

Clinical Pharmacokinetics

Application of a Systems Approach to the Bottom-Up Assessment of Pharmacokinetics in Obese Patients

Expected Variations in Clearance

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Supplemental Digital Content

This Supplemental Digital Content (SDC) contains Appendix A and supplemental figures S-1 to S-8, which are referred to in the full version of this article, available online at <http://adisonline.com/pharmacokinetics>. The publication references cited in this document are listed on page 14 of the document.

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Appendix A

On this basis, the weighted average fold changes in hepatic intrinsic clearances (intrinsic clearances for whole liver) were back-calculated as follows:

(a) For the reported orally administered compounds (equation S-1):

$$CL_{PO \text{ Ratio}} = \frac{CL_{PO \text{ Obese}}}{CL_{PO \text{ lean}}} \quad (\text{Eq. S-1})$$

where $CL_{PO \text{ Ratio}}$ is the ratio of the mean absolute oral clearance of the compound in obese individuals to that in lean individuals, extracted from the published clinical studies. Subsequently, equation S-1 was extended as equation S-2:

$$\begin{aligned}
CL_{PO \text{ Ratio}} &= \frac{\frac{CL_{IV \text{ Obese}}}{F_{Obese}}}{\frac{CL_{IV \text{ Lean}}}{F_{Lean}}} \\
&= \frac{\frac{Qh \cdot fu_B \cdot CL_{int,H \text{ Obese}}}{Qh + fu_B \cdot CL_{int,H \text{ Obese}}}}{fa \cdot Fg \cdot FH} \\
&= \frac{\frac{Qh \cdot fu_B \cdot CL_{int, \text{ Lean}}}{Qh + fu_B \cdot CL_{int,H \text{ Lean}}}}{fa \cdot Fg \cdot FH} \\
&= \frac{\frac{Qh \cdot fu_B \cdot CL_{int,H \text{ Obese}}}{Qh + fu_B \cdot CL_{int,H \text{ Obese}}}}{fa \cdot Fg \cdot \frac{Qh}{Qh + fu_B \cdot CL_{int,H \text{ Obese}}}} \\
&= \frac{\frac{Qh \cdot fu_B \cdot CL_{int,H \text{ Lean}}}{Qh + fu_B \cdot CL_{int,H \text{ Lean}}}}{fa \cdot Fg \cdot \frac{Qh}{Qh + fu_B \cdot CL_{int,H \text{ Lean}}}} \\
&= \frac{fu_b \cdot \frac{Qh}{Qh + fu_B \cdot CL_{int,H \text{ Obese}}} \cdot (CL_{int,H \text{ Obese}})}{fa \cdot Fg \cdot \frac{Qh}{Qh + fu_B \cdot CL_{int,H \text{ Obese}}}} \\
&= \frac{fu_b \cdot \frac{Qh}{Qh + fu_B \cdot CL_{int,H \text{ Lean}}} \cdot (CL_{int,H \text{ Lean}})}{fa \cdot Fg \cdot \frac{Qh}{Qh + fu_B \cdot CL_{int,H \text{ Lean}}}} \\
&= \frac{fu_B \cdot CL_{int,H \text{ Obese}}}{fu_B \cdot CL_{int,H \text{ Lean}}} \\
&= \frac{CL_{int,H \text{ Obese}}}{CL_{int,H \text{ Lean}}} \tag{Eq. S-2}
\end{aligned}$$

where, for both obese and lean individuals, CL_{IV} is hepatic blood clearance with the well-stirred model (in mL/min), F is bioavailability, Qh is hepatic blood flow (mL/min), fu_B is the free fraction of the drug in blood, $CL_{int,H}$ is the intrinsic clearance per whole liver (μ L/min), fa is the free fraction available for

absorption from the dosage, Fg is the fraction escaping gut-wall first-pass metabolism, and FH is the fraction escaping hepatic first-pass metabolism.

It is important to note that the majority of published reports found no difference in drug absorption when comparing obese and lean individuals; it is generally accepted that obesity has little impact on the absorption of drugs.^[1,2] Therefore, extending equation S-1, the fa and Fg were assumed to be unaltered.

