Canadian Journal of Cardiology 31 (2015) 167–176

Review

The Impact of Obesity on the Pharmacology of Medications Used for Cardiovascular Risk Factor Control

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ABSTRACT

Most drugs are currently dosed empirically (fixed-dose) or based on total body weight. In obese patients, these dosing strategies might, in theory, lead to inadequate clinical effect (empiric dosing) or toxicity (weight-based dosing). Our objective was to first review body size descriptors used for drug dosing and then to examine the effect of obesity on the pharmacokinetics and pharmacodynamics of drugs used for cardiovascular risk reduction (antihypertensive agents, statins, aspirin, antidiabetic agents). We found a limited number of published studies for most drug classes. For β-blockers, volume of distribution was increased in the obese and this appears to be primarily due to greater distribution into lean tissue. In contrast, clearance was decreased, unchanged or increased, depending on the agent. This suggests that loading doses should be based on lean body weight and maintenance doses adjusted in a drug-specific fashion according to clearance alterations. For antidiabetic agents, glucose-lowering effects were slightly diminished in most studies in obese patients. Outside of these findings, in the studies reported to date, obesity did not exert a consistent, clinically important effect on drug pharmacology. Because obesity can cause drug-specific pharmacological changes for some drug classes (eg, β-blockers), there is a need to conduct further studies. To avoid detecting pharmacokinetic changes

RÉSUMÉ

La plupart des médicaments sont habituellement dosés de manière empirique (doses fixes) ou selon le poids corporel total. Chez les patients obèses, ces stratégies de dosage entraîneraient, en théorie, un effet clinique inadéquat (dosage empirique) ou une toxicité (dosage établi selon le poids). Notre objectif était d'abord de passer en revue les descripteurs de la masse corporelle utilisés pour doser les médicaments et ensuite d'examiner l'effet de l'obésité sur la pharmacocinétique et la pharmacodynamie des médicaments utilisés pour réduire le risque cardiovasculaire (antihypertenseurs, statines, aspirine, antidiabétiques). Nous avons trouvé un nombre limité d'études publiées sur la plupart des classes de médicaments. En ce qui concerne les β-bloquants, le volume de distribution était augmenté chez l'obèse, ce qui semble être principalement dû à la plus grande distribution dans les tissus maigres. En revanche, la clairance était diminuée, inchangée ou augmentée selon l'agent. Cela suggère que les doses de charge devraient être établies selon la masse du corps excluant la graisse et les doses d'entretien ajustées de manière spécifique au médicament selon les modifications de la clairance. En ce qui concerne les antidiabétiques, les effets hypoglycémiants étaient légèrement diminués dans la plupart des études chez les patients obèses. Au-delà de ces résultats, les études rapportées à ce jour ont

Obesity has increased markedly in prevalence over the past 4 decades and currently affects 500 million individuals worldwide.[1-4] Obesity leads to numerous medical complications and, in particular, is associated with a substantially increased risk of cardiovascular disease.[5] Cardiovascular-related sequelae of obesity include hypertension, coronary artery disease, stroke, type 2 diabetes mellitus, and dyslipidemia.[6,7]

Pharmacotherapy is often indicated to optimally manage obesity-related cardiovascular complications; therefore, obese patients have a high likelihood of requiring treatment with cardiovascular drugs. When prescribing cardiovascular pharmacotherapy to an obese patient, the effect of obesity per se on drug pharmacokinetics (ie, drug disposition pathways) and pharmacodynamics (ie, drug response) requires consideration. Failure to account for the underlying excess adiposity could, in theory, result in a suboptimal dosing regimen and treatment failure.

The purpose of this review was to systematically examine the effect of obesity on the pharmacokinetics and pharmacodynamics of important cardiovascular medications used to control cardiovascular risk factors in obese patients and to make dose modification recommendations, if necessary. We begin by reviewing some fundamental pharmacological principles of relevance to the present topic, followed by a review of various methods of

Received for publication September 4, 2014. Accepted October 22, 2014.

