

# Effects of Obesity on Pharmacokinetics

## Implications for Drug Therapy

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### Abstract

Obesity is a worldwide problem, with major health, social and economic implications. The adaptation of drug dosages to obese patients is a subject of concern, particularly for drugs with a narrow therapeutic index. The main factors that affect the tissue distribution of drugs are body composition, regional blood flow and the affinity of the drug for plasma proteins and/or tissue components.

Obese people have larger absolute lean body masses as well as fat masses than non-obese individuals of the same age, gender and height. However, the percentage of fat per kg of total bodyweight (TBW) is markedly increased, whereas that of lean tissue is reduced. Cardiac performance and adipose tissue blood flow may be altered in obesity. There is uncertainty about the binding of drugs to plasma proteins in obese patients. Some data suggest that the activities of hepatic cyto-

chrome P450 isoforms are altered, but no clear overview of drug hepatic metabolism in obesity is currently available. Pharmacokinetic studies provide differing data on renal function in obese patients.

This review analyses recent publications on several classes of drugs: antibacterials, anticancer drugs, psychotropic drugs, anticonvulsants, general anaesthetics, opioid analgesics, neuromuscular blockers,  $\beta$ -blockers and drugs commonly used in the management of obesity. Pharmacokinetic studies in obesity show that the behaviour of molecules with weak or moderate lipophilicity (e.g. lithium and vecuronium) is generally rather predictable, as these drugs are distributed mainly in lean tissues. The dosage of these drugs should be based on the ideal bodyweight (IBW). However, some of these drugs (e.g. antibacterials and some anticancer drugs) are partly distributed in adipose tissues, and their dosage is based on IBW plus a percentage of the patient's excess bodyweight.

There is no systematic relationship between the degree of lipophilicity of markedly lipophilic drugs (e.g. remifentanyl and some  $\beta$ -blockers) and their distribution in obese individuals. The distribution of a drug between fat and lean tissues may influence its pharmacokinetics in obese patients. Thus, the loading dose should be adjusted to the TBW or IBW, according to data from studies carried out in obese individuals. Adjustment of the maintenance dosage depends on the observed modifications in clearance.

Our present knowledge of the influence of obesity on drug pharmacokinetics is limited. Drugs with a small therapeutic index should be used prudently and the dosage adjusted with the help of drug plasma concentrations.

Obesity is considered to be a worldwide concern, and in 1998 the World Health Organization (WHO) published a report on preventing and managing the global epidemic.<sup>[1]</sup> Obesity is widely recognised as being a serious and complex disease, with major health, social and economic implications, because it is a risk factor in cardiovascular, metabolic and musculoskeletal disorders. Nevertheless, our understanding of the pathophysiology of obesity is still a considerable challenge to science and medicine. The discovery of leptin has greatly promoted research into the molecular control of obesity, leading to therapeutic approaches and, very recently, clinical trials.

Healthcare professionals may be surprised by the discrepancy between the great concern about obesity from the pathophysiological, social and economic viewpoint, and the limited number of studies devoted to its pharmacokinetic consequences, as these provide the rationale for better targeted drug use. Physicians and pharmacists must be conscious that obesity can significantly alter the tissue

distribution and elimination of drugs, and may necessitate modified loading and/or maintenance doses. This is a subject of concern, particularly for drugs that have narrow therapeutic indices (e.g. anticancer drugs) or minimal effective concentrations (e.g. antibacterial drugs).

This article is a review of literature on this topic that has appeared since previous reviews were published.<sup>[2,3]</sup> To present a clearer overview, the analysis of pharmacokinetic information is preceded by a reminder of the definitions and prevalence of obesity and factors affecting pharmacokinetics in obesity. The implications for therapy with each of the drug classes studied are considered.

## 1. Definitions and Prevalence of Obesity

Obesity is defined as an excess of fat tissue compared with normal values for age and gender, but the way data are expressed may differ from one study to another. Thus, standard definitions of excess bodyweight have been proposed. The most frequently used method was initially the ideal

bodyweight (IBW), with a formula taking height and gender into account; an individual was said to be obese when the actual bodyweight exceeded the IBW by more than 20%.<sup>[4]</sup>

The international recommended classification of obesity recently published by the WHO<sup>[1]</sup> is based on the body mass index (BMI), calculated as bodyweight (in kg) divided by the square of the height in metres. Overweight is defined as a BMI  $\geq 25$  to 29.9 kg/m<sup>2</sup> and obesity as a BMI  $\geq 30$  kg/m<sup>2</sup>. Obesity is divided into 3 classes: moderate (BMI 30.0 to 34.9), severe (BMI 35.0 to 39.9) and morbid (BMI  $\geq 40.0$ ).

Large epidemiological studies have recently been carried out to collect information on trends in the prevalence of overweight and obesity, as classified by the WHO.<sup>[1]</sup> The prevalence of obesity has increased by between 10 and 40% in the majority of European countries over the past 15 years, the most dramatic increase being reported in the UK, where the prevalence has nearly doubled.<sup>[5]</sup> In France there was a limited increase in the prevalence of obesity in adults between 1980 and 1991. In men the prevalence shifted from 39.4 to 48.0% for overweight and from 6.4 to 6.5% for obesity, whereas the figures for women were 26.8 to 27.5% and 6.3 to 7.0%, respectively. The change was most pronounced among young women (20 to 29 years old), with an increase in the prevalence of overweight from 8.8 to 11.5%, and in obesity from 1.4 to 2.1%. The French figures for obesity in 1991 were not very different from those in countries such as Sweden (5.3% of men and 9.1% for women) or the Netherlands (5.1% and 9.1%, respectively).<sup>[6]</sup>

In addition, one epidemiological study has shown a major increase in the prevalence of obesity in young children (from 1.8 to 4.9%) in one district in France.<sup>[7]</sup> Between 1987 and 1993, the increase in prevalence in the adult population of the US was 2 to 3 times greater than in most European countries: in the US, 19.7% of men and 24.7% of women were obese in 1993.<sup>[5,8]</sup>

## 2. Factors Likely to Affect Pharmacokinetics in the Obese

The altered pathophysiology of the obese body is likely to affect drug distribution within the tissues and drug elimination, whereas absorption does not seem to be modified.<sup>[3]</sup> The main factors that affect the distribution of drugs in tissues, and consequently their volume of distribution (Vd), are body composition, regional blood flow and binding to plasma proteins.

Obese individuals have a larger absolute lean body mass (LBM), as well as fat mass, than normal healthy individuals of the same age, gender and height. Lean components of the body account for 20 to 40% of the excess bodyweight. However, the percentage of lean tissue calculated per kg of total bodyweight (TBW) is reduced, whereas that of fat is about doubled.<sup>[9]</sup> LBM can be determined by whole-body densitometry, bioelectric impedance or anthropometric measures. Anthropometric calculations based on height and bodyweight are easy to perform in a clinical setting and are widely used:

$$\text{LBM (kg)} = a \times \text{TBW (kg)} - b \times [\text{TBW/height (cm)}]^2$$

where a and b are 1.10 and 120 for men and 1.07 and 148 for women. This formula is similar, but not identical, to that for IBW based mostly on height.