The free fraction of the drug in blood, fu_B , can be expressed as equation S-3:

$$fu_B = \frac{fu}{B : P} \quad (\text{Eq. S-3})$$

where fu is the free fraction of the drug in plasma, and $B : P$ is the blood to plasma concentration ratio of the drug. Equation S-3 can be extended to equation S-4:

$$fu_B = \frac{fu}{(E : P) \times HC + (1 - HC)} \quad (\text{Eq. S-4})$$

where HC is the subject's haematocrit, and $E : P$ is the relative drug concentrations in erythrocytes and in plasma, and is a compound-specific parameter.^[3]

From equations S-3 and S-4, it is obvious that the value of the fu_B is ultimately a function of $E : P$ and the individual's HC . Therefore, taking into account that serum albumin is the main protein responsible for protein binding of the compound, the value of the fu_B for equation S-2 is similar in the lean and obese groups.

In the absence of any data suggesting differences in the inter-system extrapolation factor (ISEF) and the fraction unbound in microsomes (fu_{mic}) between obese and lean populations, these values were also assumed to be unaltered between the two groups.

(b) For the reported intravenously (IV) administered compounds (equation S-5):

$$CL_{IV \text{ Ratio}} = \frac{CL_{IV \text{ Obese}}}{CL_{IV \text{ Lean}}} \quad (\text{Eq. S-5})$$

where $CL_{IV \text{ Ratio}}$ is the mean ratio of the absolute IV clearances, extended as follows (equation S-6):

$$\begin{aligned} CL_{IV \text{ Ratio}} &= \frac{CL_{IV \text{ Obese}}}{CL_{IV \text{ Lean}}} \\ &= \frac{\frac{Qh \cdot fu_b \cdot CL_{int,H \text{ Obese}}}{Qh + fu_b \cdot CL_{int,H \text{ Obese}}}}{\frac{Qh \cdot fu_b \cdot CL_{int,H \text{ Lean}}}{Qh + fu_b \cdot CL_{int,H \text{ Lean}}}} \\ &= \frac{\frac{CL_{int,H \text{ Obese}}}{Qh + fu_b \cdot CL_{int,H \text{ Obese}}}}{\frac{CL_{int,H \text{ Lean}}}{Qh + fu_b \cdot CL_{int,H \text{ Lean}}}} \end{aligned} \quad (\text{Eq. S-6})$$

for back calculation of intrinsic clearance (CL_{int}), from hepatic intrinsic clearance ($\mu\text{L}/\text{min}$) to CL_{int} ($\mu\text{L}/\text{min}/\text{mg}$ of microsomal protein), the final products of equations S-2 and S-6 were extended as follows:

For equation S-2 (equation S-7):

$$\begin{aligned}
 CL_{PO \text{ Ratio}} &= \frac{CL_{int,H \text{ Obese}}}{CL_{int,H \text{ Lean}}} \\
 &= \frac{CL_{int \text{ Obese}} \cdot MPPGL_{Obese} \cdot LW_{Obese}}{CL_{int \text{ Lean}} \cdot MPPGL_{Lean} \cdot LW_{Lean}} \\
 &= \frac{CL_{int \text{ Obese}} \cdot LW_{Obese}}{CL_{int \text{ Lean}} \cdot LW_{Lean}} \quad (\text{Eq. S-7})
 \end{aligned}$$

For equation S-6 (equation S-8):

$$\begin{aligned}
 CL_{IV \text{ Ratio}} &= \frac{\frac{CL_{int,H \text{ Obese}}}{Qh + fu_b \cdot CL_{int,H \text{ Obese}}}}{\frac{CL_{int, \text{ Lean}}}{Qh + fu_b \cdot CL_{int,H \text{ Lean}}}} \\
 &= \frac{\frac{CL_{int \text{ Obese}} \cdot MPPGL_{Obese} \cdot LW_{Obese}}{Qh + (fu_b \cdot CL_{int \text{ Obese}} \cdot MPPGL_{Obese} \cdot LW_{Obese})}}{\frac{CL_{int \text{ Lean}} \cdot MPPGL_{Lean} \cdot LW_{Lean}}{Qh + (fu_b \cdot CL_{int \text{ Lean}} \cdot MPPGL_{Lean} \cdot LW_{Lean})}} \quad (\text{Eq. S-8})
 \end{aligned}$$

