Comparison Of Plasma Cholinesterase Levels And The Duration Of Suxamethonium Apnoea In Nigerian Adult And Paediatric Patients

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Citation

Abstract
Background
Plasma cholinesterase (butrylcholinesterase) is an enzyme of importance in the practise of anaesthesia due to its role in the metabolism of suxamethonium, and other anaesthetic related drugs. Deficiency of plasma cholinesterase has been associated with prolonged duration of suxamethonium apnoea.
The study aimed to investigate the effect of varied levels of plasma cholinesterase on the duration of suxamethonium apnoea in anaesthetised patients and compare the effects in adults and children.

Methods – One hundred healthy patients with the American Society of Anesthesiologists (ASA) physical status I and II scheduled for elective surgery under general anaesthesia requiring endotracheal intubation were studied. Pre-induction serum cholinesterase levels were estimated. Suxamethonium 2mg/kg was administered after induction of anaesthesia. After the administration of thiopentone, a Fisher and Paykel peripheral nerve stimulator (PNS) Model NS272 was applied to the ulnar nerve to determine onset and the duration of neuromuscular blockade.

Results – Sixty-four adults and 36 children were studied. The mean cholinesterase level was 6573.29 ±2128.29 (ranged from 1227-14536) IU/L. The cholinesterase activity was similar in both children (7044.86 ±2448.81) IU/L and adults (6308.03 ±1894.19) IU/L p = 0.97. The mean onset time of suxamethonium was 37.83 ±9.49 seconds. This onset was similar in children and adults (p = 0.374). There was poor correlation between cholinesterase level and onset time (r = 0.031, p = 0.760).
The mean clinical apnoea time was 5.88 ±2.00 minutes. Significant difference existed between adults (6.25 ±1.85 minutes) and children (5.22 ±2.06 minutes) p = 0.012. The mean PNS apnoea time was 8.17 ±3.14 minutes which was significantly shorter in children (6.73 ±3.59 minutes) than in adults (8.97 ±2.52 minutes) p<0.001. There was moderate inverse and significant correlation between cholinesterase level and PNS apnoea time (r = -0.423, p<0.001), as well as clinical apnoea time (r = -0.461, p<0.001). There was a highly positive and significant correlation between clinical and PNS apnoea time (r = 0.876, p<0.001). The mean recovery time was 7.44 ±2.49 minutes which was significantly shorter in children (6.73 ±2.92 minutes) than in adults (7.86 ±2.13 minutes) p = 0.028. There was a moderate inverse and significant correlation between cholinesterase level and recovery time (r = -0.456, p<0.001).
Conclusion – The duration of suxamethonium apnoea increased with low levels of plasma cholinesterase. Children exhibited significantly shorter apnoea and recovery times compared to adults.

INTRODUCTION
The neuromuscular blocking action of suxamethonium (succinylcholine) was first recognised in 1949 and 3 years later its short duration of action was ascribed to its rapid enzymatic destruction by plasma cholinesterase. Plasma cholinesterase (BChE) is a tetrameric glycoprotein with a molecular mass of 342 kDa. In mammals BChE is synthesised in the liver and is distributed in the intestinal mucosa, blood plasma and the white matter of the central nervous system. BChE is involved in the hydolysis of the short-acting muscle relaxants suxamethonium and mivacurium and the metabolism of drugs such as diacetyl morphine, aspirin, methylprednisolone, and several ester local anaesthetics agents. The rate of destruction of suxamethonium is decreased in the presence of low enzymatic activity. Patients deficient in BChE will exhibit a prolonged reaction to suxamethonium, and apnoea can persist for a period varying from minutes to hours. BChE deficiency is secondary to different genetic alleles which can be differentiated by the action of inhibitors such as dibucaine.
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There is an inverse relationship between BChE level and the duration of suxamethonium apnoea. The blood volume and extracellular fluid (ECF) volume are significantly greater in children than in adults, on a weight basis. Therefore, infants require about twice as much suxamethonium to produce 50% neuromuscular blockade compared to adults when administered this drug on a weight basis (mg/kg). However, the larger ECF in children may account for the shorter duration of action of suxamethonium in paediatric patients in comparison to adults.

