Pharm-02B5 Outline the possible reasons for prolongation of paralysis induced by an intravenous dose of 1 mg.kg\(^{-1}\) of suxamethonium. Briefly indicate the consequences of such a prolonged block.

**Background**

Suxamethonium is a depolarising muscle relaxant
Two acetylcholine molecules joined together via C–C bond
Rapid onset and offset of action .,. commonly used for rapid sequence induction
Typical doses:
- 1 mg/kg intravenous \(\rightarrow\) 30 ~ 60 seconds to intubation condition
- 2 mg/kg intramuscular \(\rightarrow\) 2 ~ 3 minutes to intubation condition

Normally, duration of action (return to > 95% baseline twitch height) after standard 1mg/kg iv dose is ~ 10 minutes

**Mechanism for Offset of Action**

Sux is rapidly metabolised by plasma butyrylcholinesterase (BChE)
Normally, after intravenous injection of sux \(\rightarrow\) 90% metabolised by BChE \(\rightarrow\) 10% reaches NMJ resulting in depolarising block

There is no BChE at NMJ .,. sux needs to diffuse out of NMJ in order to be metabolised by plasma BChE .,. rate of offset depends on plasma BChE activity

Prolonged block is due to ↓BChE activity, which may be due to:
(1) BChE mutations
(2) Acquired BChE deficiency
(3) BChE antagonism by drugs
(4) Other factors

**BChE mutations**

Plasma BChE activity may be reduced due to genetic variability
BChE gene is on chromosome 3 \(\rightarrow\) has four alleles:
Eu = usual; Ea = abnormal; Es = silent; Ef = fluoride resistant
This makes up 10 genotypes

Patient exhibiting aberrant allele \(\rightarrow\) prolonged block

The activity of BChE may be quantified by its response to dibucaine
Dibucaine number is the %inhibition after a standard dose of dibucaine
<table>
<thead>
<tr>
<th>Genotype</th>
<th>Incidence</th>
<th>Duration of block</th>
<th>Dibucaine #</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eu:Eu (normal)</td>
<td>96% population</td>
<td>10 min</td>
<td>80</td>
</tr>
<tr>
<td>Eu:Ea</td>
<td>~ 4% population</td>
<td>30 min</td>
<td>40 ~ 60</td>
</tr>
<tr>
<td>(Stoelting 5th ed)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ea:Ea (atypical)</td>
<td>1:3000</td>
<td>long (&gt; 2 hrs)</td>
<td>20</td>
</tr>
<tr>
<td>Eu:Es</td>
<td>1:90</td>
<td>~ 30 min</td>
<td>80</td>
</tr>
<tr>
<td>Eu:Ef</td>
<td>1:200</td>
<td>~ 30 min</td>
<td>75</td>
</tr>
<tr>
<td>Es:Es (silent)</td>
<td>1:100,000</td>
<td>very long (&gt; 3 hrs)</td>
<td>0</td>
</tr>
<tr>
<td>Ef:Ef (fluoride resistant)</td>
<td>1:154,000</td>
<td>1 ~ 2 hrs</td>
<td>70</td>
</tr>
</tbody>
</table>

**Acquired BChE deficiency**

Plasma BChE is synthesised in the liver with plasma t\(_{1/2}\) of 8 ~ 16 hrs. When [BChE] falls < 75% normal → clinically apparent ↑ duration of action of sux

Plasma BChE number may be reduced in various physiological and pathological states:

(1) old age
(2) pregnancy (high oestrogen levels approx ↓ activity by 40%, but increased Vd of sux → overall effect = minimal increase in duration of action)
(3) advanced liver disease
(4) protein losing nephropathy
(5) advanced cardiac disease
(6) malnutrition
(7) burns
(8) neoplasms
(9) treatment with plasmapheresis

Acquired BChE deficiency is unlikely to result in significantly prolonged block

**Interaction With Other Drugs**

Inhibitors of BChE can also prolong the duration of action of sux

*Non-competitive inhibitors:*
- organophosphates (insecticide, cyclophosphamide, etc): irreversible BChE antagonism
- echothiophate eye drops (anticholinesterase used in treatment of glaucoma)

*Competitive inhibitors:*
- anticholinesterase (neostigmine >> edrophonium): 30 min after neostigmine, BChE activity is halved
- ester LAs (including cocaine)
- mivacurium and pancuronium
- metoclopramide: slight prolongation of block (by 2 ~ 3 mins) normally; may cause significant prolongation of block in pts with BChE mutations

**Other:**
- oral contraceptive pill: depression of liver’s ability to synthesise BChE

**Other factors**
Myasthenic gravis → ↑ resistance to sux but more prone to phase II block; may have BChE deficiency due to plasmapheresis or on treatment with pyridostigmine

Hypothermia → ↓ BChE activity

**Consequences of Prolonged Block**

*Suxamethonium apnoea*
Prolonged block → prolonged apnoea
∴ will require sedation and mechanical ventilation until offset of action (e.g. in high dependency unit)
If unable to promptly mechanically ventilate for whatever reason → life threatening hypoxia

*Neuromuscular monitoring*
Patient with prolonged block will require NMJ monitoring for regression of block

*Family testing*
The abnormal BChE allele (Ea) has autosomal recessive pattern of inheritance
∴ Need genetic testing of family members, esp to screen for homozygotes

*Avoidance of suxamethonium*
Suxamethonium may not be an appropriate choice for RSI in patients with significant BChE polymorphism

**Examiner’s comments** - The pass rate for this question was 60%.

The main points were as follows:
- Suxamethonium 1 mg/kg is a routine dose. Phase 2 block from overdose therefore is unlikely
- Suxamethonium is metabolised by pseudo cholinesterase. Alterations in the concentration or activity of this enzyme can cause prolongation of suxamethonium action.
- A discussion of acquired alterations in concentration or activity (i.e. liver disease, pregnancy, drug interaction etc). Note that these do not often result in clinically significant prolongations in suxamethonium action.
- A discussion of the inherited alterations in concentration or activity, including the genetics, incidence, effect on duration of action, investigation with dibucaine number and other tests.
- The duration of action of suxamethonium can also be altered by other agents or disease with pharmacodynamic effects.
Consequences including the need for ventilation and sedation in a suitable environment, monitoring of neuromuscular function, possible treatments, investigation of patient and family and implications for future anaesthesia. Common mistakes included discussion of the clinical indications and other side-effects of suxamethonium and omission of information about the consequences of prolonged block. Many candidates omitted to discuss one of the three main issues (i.e. inherited, acquired or pharmacodynamic interactions).