where, for both obese and lean individuals, CL_{int} is hepatic intrinsic clearance ($\mu\text{L}/\text{min}/\text{mg}$ of microsomal protein), and $MPPGL$ is the amount (mg) of microsomal protein per gram of liver, calculated as described in equation S-9.^[4]

$$MPPGL \text{ (mg/g of liver)} = 10 (1.407 + 0.0158 \times \text{age} - 0.00038 \times \text{age}^2 + 0.0000024 \times \text{age}^3) \quad (\text{Eq. S-9})$$

Since obese and lean individuals participating in the clinical studies were reported to be matched for age, the value of $MPPGL$ appeared to be similar for both groups, with regard to equation S-9.

In order to back-calculate the relevant enzyme abundance, CL_{int} ($\mu\text{L}/\text{min}/\text{mg}$ of protein) from equations S-2 and S-6 was replaced as follows:

(a) For obese individuals (equation S-10):

$$CL_{int \text{ Obese}} = ISEF_{Obese} \times \frac{CL_{int(rCyp) \text{ Obese}} \times CYP_{abundance \text{ Obese}}}{fu_{mic \text{ Obese}}} \quad (\text{Eq. S-10})$$

(b) For lean individuals (equation S-11):

$$CL_{int\ Lean} = ISEF_{Lean} \times \frac{CL_{int(rCyp)\ Lean} \times CYP_{abundance\ Lean}}{fu_{mic\ Lean}} \quad (\text{Eq. S-11})$$

where, for both obese and lean individuals, the *ISEF* corrects for the difference in enzyme activity between recombinant systems and human liver microsomes,^[5,6] $CL_{int(rCyp)}$ ($\mu\text{L}/\text{min}/\text{pmol}$ of isoform) is hepatic intrinsic activity obtained from *in vitro* systems, cytochrome P450 (CYP) abundance (pmol CYP/mg of microsomal protein) is the amount of the enzyme per milligram of microsomal protein in the livers of the target population for which the prediction is carried out, and the fu_{mic} adjusts the data to account for non-specific binding.^[5]

All parameters for measuring $CL_{int\ Lean}$ were obtained from the default values for CYP3A4 and 2E1 probes, available from Simcyp Limited for the healthy volunteer population (data not shown).

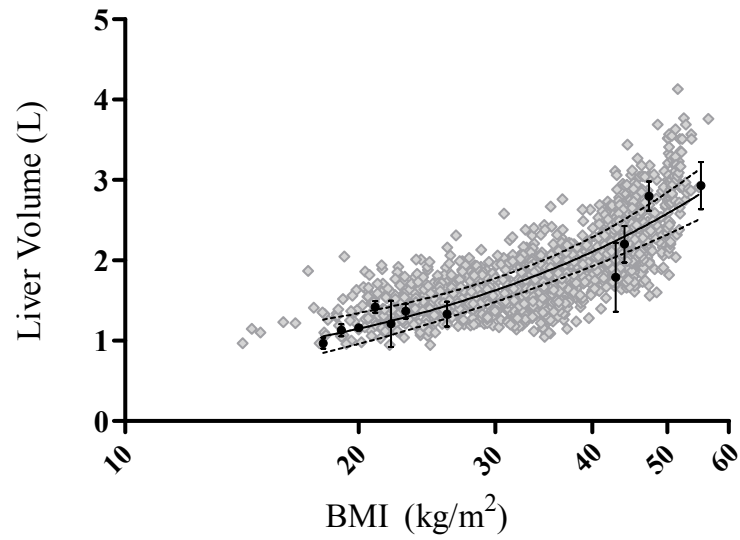


Fig. S-1. Relationship between liver volume and body mass index (BMI). The black circles are observed values, error bars \pm 90% confidence intervals (CIs). The grey diamonds (virtual subjects) are generated by simulation. The solid and dashed lines represent the means and 90% CIs, respectively, of all observations.

