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Therapeutic drug monitoring to adjust dosing in morbid obesity – a new use for an old methodology

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The phenomena of hunger and need at one end of the spectrum and obesity and plenty on the other is an anomaly of the 21st century, likely to be due to a combination of distributive inequities in food, social justice, access to education and other socio-economic factors. Both are major problems worldwide, although obesity has more media coverage due to the exponentially increasing incidence and the huge social and economic burden this is placing on Western society. For example, prevalence rates of obesity are currently exceeding 30% of adults in the USA with direct morbidity and mortality complications, in addition to the additional obesity-related health problems and death. Obesity is also rising in children. Obese people are thus a sizable group, and as with those with altered renal or liver function, require specific consideration with respect to the appropriate dosing of medications. However guidelines for how to do this in obesity are not currently available, due to the paucity of literature and regulatory rules for new medications which usually only request the demonstration of average population effectiveness. We believe it is timely for regulatory agencies worldwide to mandate studies involving consideration of body size, particularly obesity, in approving new medications across the therapeutic spectrum. This will drive the pharmaceutical industry to consider these groups in studies and will encourage investigator-initiated research using therapeutic drug monitoring (TDM), target concentration therapy (TCI) and pharmacogenetic (PGx) studies to optimize drug dosing.

Current situation

It is not uncommon on a standard ward round in a tertiary hospital to note that a 120 kg young male is getting the same dose of flucloxacillin for his cellulitis as an elderly female weighing 60 kg, in the next bed. It is similar for DVT prophylaxis, the same dose is given for people with same total body weight despite often a large variation in body composition and age. This appears to be an important and clinically relevant research question, yet the evidence for clinical data and subsequent changes in health outcomes around these practices are lacking. In fact, in the pharmacology and therapeutics area, there has instead been a large amount of media attention on advances in tests for genetic variability in proteins regulating drug absorption, distribution, metabolism and excretion and in receptors or signaling pathways. This 'pharmacogenetics' (PGx, single gene) research has certainly contributed towards the exciting possibility of patient-specific drug therapy. However to date, apart from a few instances where inheritance of a few specific mutations is known to result in clinically significant outcomes, such as TMPT testing with azathioprine, HLA*5701 and abacavir hypersensitivity and CYP2D6 testing when using tamoxifen, many genetic tests offer minimal clinical benefit over the cheaper and better validated concentration measurements. We estimate that for some therapies, specifically chemotherapy and antimicrobials, differences in anthropomorphic parameters may well explain more of the variation in clinical outcomes than expensive and clinically unvalidated PGx tests. As body size is increasing, especially in paediatrics and geriatrics, clinical studies in this area using clinically driven endpoints are badly needed.

This review is not all-encompassing for a particular specialty or therapeutic group. Rather the information presented will illustrate our concern for the lack of clinical data in this area, discussing two clinical areas where treatment of morbid obesity is often felt to be beyond the evidence,

antimicrobials and chemotherapy. We have added pharmacokinetic (PK) data when available but caution that until the clinical relevance of altered kinetics is shown to be related to efficacy and toxicity in a specific disease that care with altering dosing on these parameters should be exercised.

Pharmacokinetic processes

Obesity has a number of definitions. PK studies have mainly defined obesity using calculations of ideal body weight (IBW) defined by a formula including height and gender [3], with total body weight (TBW) > 125% IBW defined as obese and TBW > 190% IBW as morbid obesity. Lean body weight (LBW) can be measured or estimated by whole body densitometry, bioimpedence or anthropomorphic measures which take into account height, weight and gender, but usually defined from a non obese population. There is some evidence that both body size and composition influences some PK parameters [4]. The PK variables that appear to be most affected in obesity are clearance (CL) and volume of distribution (V_d), parameters which also vary depending on the degree of water solubility of the drug.

Volume of distribution (V_d)

Despite V_d being an important variable, clinical evidence on how to measure changes in CL and V_d and to adjust dosing is sparse. Average V_d reported for drugs is based on the non-obese population, so in clinical practice doses are sometimes adjusted for obesity by dosing mg kg^{-1} of either total or LBW, depending on the degree of hydro- or lipophilicity of the drug. However this practice depends on both accurate knowledge of the degree of lipo- or hydrophilicity and an assumption that most of the extra weight above the IBW is fat, which is misleading [5]. Further other chemical properties of each drug, such as pKa, affect whether the drug diffuses into adipose tissues, factors which may also vary depending on the medical state (e.g. pH) or comorbidties of the patient. Usually for most lipophilic drugs the V_d increases in obesity because of adipose binding, even after adjustment for body weight [6]. However there are other relevant factors including relative binding to plasma components, to proteins, to adipose and lean tissues, blood flow to adipose tissue and whether the adipose tissue is visceral or subcutaneous, brown or white [4]. In general, changes to V_d do not necessarily correlate with TBW.