We know that under conditions of normal bodyweight the blood flow in fat is poor and accounts for only 5% of the cardiac output, compared with 73% in the viscera and 22% in lean tissue.<sup>[10]</sup> It has also been shown that blood flow per gram of fat is significantly less in morbidly obese individuals than in moderately obese or lean individuals.<sup>[11]</sup> Finally, a study of the reduction of cardiac ventricular performance in severely obese patients showed that impairment is correlated with the degree of obesity.<sup>[12]</sup> It seems that there is no more recent publication on this topic, but the available data suggest that the haemodynamic condition of obese patients may alter drug kinetics.

Changes in the concentrations of plasma binding proteins can affect the movement of drugs into tissue compartments and consequently their therapeutic effect. Studies with drugs primarily bound

to albumin (e.g. phenytoin) showed no significant changes in protein binding in obese patients.<sup>[13,14]</sup> There is some uncertainty about the binding to  $\alpha_1$  acid glycoprotein acid (AAG) in obesity. A doubling in AAG concentrations in obese patients has been reported, with a concomitant significant increase in the protein binding of propranolol, but the clinical effects were not checked.<sup>[13]</sup> Another study with the same drug did not confirm this observation.<sup>[15]</sup>

The concentrations of AAG were more recently shown to be slightly higher in obese individuals than in normal-bodyweight individuals, but this resulted in no change in the free fraction of triazolam.<sup>[16]</sup> It should be emphasised that the amount of a drug in the plasma depends on the balance between the affinities of the drug for plasma proteins and tissue components. However, unlike plasma binding, tissue binding cannot be measured directly in the clinical setting.

The livers of obese individuals frequently suffer from fatty infiltration, one form of which is non-alcoholic steatohepatitis.<sup>[17]</sup> These lesions could significantly influence the metabolic activity of the liver. It is difficult to measure the hepatic metabolism of drugs in humans. There is no clear correlation between routine liver function tests and the capacity of the liver to metabolise drugs, but some chemicals can be used as markers to assess enzyme activities. Antipyrine has been used as a marker of hepatic oxidative metabolism in obese and normal bodyweight individuals: the systemic clearance (CL) of the antipyretic remained unchanged in the obese group, suggesting that the hepatic oxidative metabolism of drugs is not modified in obesity.<sup>[18]</sup> However, this is difficult to assess as the CL of antipyrine varies widely between individuals.

The 6-hydroxylation of chlorzoxazone has been used as a probe of the activity of hepatic cytochrome P450 (CYP) 2E1, which is involved in the activation of carcinogens and metabolism of drugs such as enflurane.<sup>[19]</sup> Obesity resulted in a significant increase in the oral CL of chlorzoxazone and the fractional CL of the hydroxylated metabolite. The authors concluded that obese individuals may

be at increased risk of CYP2E1-mediated toxicity of environmental agents.

In addition, the efficacy of a drug that is a CYP-2E1 substrate may be reduced in obese patients. The [<sup>14</sup>C]erythromycin *N*-demethylation activity, measured by the breath test, showed a strong negative correlation with the percentage of IBW in a small group of patients.<sup>[20]</sup> This finding suggests that specific CYP3A isoforms may be decreased in obesity. However, the diversity of data obtained from these studies underlines the difficulty of obtaining a clear overview of drug hepatic metabolism in obesity.

Articles on drug kinetics have provided differing data on renal function in obese individuals. Glomerular filtration is more easily assessed than tubular function: it is usually assessed by the creatinine clearance (CL<sub>CR</sub>). Studies on ciprofloxacin,<sup>[21]</sup> lithium<sup>[22]</sup> and gentamicin<sup>[23]</sup> showed no significant difference in CL<sub>CR</sub> between obese individuals and those with normal bodyweight. In contrast, a study on vancomycin reported a significant increase in CL<sub>CR</sub> in morbidly obese patients.<sup>[24]</sup> The clinical condition of the individuals (extent of obesity or associated renal disorder) and their numbers differed in these studies, which may explain the discrepancies.

The studies discussed in this section show that many pathological factors are likely to affect pharmacokinetics in obesity. The more obvious changes concern drug tissue distribution, and therefore the corresponding parameter V<sub>d</sub>. Previously published reviews emphasised that diffusion is not always correlated with the hydrophilicity or lipophilicity of drugs.<sup>[2,3]</sup> In fact, the data for molecules with weak or moderate lipophilicity are relatively consistent, all showing that these drugs are distributed to a limited extent in excess body fat. Conversely, there are great discrepancies in the distributions of markedly lipophilic drugs in obese individuals, and the size of V<sub>d</sub> is not always correlated with the degree of lipophilicity. We will now examine new information from recent publications to assess developments in this area.

### 3. Effects of Obesity on the Pharmacokinetics of Particular Drug Classes

#### 3.1 Antiinfectives

##### 3.1.1 Antibacterials

A series of pharmacokinetic studies were done with moderately lipophilic antibacterials to optimise dosages in obese individuals (table I). An initial study after a single administration of vancomycin showed that the volume of distribution at steady state ( $V_{ss}$ ) and CL were significantly higher, and elimination half-life ( $t_{1/2\beta}$ ) shorter, in 6 morbidly obese patients than in 4 non-obese individuals. There was a strong positive correlation between TBW and both  $V_{ss}$  and CL, but there was no significant difference between the 2 groups when CL was calculated per kg TBW. It was concluded that TBW should be used to determine vancomycin dosage.<sup>[25]</sup>

More recent publications have analysed data from patients given vancomycin for therapeutic purposes.<sup>[26]</sup> In a study of 230 patients, 135 of whom were obese, trough and peak vancomycin serum concentrations were measured at steady state and fitted with a Bayesian program. The patients were stratified on the basis of the difference between TBW and LBM.<sup>[26]</sup> The  $t_{1/2\beta}$  and Vd increased with bodyweight and CL tended to decrease. Regression analysis revealed that TBW and

the percentage over LBM were significant predictors of Vd. TBW was predictive for total CL, and percentage over LBM was a predictor of  $t_{1/2\beta}$ . Thus, TBW appears to be better for calculating the initial dose of vancomycin. Further dosages should be guided by the serum concentrations of the drug.