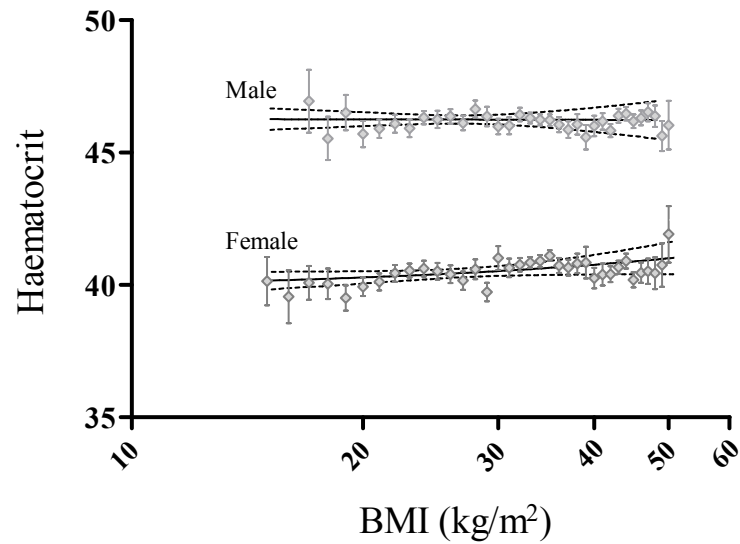


Fig. S-2. Relationship between the haematocrit and body mass index (BMI) in males and females. The grey diamonds represent mean values per BMI bin (virtual population) generated by simulation, error bars \pm 90% confidence intervals (CIs). The solid and dashed lines represent the means and 90% CIs, respectively, of all observations.

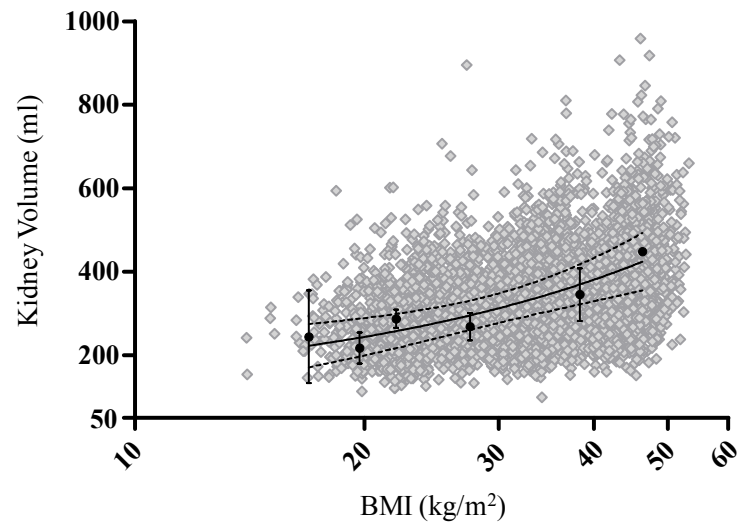


Fig. S-3. Relationship between kidney volume and body mass index (BMI). The black circles are observed values, error bars \pm 90% confidence intervals (CIs). The grey diamonds are values in virtual subjects generated by simulation. The solid and dashed lines represent the means and 90% CIs, respectively, of all observations.