Although not intuitive, obesity and the resultant increases in lean body mass [7] and body water [8] can actually result in lowered serum concentrations of hydrophilic drugs due to increased blood flow via the liver and kidneys in early obesity. Lean body mass, increased in obesity, also correlates with size and function of metabolic and clearance organs [4, 9].

Clearance

Increases in clearance via increased glucuronidation, sulphation and CYP 2E1 activity have been documented in obese subjects. However CYP 3A4, an enzyme responsible for nearly half of metabolism, may be reduced in obesity [10], leading to higher concentrations of antibiotic where the parent drug is active, but less where the metabolite is active [11]. Further, the effect of steatosis, hepatitis and fibrosis in liver and kidney in chronic obesity are known to have some effect on clearance but we do not often have either accurate surrogates or better still clinical outcome data, to estimate the degree of impairment. For example, accurate estimation of renal clearance can be difficult in obesity as estimations are all derived from estimates of people of average body size. However this estimation is very important in renally cleared drugs where knowledge of renal function that predicts drug clearance could be critical in dosing [12]. Pai *et al*. using a population of people with an average BMI of 50 found that various estimates of creatinine clearance (CL_{cr}) that used anthropomorphic variables in their estimations were very biased compared with the actual measured 24 h CL_{cr}. However substitution of a LBW estimate, based on TBW and BMI in the Cockcroft–Gault equation gave a relatively precise, accurate and clinically practical estimate of 24 h measured CL_{cr} [13].

Whether the population is obese or morbidly obese may affect CL, e.g. there was no difference in CL of ciprofloxacin and gentamicin between obese individuals and those with normal bodyweight but in a population of morbidly obese on vancomycin there was a significant increase in CL_{cr} [14].

Other PK parameters

Protein binding (PB) The theoretical relevance of PB is that it can affect the movement of drugs into tissue and blood cell compartments and may also affect interpretation of TDM results. Changes in the concentrations of plasma binding proteins such as albumin and α_1-acid glyocoprotein has been reported in obesity. However, whether or not this is of clinical relevance has yet to be shown [3]. Several studies with lipophilic drugs have in fact shown either no clinical effect of binding in obesity [15, 16], or no measured clinical relevance [17, 18].

Absorption Data on the effects of drug absorption and obesity are limited. Changes in absorption are predicted in obesity due to observed changes in CYP 3A4 expression in the liver, increased body surface area and increased cardiac output, with increased gut perfusion. However, studies to date have not shown a clinically relevant difference [19].

Pharmacodynamic effects of obesity

Blood flow

Adipose tissue can be measured by a number of methods such as PET scanning or ^{133}Xe washout. In people with

normal body fat, blood flow to the fat only accounts for 5% of cardiac output (compared with 20% in lean tissue). However in obese people, blood flow to fat is reduced, and the post prandial adipose blood flow is further reduced as compared with non obese people [20], possibly associated with insulin resistance as well as increased vascular resistance.

Cardiac performance

Cardiac output, which affects organ and soft tissue perfusion can be affected variably by obesity. Initially, obesity causes a hyperdynamic system with increased cardiac output and blood volume [19]. However adiposity increases vascular resistance and over time leads to structural changes in the heart and ultimately heart failure [19]. This affects blood flow to the gut and to soft tissue. Although measurement of an ejection fraction is not usually requsted *per se* for infection in an obese person, in the absence of clinical evidence it is recommended to consider the issue of cardiac function on pharmacokinetic variables and adjust if considered appropriate.