A recent study<sup>[24]</sup> reassessed vancomycin dosages in 24 morbidly obese patients with normal renal function. The values of Vd in the obese and normal bodyweight individuals were statistically similar, and there was a positive modest correlation between TBW and Vd. The principal pharmacokinetic change in obese patients was a clear increase in the CL of vancomycin, which was positively correlated with TBW. However, the values were similar in obese and normal bodyweight individuals when TBW was used to normalise CL.<sup>[24]</sup> The findings suggested that the daily doses required to obtain the desired vancomycin plasma concentrations in obese patients were similar to those required for the controls (approx. 30 mg/kg TBW). Because of the large increase in CL,  $t_{1/2\beta}$  was much less in obese patients and the intervals between doses may have to be shorter. In a case report,<sup>[27]</sup> 4 nomograms and an individualised method were compared in simulated vancomycin administration. It was concluded that the available nomograms were not designed for morbidly obese patients and that TBW should be used to select the dosage, rather than IBW.

**Table I.** Pharmacokinetic parameters for antibacterials administered to obese and non-obese individuals

Drug	Vd (L)		Vd (L/kg TBW)		CL [L/h (ml/min)]		$t_{1/2\beta}$ (h)		Recommendations for dosage in obese patients	Reference
	control	obese	control	obese	control	obese	control	obese		
Vancomycin	28.9	43.0*	0.39	0.26*	4.85 (80.8)	11.25 (187.5)*	4.7	3.2**	Dose based on TBW, as Vd and CL are correlated with TBW	25
	46	52	0.68	0.32***	4.62 (77)	11.8 (197)*	7.2	3.3***	Daily dose/kg TBW similar to controls if patient has normal renal function	24
Ciprofloxacin	219	269*	3.06	2.46***	44.6 (744)	53.8 (897)*	4.0	4.2	Calculation on IBW + 45% of excess bodyweight	21
Gentamicin	16.7	18.2			4.01 (66.9)	4.63 (77.2)	3.3	3.1	Initial dose based on calculation of $CL_{CR}$ by Cockcroft equation <sup>[29]</sup> with $IBW + 0.4 \times (TBW - IBW)$	23

CL = total body clearance;  $CL_{CR}$  = creatinine clearance; IBW = ideal bodyweight; LD = loading dose; MD = maintenance dosage;  $t_{1/2\beta}$  = terminal elimination half-life; TBW = total bodyweight; Vd = apparent volume of distribution; \*  $p < 0.05$ ; \*\*  $p < 0.01$ ; \*\*\*  $p < 0.001$ .

The  $V_{ss}$  of ciprofloxacin was significantly larger (by 23%) in obese individuals than in controls, but it was lower when normalised to the total TBW. There was a significant inverse relationship between the BMI and ciprofloxacin  $V_{ss}/kg$ . These findings indicate that the antibacterial is distributed less in adipose tissue than in other tissues, but there is some distribution to adipose tissue. To normalise obese  $V_{ss}/kg$  to that of controls, 45% of excess bodyweight (TBW – IBW) must be added to the IBW of obese individuals. CL was significantly increased (by 21%) in obese individuals, and renal CL was 29% higher than in the controls. This increase in CL in the absence of change in  $t_{1/2\beta}$  was largely explained by the large  $V_{ss}$  in the obese volunteers. The authors concluded that the ciprofloxacin dosage should be based on the IBW plus 45% of the excess bodyweight.<sup>[21]</sup> A case report<sup>[28]</sup> of a patient weighing 250kg gave the results obtained with a standard dose of ciprofloxacin 400mg plus an additional amount calculated as above. The measured peak serum drug concentration was within the recommended therapeutic range with this procedure.

The initial doses of aminoglycosides are usually based on  $CL_{CR}$ , most frequently evaluated by the Cockcroft-Gault equation<sup>1</sup> taking into account the serum creatinine, age, TBW and gender.<sup>[29]</sup> This relationship is most accurate for individuals with an average muscle mass for their age, bodyweight and height. The calculation in obese patients leads to the overestimation of  $CL_{CR}$  when TBW is used, and underestimation when IBW is used.

Salazar and Corcoran developed another equation based on the fat-free body mass.<sup>[30]</sup> The performance of these methods for calculating gentamicin dosage was compared in a population of patients being treated for infection that including 100 non-obese and 100 mildly to morbidly obese individuals.<sup>[23]</sup> The gentamicin pharmacokinetic parameters estimated by each method were compared with the pharmacokinetic values determined

from serum concentrations. Regression analysis indicated that the Cockcroft equation using weight as  $IBW + 0.4 \times (TBW - IBW)$  was the best of the methods tested for calculating  $CL_{CR}$ , and thus predicting gentamicin pharmacokinetic values. This procedure was, therefore, recommended for the initial treatment of obese patients, with later dosage adjustments based on serum drug concentrations.

### 3.1.2 Antifungal Agents

The current administration recommendations for the major antifungal agents are based on pharmacokinetic data obtained in individuals of normal bodyweight. No pharmacokinetic study or guideline for drug administration is available for this drug group in obese patients.

Case reports<sup>[31,32]</sup> on morbidly obese patients give results obtained after empirical dosage adjustment of flucytosine and fluconazole, 2 hydrophilic molecules that are eliminated by the kidney and are distributed mainly in the total bodywater.

A patient (BMI = 46) with a severe extrameningeal (cutaneous and bone) cryptococcal infection, and with normal renal function, was successfully treated with amphotericin B plus flucytosine. The dosage of flucytosine (167 mg/kg/day) was based on an approximated IBW. Measurements of serum drug concentrations on the 19th day of treatment gave values within the recommended range (30 to 90 mg/L).<sup>[31]</sup>

Another patient (BMI = 48) suffering from severe necrotising fasciitis with candidaemia was first given amphotericin B and flucytosine, plus a fluconazole infusion (1200 mg/day/185kg) in a second step. This treatment was effective. After 14 days of therapy the average fluconazole steady-state concentration was 23.9 mg/L, and the calculated CL for fluconazole was 139.4 ml/min, which is higher than in other published reports.<sup>[32]</sup> The currently recommended treatment for *Candida albicans* in patients with invasive disease is peak serum concentrations greater than 25 mg/L.<sup>[33]</sup> Thus, a higher dosage of fluconazole was recommended for obese patients.

**1**  $CL_{CR} = (140 - \text{age}) \times TBW / (A) \times \text{serum creatinine}$  where age is in years, TBW is in kg, and A = 72 for men and 85 for women.

**Table II.** Modifications of pharmacokinetics of anticancer drugs in obesity

Drug	Vd (L)		Vd (L/kg TBW)		CL [L/h (ml/min)]		t <sub>1/2β</sub> (h)		Main correlations and/or practical conclusions	Reference
	control	obese	control	obese	control	obese	control	obese		
Ifosfamide	33.7	42.8*	0.53	0.55	4.33 (72.2)	4.56 (76.0)	4.9	6.4*	Positive correlation between V <sub>z</sub> or t <sub>1/2β</sub> and %IBW. Prolonged t <sub>1/2β</sub> may increase toxicity	34
Doxorubicin	964	1119	15.3	14.0	94.1 (1569)	53.5 (891)***	13	20.4*	%IBW correlated with decreased CL and increased t <sub>1/2β</sub> . Premature to propose guidelines	35
Cyclophosphamide	34.5	37.1			5.48 (91.3)	3.60 (60.6)	4.8	8.5	TBW correlated negatively with CL, positively with t <sub>1/2β</sub> . Study concerned only the inactive prodrug	36
Busulfan					11.4 (190)	15.0 (250)*			Body surface area or adjusted IBW are appropriate for calculating dose	37
Carboplatin						6.72 (112)			Best predictor of CL was mean value between IBW and TBW	38

CL = total body clearance; IBW = ideal bodyweight; LD = loading dose; MD = maintenance dosage; t<sub>1/2β</sub> = terminal elimination half-life; TBW = total bodyweight; Vd = apparent volume of distribution; V<sub>z</sub> = volume of distribution in the terminal elimination phase; \* p < 0.05; \*\* p < 0.01; \*\*\* p < 0.001.