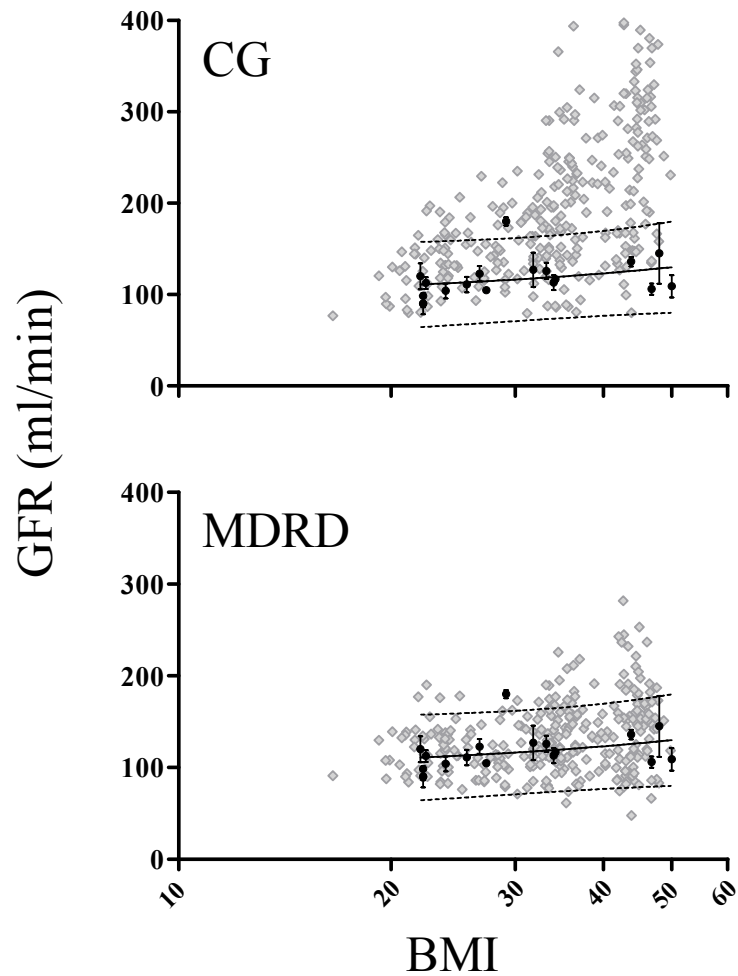


Fig. S-4. Relationship between the glomerular filtration rate (GFR) and the body mass index (BMI). The black circles are observed data, error bars \pm 90% confidence intervals (CIs). The grey diamonds are simulated virtual subjects generated in the Simcyp Simulator. The solid and dashed lines represent the means and 90% CIs, respectively, of all observations. The GFR is based on two methods: the Cockcroft-Gault (CG) method and the Modification of Diet in Renal Disease (MDRD) method. The observed values are based on 24-hour creatinine clearance (CL_{CR}).^[7-14]

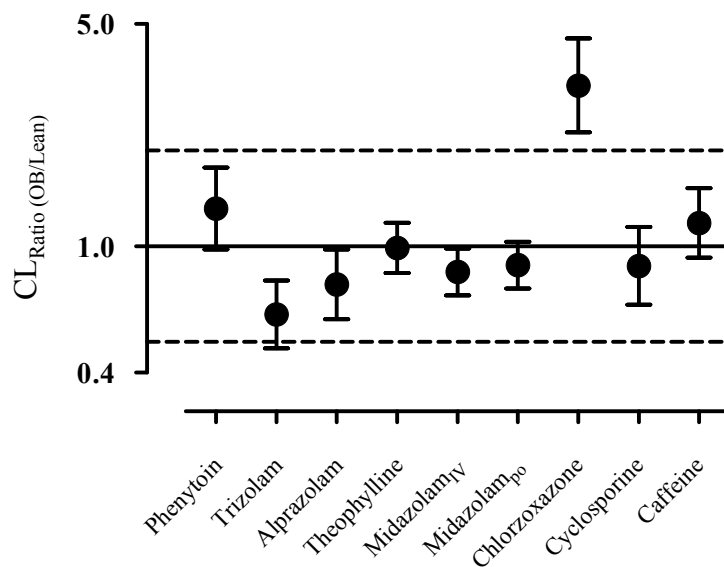


Fig. S-5. Observed clearance ratios of the reported *in vivo* clearances in obese and lean subjects [$CL_{Ratio} (OB/Lean)$] for eight different compounds: alprazolam, caffeine, chlorzoxazone, ciclosporin (cyclosporine), intravenous (IV) and oral (po) midazolam, triazolam, theophylline and phenytoin. The values are expressed as means \pm 90% confidence intervals (CIs). The solid and dashed lines represent the line of no difference and the 2-fold range, respectively.