Prolonged suxamethonium apnoea may arise from inherited or acquired abnormalities of BChE, and necessitates continued ventilation until muscle activity is restored. It was found that 96% of the general population had the “usual” phenotype and were dibucaine sensitive with inhibition of about 80%, dubbed the dibucaine number (DN) of 80%. About 4% of the population had an “intermediate” phenotype with a DN of about 62%, and an “atypical” phenotype of 1 in 4000 with a DN of about 20%. In most surgical populations 6-7% of patients have an abnormal cholinesterase activity and about 65-75% of prolonged suxamethonium apnoea is due to abnormalities of cholinesterase enzyme.

Acquired deficiency, which occurs in liver diseases, sepsis, burns, malignancy and following drug therapy result in a wide variability in the onset and duration of paralysis caused by suxamethonium. Cardiopulmonary bypass induces a decrease in cholinesterase levels which can persist for 7 days following surgery. BChE deficiency is most common in people of European descent and is rare in Asians. However, there is paucity of literature on the incidence in Africans. Since suxamethonium is readily available and frequently used in this population, there is a need to determine the mean cholinesterase levels and compare the effect of cholinesterase levels on the duration of suxamethonium apnoea in Nigerian adults and children.

PATIENTS AND METHODS

After approval of the institutional human investigation committee of the Lagos University Teaching Hospital, written informed consent was obtained from all patients and parents of paediatric patients. One hundred healthy patients with the American Society of Anesthesiologists (ASA) physical status I and II aged between 1-65 years scheduled for elective surgery under general anaesthesia requiring endotracheal intubation were recruited for the study. The sample size calculation was based on the Yamane formula:

\[ n = \frac{N}{1 + N \left( \frac{P}{100} \right)} \]

Patients with clinical conditions associated with low cholinesterase levels were exempted from the study. Others exclusions were patients receiving drugs known to affect BChE activity, those requiring repeat doses of suxamethonium, and those with known hypersensitivity to suxamethonium. Adult patients with a body mass index (BMI) < 19.9 kg/m² or > 29.9 kg/m², paediatric patients with BMI < 5percentile or > 85percentile for age and sex were also excluded from the study.

ANAESTHETIC PROCEDURE

Routine investigation was conducted and all patients were fasted according to standard guidelines. Adult patients received diazepam 10 mg orally at night and at 6.00 AM on the day of surgery, while paediatric patients received promethazine 0.5 mg/kg orally on the morning of surgery for anxiolysis. Paediatric patients had EMLA patch applied 1 hour before intravenous access was secured. Standard monitoring using Datex Ohmeda Cardiocap 7100 was instituted before induction and continued throughout the anaesthetic. Intravenous access was secured and Ringers lactate infusion started in all patients.

All patients were anaesthetised according to standard guidelines using sodium thiopentone 5 mg/kg and suxamethonium 2 mg/kg. The airway was secured with an appropriate sized cuff endotracheal tube. During the periods of respiratory depression and apnoea, ventilation was assisted with 100% oxygen in isoflurane 1.0-2.5% as needed. Anaesthesia was maintained with isoflurane 1.0-2.5% in 100% oxygen and IV pancuronium 0.1 mg/kg. Thereafter, all patients received controlled ventilation with an appropriate breathing system for age.

Anaesthesia was continued according to the discretion of the attending anaesthetist and extubation carried out after administration of reversal agents. Postoperatively adequate oxygenation and analgesia was ensured in the recovery room until discharged to the ward.