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See page 174 for disclosure information.

http://dx.doi.org/10.1016/j.cjca.2014.10.025

that are ultimately deemed clinically inconsequential, we suggest a "top down" approach in which clinically important outcomes are compared between obese and nonobese subjects. If important differences are found, further studies should be then performed to delineate underlying pharmacological mechanisms and inform the need for dose adjustment.

démontré que l'obésité n'exerçait pas de manière constante un effet cliniquement important sur la pharmacologie. Puisque l'obésité peut causer des changements pharmacologiques spécifiques au médicament pour certaines classes de médicaments (p. ex., les β-bloquants), il est nécessaire de mener d'autres études. Pour éviter la détection de changements pharmacocinétiques, qui sont finalement considérés cliniquement sans conséquence, nous suggérons une approche « descendante » où les résultats importants sur le plan clinique sont comparés entre les sujets obèses et les sujets non obèses. Si des différences importantes sont observées, d'autres d'études devraient alors être réalisées pour définir les mécanismes pharmacologiques sous-jacents et appuyer la nécessité de l'ajustement des doses.

classifying obesity and body composition, and, finally, we provide a discussion of contemporary studies that examined the effect of obesity on the pharmacokinetics or pharmacodynamics of drugs used for cardiovascular risk factor control.

Pharmacokinetic Assessment of Drug Disposition

Pharmacokinetic parameters commonly used to characterize the in vivo disposition of a drug include clearance (Cl), volume of distribution (Vd), half-life ($t_{1/2}$), and bioavailability (F).[8] These are summarized in Table 1.[9] Estimation of these parameters typically involves administering single or multiple doses, measuring the blood or plasma concentration over time, and then calculating each parameter.

Body Size Descriptors

Body composition, including fat mass and fat-free mass, can be directly assessed using underwater weighing, air displacement, dual x-ray absorptiometry, and bioelectrical impedance.[10-12] For a variety of reasons, including cost, availability, and time constraints, these methods are not often used in routine clinical practice.

Instead, a variety of different body size descriptors have been developed to indirectly estimate overall size, fat mass, and lean mass. Use of body size descriptors is necessary because dosing based on total body weight (TBW), the most widely used of dosing methods, might not accurately reflect drug disposition. Administering doses in proportion to TBW assumes that drug metabolism scales linearly as TBW increases, an assumption that might not be valid considering that 99% of the body's metabolic processes (including drug Cl) take place within lean tissues.[13]

Therefore, other body size descriptors have been proposed, including body surface area, body mass index (BMI), ideal body weight (IBW), lean body weight (LBW), or fat-free mass, adjusted body weight (ABW), and predicted normal weight (PNWT).[14] The formulas used to calculate these parameters are summarized in Table 2.

TBW

TBW is the most common size descriptor used by clinicians.[15] Although this descriptor might be useful for individuals of "normal weight" it might be unreliable in obese individuals because excess weight is primarily due to increases in adipose tissue.[16]

BMI

BMI (calculated as weight [kg]/height [m^2]) is the most widely used measure of weight for classifying obesity.

Table 1. Commonly used pharmacokinetic parameters

Pharmacokinetic parameter	Definition	Formula	Clinical significance
Bioavailability	Fraction of a drug that reaches systemic circulation after nonparenteral administration	$= \frac{100 \times AUC_{PO} \times D_{IV}}{AUC_{IV} \times D_{PO}}$	The F of an intravenously administered drug is considered to be 1 (or 100%).
Vd	Apparent volume in the body that contains the drug	$= \frac{\text{Total amount of drug in the body}}{\text{Drug plasma concentration}}$	For parenteral drugs especially, higher loading doses are generally needed for drugs with large volume distribution
Cl	The volume of plasma that is cleared of the drug per unit time	$= \frac{C_U \times Q}{C_P}$	Clearance depends on blood flow and the ability of the organ to extract the drug. Clearance is important in estimating maintenance dose
Half-life	Time required for the concentration or amount of drug in the body to be reduced by 50%	$= \frac{\ln 2 \times Vd}{Cl}$	Half-life of a drug is useful for determining the dosing frequency. It is directly proportional to volume distribution and inversely proportional to clearance

AUC, area under the curve; C, concentration; Cl, clearance; D, dose; F, bioavailability; ln2, natural logarithm of 2; IV, intravenous; P, plasma; PO, orally; Q, rate of blood flow; U, urine; Vd, volume of distribution.