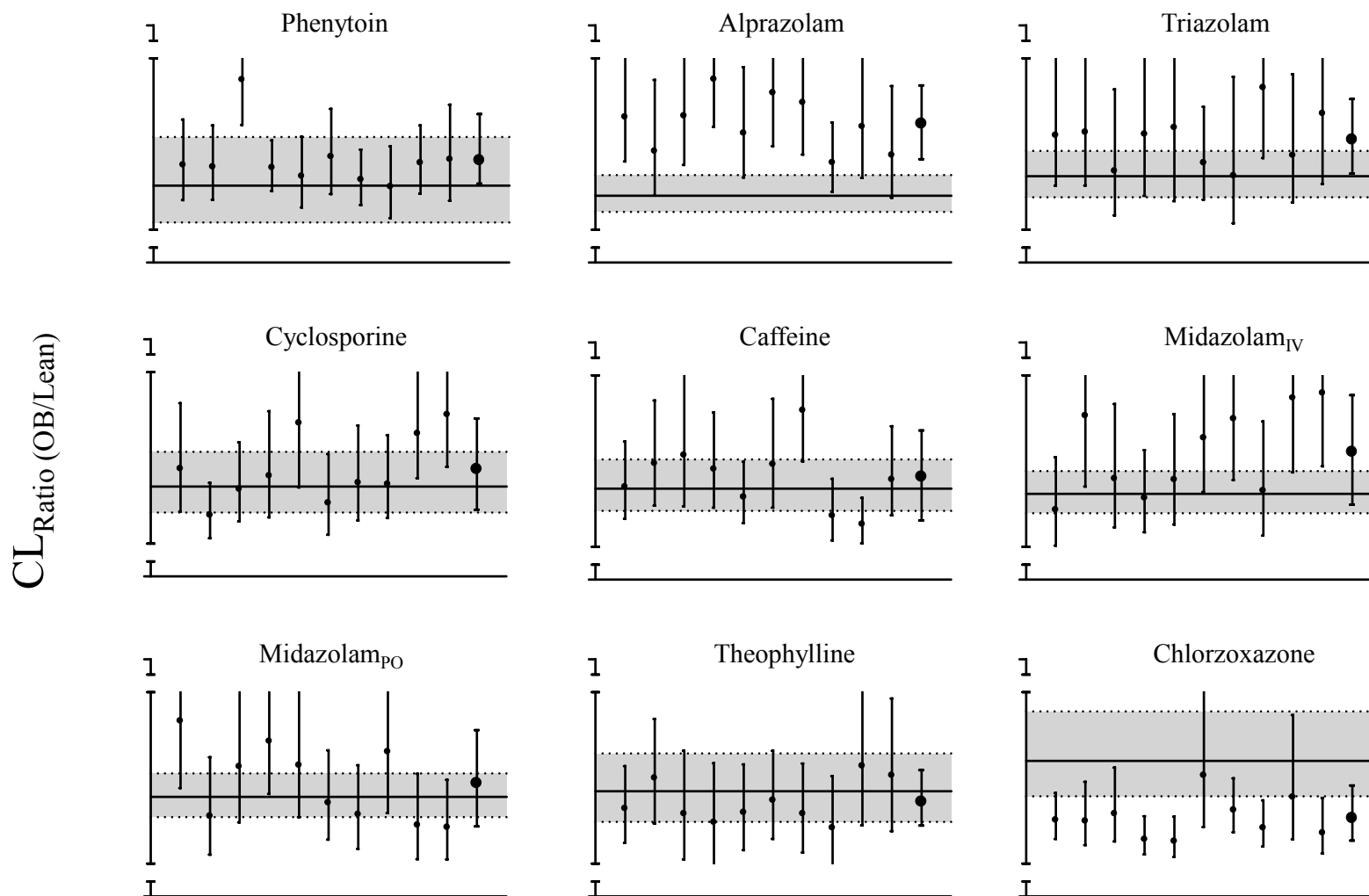


Fig. S-6. Observed vs predicted clearance ratios for obese and lean subjects [$CL_{Ratio} (OB/Lean)$] for eight different compounds: alprazolam, caffeine, chlorzoxazone, cyclosporin (cyclosporine), intravenous (IV) and oral (PO) midazolam, triazolam, theophylline and phenytoin. The small solid circles represent simulations (mimicking the clinical report with a similar size replicated 10 times), expressed as the mean \pm 90% confidence interval (CI) of the ratio. The final larger solid circles represent the overall outcome of all simulations (all 10 replicates), expressed as the mean \pm 90% CI of the ratio. The solid horizontal line represents the mean observed ratio, and the shaded area with dotted border lines represents the 90% CI of the ratio (all obtained from the literature).