A Fisher and Paykel peripheral nerve stimulator (PNS) Model NS272 (Fisher & Paykel Healthcare, Auckland, New Zealand) was applied to the ulnar nerve, following loss of consciousness. The negative (black) lead was connected to the distal electrode over the palmar aspect of the wrist and the positive (red) lead to the proximal electrode 1-2 cm
proximal to the first, parallel to the flexor carpi ulnaris tendon. Using a low current of 10-20 mA, the train of four (TOF) button was activated. TOF stimulus was given every 20 seconds until the response to TOF stimulation of the ulnar nerve reappeared as evidenced by adduction of the thumb. 

**BLOOD SAMPLE ANALYSIS**

Venous blood (5 ml) was collected into a lithium heparin bottle kept at -4°C before induction of anaesthesia for cholinesterase estimation. BChE activity was assayed by using an automated spectrophotometry method with benzoylthiocholine. Butryl cholinesterase hydrolyses butrylthiocholine to yield thiocholine and butyrate. The reaction between thiocholine and 5, 5'-dithio-bis (2 nitrobenzoic acid) yields 2-nitro-5-mercaptobenzoate; this was measured at 405 nm using Hitachi 902 Automatic analyzer (Roche Diagnostic). Normal cholinesterase values in children and in men and women over 41 years was taken as 5320-12920 IU/L. Values for non-pregnant women 18-41 years who were not taking oral contraceptives were taken as 3650-9120 IU/L.

**STATISTICAL ANALYSIS**

Demographic and clinical data collected included age, sex, weight, height, BMI, PCV and duration of suxamethonium apnoea.

Statistical analysis was performed with the Statistical Package for the Social Sciences (SPSS®) for Windows computer software version 17 programme. Numerical data was presented as mean ±SD, while categorical data was expressed as frequencies. The Student t test was used to determine difference between means. The Pearson correlation (r) was used to determine relationship between cholinesterase and the duration of suxamethonium apnoea. The correlation (r) = 0.00 to 0.19 indicate poor correlation, r = 0.20 to 0.39 indicate minimal correlation, r = 0.40 to 0.69 indicate moderate correlation, r = 0.70 to 0.89 indicate high correlation and r = 0.90 to 1.0 indicates very high correlation.

**DEFINITIONS**

Suxamethonium apnoea - cessation in breathing following the administration of suxamethonium.

Onset time - time from the administration of suxamethonium to the time of cessation of spontaneous respiration.

Clinical apnoea time - time from cessation of respiration to the first evidence of return of spontaneous respiration.

PNS apnoea time - time from cessation of respiration until the first response to TOF stimulation of the ulnar nerve as evidenced by adduction of the thumb.

Recovery time - time from administration of suxamethonium to return of normal respiration.

Prolonged suxamethonium apnoea - the absence of return of spontaneous ventilation for at least 10 minutes, or the time from cessation of respiration until reappearance of response to TOF stimulation of the ulnar nerve as evidenced by adduction of the thumb of more than 15 minutes.

**RESULTS**

The sample population consisted of 64 adults and 36 paediatric patients with mean age of 25.21 ±17.34 (1- 65) years; the mean age in children was 5.76 ±3.8 (1-16) years, and the mean age in adults was 36.16 ±11.25 (18-65) years.

The mean cholinesterase level was 6573.29 ±2128.29 IU/L. This was similar in children (7044.86 ±2448.81 IU/L) and adults (6308.03 ±1894.19 IU/L). p = 0.97 (Table I).

**Figure 1**

Table I. The Comparison of Mean Cholinesterase Levels and the Duration of Action of Suxamethonium in Nigerian Adults and children

Data represents the mean ±SD, range and p values of onset, apnoea and recovery time.

** indicate that the difference between the means was significant at p<0.05.

Normal cholinesterase level constituted 81% (51% adults
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and 30% children p = 0.417), high cholinesterase level 3% (2% adults and 1% children p = 0.223) and low cholinesterase level 16% (11% adults and 5% children of the patient population p = 0.328). The mean onset time of suxamethonium was 37.83 ± 9.49 seconds. This was similar in children and adults p = 0.374 (Table I). There was poor correlation between cholinesterase level and onset time r = 0.031, p = 0.760 (Table II).

