**Pharm-09B4** Describe the effect of obesity on pharmacokinetics and the potential clinical implications, providing relevant examples. 45%

**Definition**
WHO classification of obesity is based on BMI (kg/m$^2$)
- Normal 18.5 ~ 25
- Overweight 25 ~ 30
- Obese (class 1) 30 ~ 35
- Morbidly obese (class 2) 35 ~ 40
- Morbidly obese (class 3) ≥ 40

**Comorbidities**
- CVS – cardiac output is higher; ischaemia heart disease, cardiac failure, arrhythmias
- RESP – ↓FRC, blunted hypercapnic and hypoxic responses; OSA, obesity hypoventilation
- ENDO – diabetes
- GIT – fatty liver disease

**Effects on pharmacokinetics**

**Absorption**
Obesity → proportionally reduced FRC for TBW → ↓uptake of volatiles

Oral absorption may be slowed due to delayed gastric emptying (diabetic autonomic neuropathy)

Transdermal and subcutaneous routes → more deposition into fat compartment → less bioavailability → may need ↑dose

**Distribution**
Fat and lean mass both increased → but ↑fat > ↑lean mass
∴ $V_d$ is increased
some drug need to be dosed based on ideal body weight (IBW), some based on total body weight (TBW)

$V_d$ increases more for lipophilic drugs (e.g. barbiturates and benzodiazepines) than hydrophilic drugs (non-depolarising muscle relaxants)
→ there are exceptions to this rule (e.g. remifentanil, suxamethonium)

More accumulation in fat compartment of lipid soluble volatile agents → prolong washout time on emergence
∴ preferable to use less lipid soluble agents (e.g. desflurane) compared to agents with higher oil:gas partition coefficients (e.g. halothane)
Metabolism

Due to increase in TBW → more volatile anaesthetic required → increased toxic metabolite formation (e.g. F\textsubscript{3}, trifluoroacetyl chloride, etc) → more prone to hepatitis

Fatty liver disease may ↓ metabolic capacity of liver → ↓ metabolism of low HER drugs

Some studies found hepatic CYP2E1 upregulated in obesity → ↑ metabolism of volatiles

Elimination

↑ renal blood flow → ↑ renal clearance

Clinical implications

Dosage of some common drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Alteration in obesity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volatiles</td>
<td>May be preferable to use agents with low oil:gas partition coefficients (e.g. desflurane, sevoflurane) → quicker emergence</td>
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<tr>
<td>Propofol</td>
<td>Induction based on IBW</td>
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<td></td>
<td>Maintenance based on TBW</td>
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<tr>
<td>Thiopentone</td>
<td>Induction based on reduced TBW</td>
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<tr>
<td></td>
<td>Maintenance based on TBW</td>
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<tr>
<td>Fentanyl</td>
<td>Dosage based on TBW</td>
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<td>Midazolam</td>
<td>Bolus dose based on TBW</td>
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<tr>
<td>Rocuronium</td>
<td>Dosage based on IBW</td>
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<tr>
<td>Vecuronium</td>
<td>Dosage based on IBW</td>
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<tr>
<td>Cisatracurium</td>
<td>Dosage based on TBW (Hoffman elimination from all compartments)</td>
</tr>
<tr>
<td>Suxamethonium</td>
<td>Dosage based on TBW (up to ~ 140 mg)</td>
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Note: IBW = height – 100 (XY) or height – 105 (XX)

Depending on the entered body weight, TCI results may variable
e.g. entering total body weight into Marsh model for propofol may result in gross overdosage on induction
**Examiner’s comments** - 45% of candidates passed this question.

This was a question with which most candidates struggled, possibly because it required bringing together information from a variety of areas. Most candidates started off, appropriately, with a definition of obesity and then went on to point out that it was often associated with a range of other co-morbidities such as diabetes and gastric reflux. Then, possibly relying on clinical experience, candidates often remarked that in the obese patient FRC can be reduced, thus affecting uptake of volatile anaesthetic agents and that transdermal, intramuscular and subcutaneous drug absorption was also likely to be affected. Many candidates also mentioned that some computer based programmes for TCI could give variable results when actual (rather than lean) body weight was entered. However there were few instances where specific examples were given (as asked for in the question). Pharmacokinetic handling of some opioids are altered in the obese patient, and only a few candidates mentioned the possible pharmacokinetic advantages of poorly lipid soluble volatile agents such as desflurane over other volatile agents in the obese patient. With regard to non-depolarising muscle relaxant drugs, although their polarity generally restricts their distribution, volume of distribution may be increased in the obese, simply by virtue of increased absolute total body water. There will be differences in the distribution, and hence duration of action depending on whether dosage is calculated on the basis of ideal body weight or total body water. From a clinical context, obese patients are comprising an increasing proportion of our population, and candidates should be aware of how this condition influences drug disposition.