### 3.2 Anticancer Drugs

Many anticancer drugs are relatively lipid insoluble and may be poorly distributed in adipose tissue. Their elimination may also be altered in obese patients. Therefore some oncologists calculate the doses used in the chemotherapy of obese patients on the basis of IBW rather than TBW. However, only a few studies have investigated the effects of obesity on the disposition of anticancer drugs (table II).

The pharmacokinetics of ifosfamide were studied in 16 patients with bronchial carcinoma.<sup>[34]</sup> t<sub>1/2β</sub> was prolonged in 4 obese women, the difference being attributed to a change in Vd rather than a change in CL. There was a positive correlation between the Vd in the terminal elimination phase (V<sub>z</sub>) [L or L/kg] and the percentage of IBW, implying that the drug can be distributed in body fat. Thus, toxicity might be modified in obese patients because of the prolonged t<sub>1/2β</sub>.

Doxorubicin undergoes extensive hepatic metabolism by aldoreductases that convert the drug to doxorubicinol, which also possesses cytotoxic properties.<sup>[39]</sup> The pharmacokinetics were investigated in 21 adults with cancer, 7 of whom were obese and 7 severely obese.<sup>[35]</sup> The area under the

concentration-time curve (AUC) for doxorubicin in the severely obese patients was significantly greater than in normal bodyweight patients and the CL was significantly smaller. The V<sub>ss</sub> was similar among the 3 groups of patients, indicating that the prolonged t<sub>1/2β</sub> in obese patients was related to the reduced CL. Nevertheless, there was no difference in the AUC of doxorubicinol in obese and normal bodyweight patients. Obesity may reduce the CL of doxorubicin by inhibiting the aldoketoreductases. However, the number of patients was considered to be too small to propose specific dosage guidelines.

The pharmacokinetics of cyclophosphamide were studied in 16 women with breast cancer, 12 of whom were obese.<sup>[36]</sup> t<sub>1/2β</sub> was positively and significantly correlated with TBW, but there was no significant correlation between bodyweight and Vd. CL was significantly reduced with increasing TBW, normalised to body surface area (BSA) or to IBW. This decrease in CL in obese patients presumably reflected a reduced drug metabolism by hepatic CYP. However, dosage guidelines could not be inferred, as there was no significant correlation between any of the cyclophosphamide pharmacokinetic parameters and the therapeutic or

**Table III.** Pharmacokinetic parameters in obese and non-obese patients of drugs used for diseases of the central nervous system

Drug	Vd (L)		Vd (L/kg TBW)		CL [L/h (ml/min)]		t <sub>1/2β</sub> (h)		Recommendations for dosage adjustment in obese patients	Reference
	control	obese	control	obese	control	obese	control	obese		
Lithium			0.66	0.42***	1.38 (23.0)	2.03 (33.9)***	25.6	18.7*	LD based on IBW. MD larger than in non-obese	22
Phenytoin	40.2	82.2***	0.61	0.68*	2.34 (39)	3.54 (59)	12.0	19.9*	LD calculated on IBW + 1.33 × (TBW – IBW)	14
Carbamazepine	69.7	98.4***	0.96	0.87*	1.38 (23.0)	1.19 (19.8)	31.0	59.4***	MD based on IBW	40

CL = total body clearance; IBW = ideal bodyweight; LD = loading dose; MD = maintenance dosage; t<sub>1/2β</sub> = terminal elimination half-life; TBW = total bodyweight; Vd = apparent volume of distribution; \* p < 0.05; \*\*\* p < 0.001.

myelosuppressive effects. This could be because only the inactive prodrug, and not the cytotoxic metabolite, was assayed in this study.

Busulfan is commonly used in a preparative regimen before transplanting haemopoietic stem cells. The drug is eliminated by conjugation with glutathione in the liver. Its apparent oral clearance (CL/F) was measured in a cohort of 279 adult and adolescent patients undergoing cell transplantation and classified as underweight, normal, obese and severely obese, according to their BMI.<sup>[37]</sup> The major finding was that the CL/F was lower in normal bodyweight patients than in the obese and severely obese patients. However, expressing the busulfan CL/F relative to BSA or the adjusted ideal bodyweight,<sup>2</sup> provided the smallest variation between patients, and there was no difference in the value of CL/F among BMI classes. Therefore, these measures of body size seem appropriate for calculating the busulfan dosage in adults with obesity or normal bodyweight.

Unlike the above-mentioned drugs, carboplatin is mainly eliminated via the kidneys. Bénézet et al.<sup>[38]</sup> studied the accuracy of a formula for predicting CL from patient-specific variables (serum creatinine, bodyweight, age and gender) in 25 obese patients. CL was overpredicted by more than 20% for 7 patients using the TBW, and IBW led to underprediction. The best predictor was the mean value between IBW and TBW [i.e. IBW + 0.512 × (TBW – IBW)]; the percentage error was –21 to +22%.

$$2 \quad \text{Adjusted IBW (kg)} = \text{IBW} + 0.25 \times (\text{TBW} - \text{IBW}).$$

This series of publications clearly shows that our understanding of the influence of obesity on the pharmacokinetics of anticancer drugs is patchy. Most studies were done on a small number of patients with a particular type of malignancy and who were treated with specific chemotherapy regimens. Therefore, the conclusions drawn by the authors are cautious and mention the importance of determining target plasma concentrations.

### 3.3 Drugs Used for Diseases of the Central Nervous System

Only 7 studies have investigated the effects of obesity on the disposition of central nervous system drugs (table III).

#### 3.3.1 Psychotropic Drugs

The efficacy of lithium in patients with bipolar illness and its narrow therapeutic window warrant consideration in obesity. Studies on obese and normal bodyweight individuals showed that the V<sub>ss</sub> of lithium was significantly correlated with IBW and fat-free mass, but not with TBW in the combined groups, and that V<sub>ss</sub>/kg was significantly smaller in the obese individuals.<sup>[22]</sup> This is consistent with the hydrophilic nature of lithium. The CL of lithium was significantly greater in the obese individuals compared with in the control group, although CL<sub>CR</sub> had similar values in the 2 groups.