Other pharmacokinetic/dynamic parameters

Extremes of age Paediatrics are another group which generally has been neglected by Pharma and the regulatory world. Experience has helped guide us as to when dosing using mg kg^{-1} or BSA and TDM is appropriate. It should be noted that the World Health Organization uses BMI as a definition for obesity [1,21]. Obesity adds to the literature deficiencies we currently see in the paediatric dosing area [2]. The problem is compounded as the proportion of children who are overweight is increasing in the general population. There are modelling studies emerging [22] which are contributing significanlty to this area but the combination of this plus clinical outcomes in paediatrics, specifically in paediatric obesity are much needed. This recommendation holds for obese elderly patients also, although there is an emerging literature in underweight elderly [23].

Ethnicity There is evidence also that ethnicity may further have effects on the known PK effects of obesity with data, perhaps due to PGx effects on drug metabolizing enzymes [24]. A metabolic difference in metabolic enzyme activity (CYP 3A, 2D6 and 1A2) in African-American obese *vs.* normal weight children has been reported [23].

Critical illness and obesity The setting of intensive care with patients who are morbidly obese is another new phenomenom with new dosing questions arising. Although these patients have their own specific clincial challenges around diagnosis and management, investigations into the area of pharmacotherapy are urgently needed. Groups examining antimicrobial therapy in ICU settings are poised to develop clinically relevant guidelines [25].

Specific therapeutic areas where TDM in obesity may be helpful

Chemotherapy

Accurate initial and maintenance dose selection of anticancer agents in the obese is especially challenging in oncology. Because of their inherently toxic effects, clinicians balance the risks of high doses with potentially worse treatment outcomes if doses are relatively inadequate for the body size. Despite the high frequency of obesity in the population, surprisingly, the clinical impact of obesity in the context of chemotherapy has been studied only minimally in adults and even less in children, although there have been several studies examining total body exposure in obesity with other therapies that could be extrapolated to chemotherapy [26]. Since clinically valid guidelines have not been developed, clinicians often calculate the requisite dose using an alternative to TBW in the obese. However the actual clinical effect of this is of concern to local clinicians (personal communication Maree Colissimo, Princess Alexandra Hospital).

The current practice for the dose calculation of most anticancer agents is based on BSA in m^2. However many oncology services have subsequently decided to 'cap' chemotherapy doses at BSA of 2.0 m^2 when treating the obese [27]. However, recent studies have shown systematic under-dosing of chemotherapy in overweight and obese patients with breast cancer [27–33], which occurs in up to 40% of patients, may contribute to the poorer survival rates, particularly among those with oestrogen receptor (ER)–negative cancers [34]. Animal data confirm that dosing to a 'capped' BSA in mice can result in an AUC 36% less than that achieved in non obese controls [35]. There are many human trials showing adverse PK profiles in obese patients having chemotherapy [36–38].

Area under the plasma concentration–time curve (AUC) appears to be more closely correlated with pharmacodynamics than does the dose per unit of BSA. In particular, the AUC guided administration of carboplatin has been extensively studied, with formulae and limited sampling models derived to predict the AUC of carboplatin [36–39]. The relationship between AUC and pharmacodynamics has also been studied for other anticancer agents, for example fluorouracil, topotecan, etoposide, cisplatin and busulfan, but all less extensively than for carboplatin.

A further point includes the fact that current clinical practice involves the administration of multiple chemotherapeutic agents, often in different regimens or larger regimens than that studied in the original trials. This makes an assessment of the pharmacokinetics *per se*, and in obesity, even more challenging.

Although cost-effectiveness analyses on TDM in oncology have yet to be undertaken, emphasis should be placed on how such interventions can be applied in the most clinically useful manner [40], especially as newer and more expensive medications become available. Although

further modelling studies can add to the literature in terms of initial dose guidance, these data have to come from clinical trials using clinically relevant endpoints. These endpoints can then drive the cost-effectiveness analysis.

Antimicrobials

Obesity has a number of effects on disease outcomes both directly and indirectly via its effects on medications. For example, the outcome of patients with infections is much worse if obesity is present due to leg oedema, poor mobility and other similar factors [41]. Additionally, obesity may affect the bactericidal index differently for antibiotics, depending on their PK/PD factors. For example for β-lactams, percentage time above MIC of the pathogen appears to be the critical determinant in determining efficacy, with drug CL an important PK factor in this. Similarly the *in vivo* MIC in soft tissue which is stranded with fat (especially apron cellulitis) is likely to be different from the standard *in vitro* concentration [42].