Figure 2
Table II. The Relationship between Cholinesterase level and Suxamethonium Onset, Apnoea and Recovery time

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Data represents the correlation (r) between cholinesterase and the onset, apnoea and recovery time. ** indicates the correlation was significant at p < 0.05. * indicates poor correlation and + indicates moderate correlation.

The mean clinical apnoea time was 5.88 ± 2.00 minutes. This was significantly shorter in children than in adults (p = 0.012). There was moderate inverse and significant correlation between cholinesterase level and clinical apnoea time r = -0.461, p < 0.001 (Table II and Figure 1).

Figure 3
Figure 1. The Relationship between Cholinesterase Level and Clinical Apnoea Time

Scattered graph showing moderate inverse and significant correlation between cholinesterase and clinical apnoea time.

The mean PNS apnoea time was 8.17 ± 3.14 minutes. This was significantly shorter in children than in adults’ p < 0.001 (Table I). There was moderate inverse and significant correlation between cholinesterase level and PNS apnoea time r = -0.423, p < 0.001 (Table II and Figure 2).

Figure 4
Figure 2. The Relationship between Cholinesterase Level and PNS Apnoea Time

Scattered graph showing moderate inverse and significant correlation between cholinesterase and PNS apnoea time.

There was a highly positive and significant correlation between clinical and PNS apnoea time r = 0.876, p < 0.001 (Figure 3). Prolonged apnoea had an incidence of 7% (5% adults and 2% children) with cholinesterase levels between 1227-4206 IU/L.
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**Figure 5**
Figure 3. The Relationship between Clinical and PNS Apnoea Time

Scattered graph showing very high positive and significant correlation between clinical and PNS apnoea time.

The mean recovery time was 7.44 ±2.49 minutes. This was significantly shorter in children than in adults (p = 0.028). There was a significant moderate inverse correlation between cholinesterase level and recovery time $r = -0.456$, $p <0.001$ (Table II and Figure 4).

**Figure 6**
Figure 4. The Relationship between Cholinesterase Level and Recovery Time

Scattered graph showing moderate inverse and significant correlation between cholinesterase and recovery time.

**DISCUSSION**
This study demonstrated insignificant difference in cholinesterase levels in a sample of Nigerian adults and children. However, there was significant difference between clinical apnoea time as well as PNS apnoea time in children and adults with both being significantly shorter in children. Mirakhur et al.\(^\text{13}\) also reported the same observation when suxamethonium was administered on the basis of body weight. It has been documented that the shorter duration of action of suxamethonium in children may be due to their relatively larger ECF volume and smaller muscle mass in comparison to adults.\(^\text{4}\) Suxamethonium is rapidly distributed throughout the extracellular fluid because of its relatively small molecular size. In children, on a weight basis, both blood volume and extracellular fluid (ECF) volume are significantly greater than those of adults. Therefore, when suxamethonium is administered on a weight basis (mg/kg), infants require about twice as much suxamethonium to produce 50% neuromuscular blockade as do adults. There is a constant relationship between ECF and surface area throughout life (6 to 8 L/m\(^2\)). This accounts for the good correlation between suxamethonium dose (mg/m\(^2\)) and response throughout life. The duration of action of suxamethonium in adults is dose-related and follows linear first-order elimination kinetics over a dose range of 0.5-4mg/kg.\(^\text{4}\)