This observation is surprising for a drug essentially excreted after glomerular filtration, but may be due to a greater tubular reuptake of lithium in control individuals than in obese individuals. The results of this study suggest that the loading dose for obese patients should be based on IBW, and that



a larger maintenance dosage is required to obtain an adequate serum concentration in obese patients than in lean patients.

The antidepressant drug fluoxetine is a selective serotonin reuptake inhibitor. The plasma concentrations of the parent drug and of its active metabolite, norfluoxetine, in obese and lean individuals were similar. Thus, it appears that this drug is not readily distributed in adipose tissue, and that its pharmacokinetics are not affected by obesity.<sup>[41]</sup>

### 3.3.2 Anticonvulsants

The loading doses of phenytoin required for obese and control individuals were determined after a single intravenous infusion.<sup>[14]</sup> The  $t_{1/2\beta}$  of phenytoin was significantly prolonged in the obese group and the metabolic CL tended to be increased. The change in  $t_{1/2\beta}$  was the result of a marked increase in total Vd and Vd corrected for TBW in obese patients. Vd expressed in either way was positively correlated with the percentage of IBW. This indicates that the distribution of this lipophilic drug is greater in individuals with excess bodyweight than in IBW. The authors concluded that phenytoin loading dose should be calculated on the basis of IBW plus the product of 1.33 times the excess bodyweight over IBW.

Recent case reports<sup>[42,43]</sup> have extended this earlier publication and confirmed that obesity may affect the pharmacokinetics of phenytoin. The phenytoin plasma concentration of a morbidly obese male, treated for thrombotic thrombocytopenic purpura with plasmapheresis and phenytoin, rebounded markedly 1 hour after the cessation of plasmapheresis, suggesting drug redistribution.

The high value of the total body stores of phenytoin, together with its large Vd, may have contributed to this rebound.<sup>[42]</sup>

In another case, a severely obese female with epilepsy (BMI = 36) was treated long term with anticonvulsants; she lost 7kg over 5 months. There was a positive correlation between the CL of phenytoin and the change in her TBW.<sup>[43]</sup> This suggests that her bodyweight reduction may have caused a decrease in phenytoin metabolism.

Several studies have evaluated the pharmacokinetics of a single oral dose of carbamazepine in obese patients. In 6 severely obese individuals there was a substantial bodyweight reduction associated with a marked decrease in Vd/F and  $t_{1/2\beta}$  and a 50% increase in CL/F.<sup>[44]</sup> Another trial compared the pharmacokinetics in 18 obese and 13 lean individuals.<sup>[40]</sup> Vd/F and  $t_{1/2\beta}$  were significantly greater in the obese group. Vd/F corrected for total bodyweight was slightly smaller in the obese than in the lean individuals. This small difference suggests that carbamazepine is distributed almost as extensively in excess bodyweight as in IBW. The small effect of obesity on the CL/F suggests that the daily dose given to obese individuals should be based on IBW, rather than TBW. Physical exercise has been shown to be associated with the accelerated hepatic transformation of low clearance drugs.<sup>[45]</sup> Thus, the enhancement in CL/F reported in the first publication<sup>[44]</sup> may be related to the physical training program followed by the patients.

**Table IV.** Pharmacokinetics of drugs used in anaesthesiology in obese and non-obese patients

Drug	Vd (L)		Vd (L/kg TBW)		CL [L/h (ml/min)]		$t_{1/2\beta}$ (h)		Recommendations for dosage in obese patients	Reference
	control	obese	control	obese	control	obese	control	obese		
Propofol	13.0	17.9	2.09	1.8	1.70 (28.3)	1.46 (24.3)	4.1	4.05	MD based on TBW	46
Sufentanil	346	547*	4.8	5.8	1.51 (25.2)	1.25 (20.8)	2.2	3.4*	LD based on TBW. MD reduced	47
Remifentanil			0.22	0.14*	2.54 (42.3)	1.67 (27.9)**			Dosage calculated on IBW basis	48
Vecuronium	59.0	44.7	0.99	0.47**	19.5	15.6	2.2	2.0	Dosage calculated on IBW	49
Rocuronium			0.14	0.09*	0.45	0.30*			Reduced infusion rate	50

CL = total body clearance; IBW = ideal bodyweight; LD = loading dose; MD = maintenance dosage;  $t_{1/2\beta}$  = terminal elimination half-life; TBW = total bodyweight; Vd = apparent volume of distribution; \*  $p < 0.05$ ; \*\*  $p < 0.01$ .

### 3.4 Drugs Used in Anaesthesiology

Few studies have investigated the effects of obesity on the disposition of anaesthetics (table IV).

#### 3.4.1 General Anaesthetics

The great lipophilicity of propofol and the rather long duration of infusion used to maintain general anaesthesia are the rationale for pharmacokinetic studies in morbidly obese patients.<sup>[46]</sup> Comparison with non-obese controls showed that the CL and  $V_{ss}$  of propofol was significantly correlated with TBW in the obese group, so that the values of  $t_{1/2\beta}$  in non-obese and obese individuals were similar. Therefore, the high hepatic extraction and conjugation of propofol appear to be related to TBW. This could explain why there were no signs of drug accumulation in obese patients. These pharmacokinetic data suggest that the maintenance dosage of propofol for obese patients may, theoretically, be established on the same basis as for lean patients, taking into account the TBW. In spite of the lipophilic nature of the drug, the  $V_{ss}$  corrected for TBW for the 2 groups did not differ. This may be the result of affinity not only for the excess fat, but also for other tissues, such as well-perfused organs.

Sevoflurane is a new inhalational anaesthetic. It differs from halothane by its low solubility in the blood. This results in a more rapid uptake and induction. Data are not yet available on the pharmacokinetics of sevoflurane in obese patients, but there have been reports on the serum concentrations of the fluoride metabolite after anaesthesia. Some investigators observed significantly higher concentrations in obese patients than in non-obese patients, whereas others have found no difference between the 2 groups.<sup>[51]</sup>

#### 3.4.2 Opioids

The synthetic opioid analgesics, fentanyl congeners such as sufentanil and more recently remifentanil, are used in anaesthesiology. Because of their high lipid solubility, their pharmacokinetics have been studied in very obese (>60 to 80% over IBW) and matched control patients. Vd and  $t_{1/2\beta}$  were significantly increased in obese patients in the sufentanil study.<sup>[47]</sup> The Vd was correlated

positively with the degree of obesity. In contrast, Vd/kg TBW was similar in the 2 groups. This indicates that the drug was distributed at least as extensively in the excess body mass as in the lean tissues, and that the loading dose should account for total body mass. In spite of the absence of a significant difference in CL between the 2 groups, the longer  $t_{1/2\beta}$  of elimination in obese patients suggests that maintenance doses should be prudently reduced in these individuals.