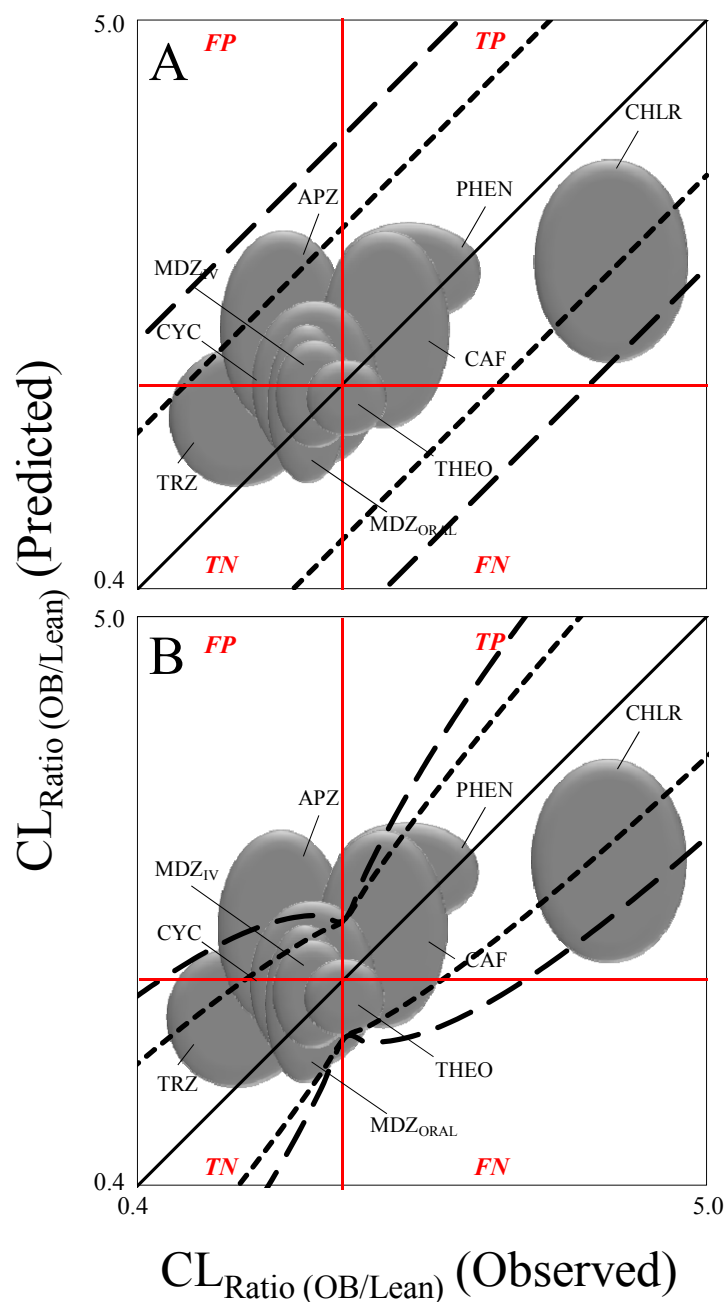


Fig. S-7. (A) Observed vs predicted clearance ratios for obese and lean subjects [$CL_{Ratio} (OB/Lean)$] for eight different compounds: alprazolam (APZ), caffeine (CAF), chlorzoxazone (CHLR), cyclosporin (cyclosporine; CYC), intravenous (IV) and oral midazolam (MDZ), triazolam (TRZ), theophylline (THEO) and phenytoin (PHEN). The ellipses delineate the 90% confidence intervals (CIs) of both the predicted and the observed values. The solid black line is the line of unity (unity between the predicted and observed values). The black short-dashed and long-dashed lines represent 2- and 3-fold deviations from unity, respectively. The red lines represent no change in the clearance ratio [$CL_{Ratio} (OB/Lean) = 1$]. (B) This graph is identical to graph (A), with the difference of an alternative method to plot the 2- and 3-fold deviations from unity, depending on the particular ratio, incorporating 30% variability.