slow and fast metabolizers). The various physiologic and pathophysiologic differences described earlier in obese and lean patients can cause changes in the PK and PD behaviour of drugs. Keeping in view the primary focus of the present review, we have attempted to highlight alterations in the metabolic disposition and other PK parameters of various groups of drugs as well as the safe usage of drugs in obese patients. Here we just describe the clinical relevance of PK and PD with some selected examples, which are important and may be applicable in the pharmacotherapy as well as pre- and post-surgical use of drugs in obese patients.

In this section, we also describe the PD effects of obesity-related hormones secreted by WAT in obese subjects. The estrogen hormones secreted by WAT appear to affect body functions in postmenopausal women, and cellular signaling mechanism (66). The receptor selectivity, specificity, and cellular signaling means that WAT-secreted hormones and bioactive molecules seem to play several useful physiological functions. On the contrary, obesity-induced hypertension may be associated with mineralocorticoid receptor activation in obesity (67), and this hyperaldosteroidemia may influence pharmacotherapy in obesity. The production of sex hormones by WAT may modify the activity of drug metabolizing CYP isozymes in the liver. How much influence the WAT produced hormones exert on the PK and PD of drugs remains to be ascertained.

Westhoff *et al* (68) conducted a PK study in 15 normal weight (BMI, 19.0 - 24.9 kg/m²) and 15 obese (BMI, 30.0 - 39.9 kg/m²) women given combined oral contraceptive containing 30 µg ethinyl estradiol (EE) and 150 µg levonorgestrel (LNG) packaged with 21 active and 7 placebo tablets. Obese women had a lower AUC (1,077.2 vs. 1,413.7 pg*h/mL) and lower C_{max} values (85.7 vs. 129.5 pg/mL serum) for EE than normal-weight women. While the serum levels of LNG were lower in obese women, there were no statistically significant differences in their LNG levels for AUC and C_{max} values. The results of this small study showed that the follicular diameters tended to be larger among obese women, but the observed PK differences did not reveal greater follicular activity among obese OC users.

A prospective cohort study was done in normal weight (BMI < 25 kg/m², N=10) and obese (BMI > 30 kg/m², N = 10) women who received OCs for 2 cycles. Mean LNG plasma concentration on cycle 2, day 1 (1.9 ng/mL vs. 2.5 ng/mL) took 2-fold longer time to reach steady state (10 vs. 5 days) in obese women

compared with normal weight women. The LNG half-life ($t_{1/2}$) was twice longer in the obese group (52.1 vs. 25.6 h), which correlated with a lower C_{max} LNG concentration on cycle 2, day 1 (1.9 ng/mL vs. 2.5 ng/mL) and a longer time to reach steady state in obese women. There was no significant difference in V_d between groups. The LH surge parameters did not differ between groups, but showed greater suppression of hypothalamic-pituitary-ovarian (HPO) axis activity in the obese group. The results of this prospective study suggested that obese women not only showed marked differences in OC pharmacokinetics that are associated with greater HPO activity but also development of dominant follicles with ovulation (2/10 vs. 1/10) during cycle 2 of OC use (69).

In a prospective open label clinical trial 20 normal BMI and 20 obese women were enrolled to evaluate the effectiveness of contraceptive vaginal ring (CVR) containing ethinyl estradiol (EE) and etonogestrel (ENG). Serum hormone concentrations, ovarian follicle development, endometrial thickness and bleeding patterns were assessed twice weekly. Eighteen normal-weight and nineteen obese women completed the six weeks study. EE and ENG concentrations remained within therapeutic range for all women. ENG levels, which are considered to be of greater importance for the efficacy of CHC did not differ in study groups over 4-6 weeks of use (70). The contraceptive device releases an average of 15 µg EE and 120 µg ENG each day from a flexible ring 54 mm in diameter and 4 mm in thickness. CVR could effectively prevent pregnancy in both normal-weight and obese women. All the above mentioned studies confirmed the statements of Robinson and Burke (71) and the Cochrane Database (72) analysis that all registered hormonal combined OCs are safe enough for obese women.

Finally, we would like to mention the role of polymorphism in obesity. It's well established that pharmacological actions of drugs can differ due to interindividual variations, racial and gender differences, and the functional state of drug metabolizing and excretory organs. On account of the pharmacogenetic differences in obese patients, and the obesity-induced pathological changes in the intestine, liver, and kidney, alterations in the ADME, PK and PD parameters are expected to occur in obese men and women. Recently Majer-Lobodzinska and Adamiec-Mroczek (73) demonstrated the glucocorticoid receptor polymorphisms in obesity. Barton and co-workers (74) published a summary on G-protein coupled estrogen receptor (formerly called GPER) that has specific role in obesity and other diseases. The estrogen hormones change the pharmacological efficacy of certain compounds, like ketoprofen (75). These examples illustrate the complexity of PK and PD of drugs/ingredients in obese patients.

Obesity can also affect therapeutic responses to certain non-classical drugs, i.e., adalimumab (76), and biological agents, i.e., influenza vaccine (77), and soluble IL-6 that is related to insulin resistance in obese subjects (78). Once again, these examples demonstrate that in obesity both the PK and PD values are altered by a diverse number of factors. Hence, it's hard to predict with certainty the safe dose regimens of drugs and bioactive compounds in obese subjects. Perhaps, individualized medication may be the answer to all these difficulties encountered in obesity.

Conclusion

During the last 20-30 years, obesity has become a major public health problem in developed and developing countries with social and economic implications. Obesity in children and adults often leads to chronic diseases like diabetes mellitus, cardiovascular disorders, and some cancers. Many co-morbid conditions associated with obesity would require thoughtful drug dose adjustment in therapeutic and surgical interventions. Physicians, surgeons, dentists, pharmacists and nurses need to learn importance for adjustment of drug dosages in obese patients. Dose selection of several classes of drugs (general anesthetics, opioids, analgesics, anticoagulants, antidiabetics, oral contraceptives, neuromuscular blockers, β -blockers, antibacterials, anticancer drugs, psychotropics, anticonvulsants) can neither be based on the ideal body weight (IBW) nor on the actual body weight. An ideal way of adjusting the loading and maintenance dosage regimen should be to follow PI/SPC and afterwards may be by using therapeutic plasma concentrations of drugs in obese men and women. With regards to healthy women, gynecologists should be well aware about the hormonal contraceptive failures in obese childbearing women and the intervention of other methods (IUDs, vaginal spermicides, condoms etc.) for pregnancy control.

Most challenging issues in treating obese patients concern the administration of narrow therapeutic index drugs such as warfarin, theophylline, digoxin and antiarrhythmic agents as well as highly toxic anticancer drugs, antibiotics and aminoglycosides etc. The metabolic disposition of pro-drugs like leflunomid and sulphasalazine those are activated by metabolism is also influenced in obese individuals. As majority of Product Monographs (PMs) or Summary of Product Characteristics (SPCs) in UK and Europe or Prescribing Information (PI) in USA and Canada do not contain any information regarding dosage adjustment in obese patients, it is suggested that the PK data should be included in these documents wherever applicable.

Inclusion of obese men, women, and children in well designed clinical trials should be done for determining the volume of

distribution (Vd), absolute renal drug clearance (CL), elimination half-life ($t_{1/2}$), T_{max} , C_{max} , and AUC of drugs and their major metabolites. Such studies would be helpful to predict the right loading dose and for keeping the optimal maintenance dose in obese patients. Literature-based recommendations for rational therapeutic dose-modifications are reported in this review.

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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