Mirakhur et al.\(^\text{13}\) using 1 mg/kg of suxamethonium, observed a shorter duration of apnoea in both children and adults (2.73 and 5.03 minutes) than our study when 2 mg/kg was used (5.22 and 6.25 minutes). This observation is of clinical importance especially as it relates to the treatment of laryngospasm in children when a small dose of suxamethonium 0.25 mg/kg is used, taking advantage of its short duration of action. The prospect of spontaneous recovery of muscle power within 3 minutes after suxamethonium administration can be extremely useful should tracheal intubation prove difficult especially in paediatric patients with reduced tolerance to apnoea. This group of patients can quickly resume spontaneous respiration if there is difficulty in securing the airway. El-Orbany et al.\(^\text{14}\) observed that 0.5-0.6 mg/kg IV dose of suxamethonium is as effective as 1.0 mg/kg with regard to intubating conditions, but with a more rapid recovery from neuromuscular blockade and apnoea time. Therefore suxamethonium because of its rapid onset and good intubating condition at low dose is still irreplaceable in obstetric anaesthesia.
We observed that there was significant moderate inverse correlation between cholinesterase level and apnoea time in the total population. This was reflected by a longer apnoea time with decreasing levels of cholinesterase. Similar observations were noted in children and adults. This differs from observation by Mirakhur et al.\textsuperscript{13} in which the correlation between cholinesterase level and the duration of suxamethonium apnoea was minimal in children ($r = -0.28$) and poor in adults ($r = -0.02$). This difference may have been due to the fact that only 40 out of 89 children recruited for their study were monitored with a PNS, as well as the fact that a lower dose of suxamethonium was used (1mg/kg). The authors however commented that the disparity in sample population in terms of age might have accounted for this observation since they had a greater proportion of children in their study.\textsuperscript{15}

The mean recovery time in children [6.73 ±2.9 minutes (3.30-17.00)] was significantly shorter ($p = 0.028$) than in adults [7.86 ±2.13 minutes (4.15-13.55)] . Similar observations were reported by other workers.\textsuperscript{13,15} The recovery from suxamethonium depends on the redistribution of the drug from the endplate and metabolism by cholinesterase. The redistribution of suxamethonium from a relatively small muscle mass into a relatively large ECF volume appears to rapidly terminate suxamethonium’s neuromuscular blocking effects.\textsuperscript{4,15} This results in the shorter recovery time documented in children and was collaborated by our study. A shorter recovery time using a lower dose (0.5 and 1 mg/kg) of suxamethonium was demonstrated by Cook et al.\textsuperscript{12} (3.0 ±1.0 and 4.8 ±1.1 minutes).

The recovery from neuromuscular blockade in adults using PNS was delayed by 1.82 minutes when compared to return of spontaneous respiration. This may be because the muscles of the diaphragm recover faster than the muscles of the extremities. Return of spontaneous respiration occurs as soon as diaphragmatic muscles begin to recover from neuromuscular blockade. The PNS however monitors the adductor pollicis which is the last muscle to recover from neuromuscular blockade. We have also demonstrated that the recovery from neuromuscular blockade using PNS was delayed by 36.72 seconds in children when compared to return of spontaneous respiration. This was however longer than that reported in the literature (10-15 seconds apart).\textsuperscript{4,15} In contrast, Mirakhur et al.\textsuperscript{13} reported that both respiration and neuromuscular transmission at the periphery recovered together in children. They suggested that this might be due to a quicker overall recovery in paediatric patients and to a wide age group used in their study.

The recovery of spontaneous respiration was longer in our study when compared with others.\textsuperscript{4,15} This may be because we monitored the return of spontaneous respiration via movement of the reservoir bag which depends on the volume of expired air (tidal volume). This technique may not be as precise as a mass spectrophotometer which allows earlier recognition of spontaneous respiratory effort with lesser volume of air.\textsuperscript{15} Similarly the PNS apnoea time in our study was longer than that reported by other scholars.\textsuperscript{4,13,17} The differences could be due to the use of visual observation of contraction of the adductor pollicis brevis , which is less sensitive and accurate than mechanography used in the other studies.\textsuperscript{4,13,15} This further reinforces the fact that there is no substitute for objective neuromuscular monitoring.\textsuperscript{16}

**CONCLUSION**

We have demonstrated that amongst a sample of Nigerian patients, cholinesterase levels did correlate inversely with clinical apnoea time, PNS apnoea time and recovery time in both adults and children. There was a highly strong positive correlation between clinical and PNS apnoea time. Children however had significantly shorter clinical and PNS apnoea time as well as recovery time.

**References**

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