Conversely, the CL and  $V_{ss}$  of remifentanil corrected per kg of TBW were significantly smaller in obese patients. Accordingly, the doses used for obese individuals should be calculated on the basis of IBW.<sup>[48]</sup> Mino et al.<sup>[52]</sup> used an electroencephalogram model to measure the opioid effect, and determined that age and LBM are demographic factors that should be considered when choosing a dosage regimen for remifentanil in healthy volunteers.

#### 3.4.3 Neuromuscular Blockers

Neuromuscular blockers are polar and hydrophilic. A study on 9 obese and 9 non-obese surgical patients receiving vecuronium 0.1 mg/kg TBW showed that the  $V_{ss}$ , CL and  $t_{1/2\beta}$  were similar for both groups. The  $V_{ss}$ , expressed on the basis of total bodyweight, was 2-fold smaller in obese patients compared with non-obese patients, which is consistent with the hydrophilicity of the drug.<sup>[49]</sup> The main difference was in the duration of action, which was prolonged in obese patients because of the excess dose administered as a result of the drug being administered on the basis of TBW. Therefore, IBW should be used to calculate doses of vecuronium in obese patients.

A similar observation was made more recently following an infusion of rocuronium designed to maintain a 95% neuromuscular block.<sup>[50]</sup> 53 patients were assigned to 1 of 4 groups according to their BMI. CL/kg and  $V_{ss}$ /kg were significantly lower in obese (BMI > 26) than in non-obese patients. This could explain why reduced infusion rates of the drug were required in obese patients. Another study investigated the time course of action of rocuronium 0.6 mg/kg TBW in 48 patients divided into 4

groups according to their BMI.<sup>[53]</sup> The onset tended to be faster in the obese patients, and the duration of action longer than in other patients. Although this difference was not statistically significant, the authors insisted on the clinical relevance of the duration of action and concluded that rocuronium should be administered to obese patients on the basis of IBW and not TBW.

### 3.5 Drugs Used in the Management of Obesity

#### 3.5.1 Appetite Suppressants

The pharmacokinetics of drugs designed to suppress appetite and cause loss of bodyweight have been studied in obese patients and normal bodyweight volunteers (table V).

Intravenous infusion of dexfenfluramine in obese patients led to a  $V_{ss}$  that was significantly higher than that in the controls. The CL was not significantly different and  $t_{1/2\beta}$  tended to be longer. Data from obese and non-obese individuals indicated a positive correlation between  $V_{ss}$  and the percentage of IBW, and this is in keeping with the lipophilic nature of the drug. However, the bodyweight-adjusted  $V_{ss}$  for the 2 groups of patients was similar. This indicates that dexfenfluramine is equally well distributed in the excess fat and lean tissues.<sup>[54]</sup> In view of the similarities of  $V_{ss}/\text{kg TBW}$  and CL in obese and non-obese individuals, the loading dose should be based on TBW and the maintenance dosage calculated using the IBW.

Nevertheless, the application of these principles is limited by uncertainty, as the relationship between the drug concentration in the plasma and its anorectic activity is unclear.<sup>[59]</sup>

Sibutramine is another centrally-acting body-weight management agent; it acts mainly via its desmethyl metabolites M1 and M2. The plasma concentrations and pharmacokinetics [peak plasma drug concentration ( $C_{max}$ ), AUC, and  $t_{1/2\beta}$ ] of the 2 metabolites in obese and non-obese individuals were reported to be similar ( $t_{1/2\beta}$  was about 17 hours in both groups) after oral administration of the drug for 2 weeks, but no detailed data have been provided.<sup>[60]</sup>

#### 3.5.2 Oral Hypoglycaemic Agents

Sulfonylurea agents are effective regulators of blood glucose in patients with type 2 (non-insulin-dependent) diabetes mellitus. The majority of patients with this disease are overweight. Jaber et al.<sup>[55,56]</sup> studied the pharmacokinetics of glipizide and glibenclamide (glyburide) in obese and non-obese patients with type 2 diabetes mellitus. Patients were treated for 12 weeks with individual daily doses titrated to give similar blood glucose concentrations. The values of CL/F, Vd/F and  $t_{1/2\beta}$  for these drugs in the obese and normal bodyweight patients were not statistically different. The correlations between the  $V_z$  and CL of glibenclamide and TBW were calculated, but the large inter-individual differences resulted in poor statistics, which were considered to be nonpredictive. The

**Table V.** Pharmacokinetics in obese and non-obese individuals of some drugs used in the management of obesity

Drug	Vd (L)		Vd (L/kg TBW)		CL (L/h)		$t_{1/2\beta}$ (h)		Recommendations for dosage in obese patients	Reference
	control	obese	control	obese	control	obese	control	obese		
Dexfenfluramine	668.7	969.7**	11.3	10.2	37.3	43.9	13.5	17.8	LD based on TBW. MD based on IBW	54
Glipizide	17.2	19.5	0.21	0.20	2.0	2.3	5.2	5.0		55
Glibenclamide (glyburide)	56.8	47.0	0.81	0.44*	3.1	3.2	15.2	10.0	Lower daily dosage due to greater sensitivity	56
Caffeine	40.1	48.3*	0.59	0.44*	6.04	4.9	6.08	6.54	No dosage modification required	57
Theophylline		40.5		0.40		3.3		8.9	Unchanged Vd and decrease of CL after bodyweight loss. LD based on IBW. MD could be corrected	58

CL = total body clearance; IBW = ideal bodyweight; LD = loading dose; MD = maintenance dosage;  $t_{1/2\beta}$  = terminal elimination half-life; TBW = total bodyweight; Vd = apparent volume of distribution; \*  $p < 0.05$ ; \*\*  $p < 0.01$ .

**Table VI.** Pharmacokinetics of  $\beta$ -blockers in obese and non-obese individuals

Drug	$V_{ss}$ (L)		$V_{ss}$ (L/kg TBW)		CL (L/h)		$t_{1/2\beta}$ (h)		Reference
	control	obese	control	obese	control	obese	control	obese	
Propranolol	180.0	226.8	3.1	2.4	41.6	46.2	3.4	3.9	63
Nebivolol	673.0	898.0*	11.2	9.4	51.6	71.6*	10.3	10.0	63
Labetalol	278.6	367.9*	4.8	3.8	81.5	89.9	4.4	4.5	63
Bisoprolol	146.0	173.0**	2.9	1.9**	12.8	14.8*	7.6	8.6	64
Sotalol	70.8	81.0	1.1	0.9	7.0	9.4	7.3	6.2	62

**CL** = total body clearance;  $t_{1/2\beta}$  = terminal elimination half-life; **TBW** = total bodyweight;  **$V_{ss}$**  = volume of distribution at steady state; \*  $p < 0.05$ ; \*\*  $p < 0.01$ .

obese patients required a significantly lower mean daily dosage of glibenclamide than the controls, and appeared to be more sensitive to the drug. The glipizide study<sup>[55]</sup> reported marked hyperglycaemia in obese patients in response to the glucose tolerance test, but large interindividual variations impaired the clinical significance of the observation.