^[15] **FN** = false negative [$CL_{Ratio} (OB/Lean)$ is falsely predicted to be <1]; **FP** = false positive [$CL_{Ratio} (OB/Lean)$ is falsely predicted to be >1]; **TN** = true negative [$CL_{Ratio} (OB/Lean)$ is correctly predicted to be <1]; **TP** = true positive [$CL_{Ratio} (OB/Lean)$ is correctly predicted to be >1].

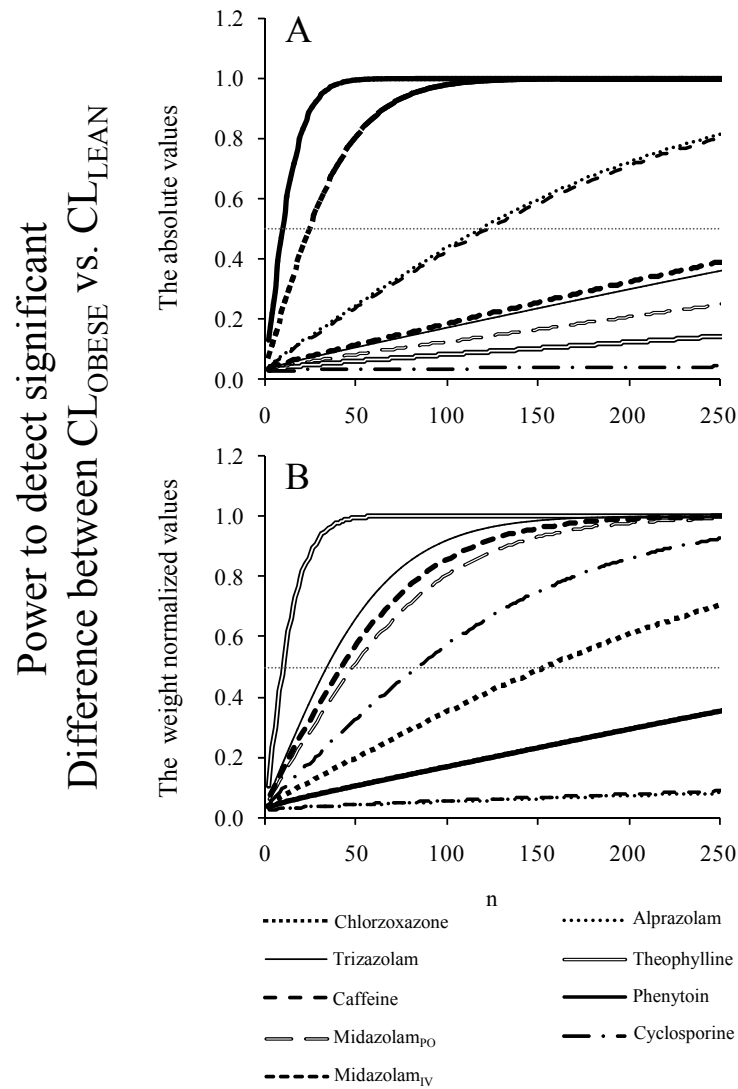


Fig. S-8. Outcomes of simulations to determine the statistical power of pharmacokinetic studies of eight different drugs to detect differences between (A) absolute clearances (CL) and (B) weight-normalized CL in obese and lean populations, under conditions of a different sample size for the study. The thin grey dotted horizontal line is the line above which 50% or more power is achieved, with a different sample size. **IV** = intravenous; **PO** = oral.

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