Vancomycin and the aminoglycosides are the antibiotics for which there are the most clinically robust details available on effects of obesity. With vancomycin, it is known that V_d and CL are increased and are correlated with TBW rather than LBW [43–45] with the dosing interval based on measured or estimated (with awareness of the caveats) renal function [46]. It is now recognized that adequacy of dosing is an important determinant of efficacy, with cumulative toxicity a less important consideration of monitoring.

Aminoglycosides are the antimicrobials most widely studied in obesity. It is generally accepted that an appropriate initial empirical dosage calculation is critical to achieving the early high peak concentration of the drug that directly correlates with maximal killing of the pathogen. Subsequent dose adjustment is of critical importance in order to avoid cumulative nephro- and oto-toxicity. In contrast to vancomycin, these highly polar drugs penetrate adipose tissue poorly, and the use of TBW may lead to unwanted overdose. The use of calculated IBW to modify the initial dose in obese patients has been explored with a number of correction factors calculated such as a factor of 0.43 times the excess body weight added to the calculated IBW [47]. TDM to avoid accumulation and toxic side effects is then critical if use beyond a few days is required. Many authorities now recommend a change to a less toxic agent once a pathogen has been isolated and susceptibility determined [48].

A study with ertapenem showed that the probability of achieving bacteriostatic target attainment (T > MIC of 20%) was less than 10% in people with a BMI $\geq$ 40 kg m^{-2} [14]. The AUC : MIC ratio is the PK/PD outcome best associated with antimicrobial and clinical outcomes in fluoroquinolone therapy, with obesity increasing CL of fluoroquinolone and significantly decreasing C_{max} and AUC. It is therefore recommended to dose ciprofloxacin on IBW plus 45% of the TBW – IBW [49]. Another recommendation has been to dose ciprofloxacin on TBW. However this was based on retrospective and modelled data and may not be accurate.

Daptomycin, a newer lipopeptide antibiotic active against Gram positive pathogens, has been studied in obese patients, and similar to vancomycin, dosing according to TBW appears to maintain or slightly increase the desired AUC : MIC ratio, which is the best PK/PD parameter to predict efficacy for this agent [50, 51].

Other newer agents have had similar studies in small numbers of obese patients, with the result that most agents appear to have a PK profile that is relatively unique to the agent, and broad rules that could be applied to drug classes will not be practicable, therefore tilting the balance toward the desirability of TDM to ensure adequacy of dosing. This is not as important with agents that have a high therapeutic index where large doses well above what is necessary can be given in critical situations with little fear of overdosage.

There are further issues looming including medications used in critical care in obese conditions including conditions such as sepsis (hyperfiltration), coronary care, obese with organ failure (e.g. pneumococcal meningitis) and obese with penicillin allergy.

Where from here?

Many of the drugs we use in our daily armamentarium have PK processes that vary depending on the physicochemical properties of the drug and the medical state of the patient. Obesity adds another factor that affects drug exposure. Whilst tables with information on degree of lipophilicity etc. are helpful, clinical evidence is desperately needed to show that the hypothetical is borne out in a real live obese patient. There is likely to be a need for TDM in drugs with a clear relationship between concentration and effect, with appropriate post analytical advice as to interpretation.

Conclusion

The most appropriate dosage regimens for medications in obese people are often unknown. The situation is compounded in children with obesity, in obese patients with organ failure, in critically ill people and in obese people with β-lactam allergy. We believe that both the mg kg^{-1} and the one-size-fits-all strategy for prescribing are outdated as individual body size and composition characteristics of patients are likely to clinically significantly affect pharmacokinetic parameters. Further, adjusting the dosing of therapies in adults to the anthropomorphic features of individual patients could improve efficacy and reduce toxicity and cost containment. Rather than the development of complicated, mathematical dosing regimens, which could no doubt be possible by the development of phar-

macy dosing systems, a general rule of thumb to adjust dosages of medications on body size, knowing something about the lipophilicity of the drug, body composition of the patient and using TDM as guidance would also be helpful.

We also believe that a review of all pharmacokinetic data to identify dosage adjustments that are currently being used for the administration of drugs at the highest range of the distribution of bodyweight is needed. Further, subsequent simulation studies based on pharmacokinetic models would be helpful. Lastly, identification of the dosage adjustments needed with respect to body size and composition could be made a vital part of the process of new drug development and should be mandated by regulatory authorities before licensing.

Competing Interests

There are no competing interests to declare.

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