### 3.5.3 Methylxanthines

Methylxanthines have recently been used to accelerate energy expenditure and enhance fat loss in obesity. This novel use has led to studies on the possible influence of bodyweight reduction on the pharmacokinetics of caffeine and theophylline.

Re-examination of caffeine disposition showed that apparent  $V_d$  is moderately greater in obese patients, but when corrected by TBW it is significantly lower than in lean individuals.<sup>[57]</sup> Apparent  $V_d$ /kg TBW was significantly increased in 6 obese patients who took part in a 11-month bodyweight reduction program. The data implied that caffeine distribution was mainly restricted to lean body mass. CYP1A2 is known to be the principal enzyme mediating caffeine metabolism.<sup>[61]</sup> However, the similarity of  $t_{1/2\beta}$  and CL/F of caffeine in obese and non-obese individuals, and the absence of any change in these parameters following a significant bodyweight loss, are consistent with a negligible influence of obesity on CYP1A2. The difference in the  $V_d$  of caffeine also seems to be of minor clinical importance, and therefore the dosage need not be modified for obese patients.

The data on theophylline, which is more lipophilic than caffeine, are a little different. A study

was carried out on obese women before and after a 3-week bodyweight-reducing treatment.<sup>[58]</sup> There were no difference in total  $V_d$  and  $V_d$ /kg TBW before and after bodyweight loss, suggesting that theophylline is largely distributed in the lean body mass. Thus, IBW should be used to calculate a loading dose for obese patients. Conversely, there was a significant increase in the AUC and  $t_{1/2\beta}$ , and a decrease in CL, after bodyweight loss. Therefore bodyweight-reducing treatment may be connected with changes in the transformation and excretion of theophylline more than with its distribution. Consequently, dosage recommendations for long term treatment with theophylline in obese patients could require correction.

### 3.6 $\beta$ -Blockers

$\beta$ -Adrenoceptor antagonists are used to treat systemic hypertension and coronary heart disease, for which obesity is a risk factor. As it has been postulated that the lipophilicity of these drugs influences their pharmacokinetics in obese patients, several studies have been done with  $\beta$ -blockers of different lipophilicity.

The pharmacokinetic parameters of sotalol, a markedly hydrophilic drug, were similar in obese and lean individuals.<sup>[62]</sup> The highly lipophilic drug propranolol had a similar or a significantly smaller total  $V_d$  in obese compared with non-obese individuals.<sup>[15,63]</sup> The total  $V_{ss}$  of the less lipophilic bisoprolol was significantly greater in obese compared with non-obese patients.<sup>[64]</sup> The  $V_{ss}$  corrected by TBW (L/kg) of both drugs was lower in obese patients, and when the results of obese and

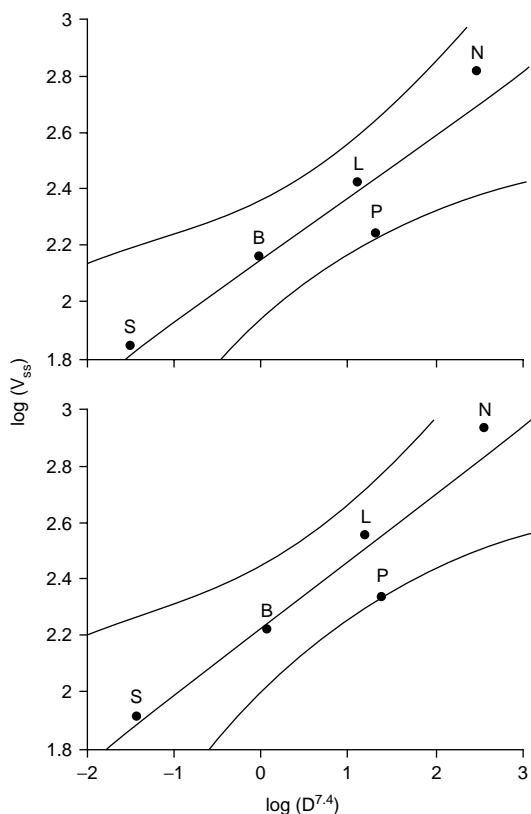
lean patients were combined there was a significant negative correlation between  $V_{ss}/kg$  and the percentage of IBW. These results suggest that such lipophilic drugs diffuse less extensively into adipose tissue than into lean tissues.

Other studies have been done to determine whether differences in  $V_d$  were specific to some  $\beta$ -blockers, and to identify the factors responsible for adipose tissue affinity. The pharmacokinetics of propranolol, labetalol and nebivolol (2 other lipophilic  $\beta$ -blockers whose pharmacodynamics differ from those of propranolol), were studied in the same population of obese and lean individuals.<sup>[63]</sup> The data from this study were compared with those for sotalol and bisoprolol studied under the same experimental conditions (table VI). The ionisation constants and lipophilicity parameters of all 5 drugs were also assessed by the same methods. The total  $V_{ss}$  for nebivolol and labetalol were larger in obese patients than in the controls, and there was a significant positive correlation with the percentage IBW. The tendency was similar for propranolol, but the correlation was not significant.

When the 5  $\beta$ -blockers are considered together, general trends become even more apparent.  $V_{ss}$ , expressed per kg of TBW, is always slightly smaller in obese than in non-obese patients. In addition, the ratio of  $V_{ss}$  or  $V_{ss}/kg$  bodyweight in obese versus control individuals ranges from 1.18 to 1.33 and from 0.65 to 0.84, respectively. Thus, obese patients appear to have about a 24% larger total  $V_d$  and a 23% smaller  $V_d/kg$  for  $\beta$ -blockers than lean individuals. These results seem to confirm that the lipophilic  $\beta$ -blockers diffuse less into adipose tissue than into lean tissue. Published data and those from this series of studies indicate that neither plasma protein binding nor the systemic haemodynamic effects can explain the limited diffusion of these drugs into adipose tissues in obese patients.

The correlations between  $V_d$  and the physicochemical parameters of the 5  $\beta$ -blockers were calculated to assess the physicochemical factors influencing the distribution. The best relationship was for total  $V_{ss}$  and distribution coefficient at pH 7.4

in the system octanol/water ( $\log D^{7.4}$ ) [fig. 1]. This parameter expresses the sum of the proportional contributions of the various electrical forms of drugs present at physiological pH (cations, neutral forms and zwitterions). The result implies that they all contribute to the distribution of these drugs. The linear regressions between  $\log V_{ss}$  and  $\log D$  in control and obese individuals are also identical, suggesting that the tissue affinity of the  $\beta$ -blockers in the 2 groups are similar. Lipophilic  $\beta$ -blockers could diffuse into both adipose and lean tissues. Their distribution could be restricted and control-



**Fig. 1.** Relationship between the logarithm of total volume of distribution at steady state ( $V_{ss}$ ) of 5  $\beta$ -blockers and the logarithm of their distribution coefficient at pH 7.4 ( $D^{7.4}$ ), for controls (**top**) and obese individuals (**bottom**). The equations used are as follows: (**top**)  $\log V_{ss} = 0.23 (\pm 0.04) \log D^{7.4} + 2.1 (\pm 0.07)$ ;  $r^2 = 0.89$ ;  $p = 0.01$ ; (**bottom**)  $\log V_{ss} = 0.25 (\pm 0.05) \log D^{7.4} + 2.2 (\pm 0.07)$ ;  $r^2 = 0.90$ ;  $p = 0.01$ . **B** = bisoprolol; **L** = labetalol; **N** = nebivolol; **P** = propranolol; **S** = sotalol.

led by the sum of the hydrophobic forces and hydrogen bonds they make in lean tissues.

Finally, this series of studies provided new information on the pharmacokinetics of lipophilic drugs in obesity and the factors involved. However, the moderate differences between obese and non-obese patients may be clinically irrelevant because of the wide therapeutic index of  $\beta$ -adrenoceptor antagonists.

### 3.7 Miscellaneous

#### 3.7.1 Antipyrine

Antipyrine is a hydrophilic antipyretic and analgesic drug. It is extensively oxidised in the liver and used to assess hepatic metabolising capacity. The drug was given to severely obese and lean individuals to study the effect of obesity on oxidative metabolism.<sup>[18]</sup> The  $V_d$  and  $t_{1/2\beta}$  of antipyrine were significantly greater in the obese patients than in the lean group, but the  $CL/F$  values for the drug were similar.  $V_d$  corrected for total bodyweight was significantly reduced in obese patients. Bodyweight loss was associated with a marked increase in  $V_d/kg$  (from  $0.43 \pm 0.06$  to  $0.52 \pm 0.08$  L/kg) without any clear change in  $CL/F$ . These data indicate the partial distribution of antipyrine in excess bodyweight and suggest that the hepatic oxidative metabolism of drugs is not markedly impaired in obesity.

#### 3.7.2 Nicotine

The plasma concentrations of nicotine were measured after a single application of a transdermal system on the arms of 13 normal bodyweight and 13 obese men.<sup>[65]</sup> The  $AUC_{\infty}$  was significantly lower in the obese group and was strongly and negatively correlated with TBW and the BMI. These data probably reflect the greater  $V_d$  of the lipophilic nicotine in obese individuals associated with an increase in  $CL$ , because  $t_{1/2\beta}$  in the 2 groups of volunteers was similar. The difference in plasma nicotine concentrations of the groups is probably not related to a difference in skin absorption, because absorption from the transdermal system is determined primarily by the release from the membrane system. In addition, there are no data sug-

gesting that the patient's bodyweight effects the clinical efficacy of the nicotine transdermal system.

#### 3.7.3 Interferon- $\alpha$

The potential negative effect of obesity on the response to interferon- $\alpha$  (IFN $\alpha$ ) in patients with chronic hepatitis C was examined by measuring serum concentrations of IFN $\alpha$  and the 2',5'-oligoadenylate (2-5OAS) synthetase activity in blood mononuclear cells, a marker of IFN activity, in 6 obese and 5 non-obese patients after a single fixed dose of IFN $\alpha$ .<sup>[66]</sup> The mean maximum serum concentration and AUC of the drug were similar in obese and non-obese patients. However, these parameters were inversely correlated to TBW, percentage over IBW and BSA. The 2-5OAS response was greater in the non-obese than in the obese patients, suggesting a greater biological response to IFN $\alpha$  in the non-obese individuals. This may be because of the reduced exposure of the obese patients to the drug because of their larger body size. Hence, the bodyweight or BSA should be taken into consideration when determining the dose of IFN $\alpha$ .

## 4. Discussion and Conclusion

Regardless of the importance of published studies on pharmacokinetics in obesity, they have limitations. First, the data provided largely concerns single doses rather than usual therapeutic use. Secondly, the number of patients included in each trial is restricted by practical and ethical conditions. Thirdly, interindividual variations sometimes hamper the assessment of results, and may lead to differences between studies. At least 2 factors can explain the heterogeneity of patient groups: individuals with the same BMI may differ in their body composition and fatness, particularly between ethnic groups. It is also difficult to assess the hepatic metabolism of drugs in clinical situations.

Nevertheless, proposals for adjusting dosages in obese patients have been formulated from the pharmacokinetic studies. The principles of pharmacokinetics and evaluation of the diffusion of a drug

into lean and fat mass by calculation of Vd and Vd/kg of bodyweight provide basic guidelines for individualising drug dosage. The loading dose is based on Vd. Thus, the loading dose should be based on IBW when Vd/kg TBW indicates that drug distribution is restricted to lean tissues. For drugs distributed mainly in the lean mass and partly in fat tissue, a calculation of loading dose should be performed with IBW plus a percentage of IBW. The loading dose of drugs equally distributed in lean and fat tissues, or markedly distributed in fat tissues, should be based on TBW.

Adjustment of maintenance dosage depends on clearance. When CL is similar in obese patients and controls, or decreased in obese patients, the dosage should be calculated using IBW. The CL for some drugs is correlated with the increase in bodyweight, and thus the maintenance dosage should be based on the actual bodyweight. Morgan and Bray<sup>[67]</sup> insisted on the importance of LBM as a predictor of loading dose for relatively hydrophilic drugs in obese patients instead of TBW. LBM is also useful for predicting the maintenance dosage of many drugs that are eliminated via the liver, because their hepatic CL is proportional to LBM. However, the pharmacokinetic data may complicate the situation. The hyper- or hyposensitivity of obese patients to some drugs (e.g. the hypoglycaemic sulfonylureas, or atracurium) must be taken into account.

This review, like previous articles,<sup>[2,3]</sup> reveals that it is very difficult to predict the impact of obesity on the pharmacokinetics of a specific drug according to its lipophilic characteristics. The data for the relatively hydrophilic drugs are fairly consistent, but there are unexpected discrepancies between lipophilic drugs and they do not always have a Vd/kg TBW in obese patients that is larger than that found in normal bodyweight individuals (e.g. propofol and some  $\beta$ -blockers). Other factors, such as blood flow, protein binding and tissue binding, probably also influence Vd in the obese.

Bickel<sup>[68]</sup> shed new light on the relationship between lipophilicity and tissue distribution, demonstrating that many lipophilic drugs are not stored

in adipose tissue *in vivo*. From experiments simulating drug distribution between blood and different tissue preparations, he concluded that the key factor for storage in adipose tissue is the so-called 'binding competition' between lean and adipose tissue. Hence, storage in adipose tissue is low when binding to lean tissues is high.

In conclusion, it is important to bear in mind that each drug may behave differently, and that our present knowledge of the influence of obesity on pharmacokinetics is limited. The best attitude to take when giving a drug with a small therapeutic index to an obese patient should be to use published information, but prudently, and to adjust the final dosage with the help of therapeutic drug monitoring.

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