Onset of neuromuscular block after tourniquet inflation: comparison of suxamethonium with vecuronium

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Summary
To determine the influence of circulatory factors on onset of neuromuscular block, we have measured twitch height in an arm with a tourniquet inflated during onset and compared this with data from a control arm in 20 patients under fentanyl–thiopentone–nitrous oxide–isoflurane anaesthesia. Patients were allocated randomly to receive either vecuronium 0.1 mg kg⁻¹ (n = 10) or suxamethonium 1 mg kg⁻¹ (n = 10). The EMG response of the first dorsal interosseous to single twitch stimulation of the ulnar nerve every 10 s was recorded in both arms. When neuromuscular block was 20 % (i.e. twitch height was 80 % of control), the tourniquet was inflated to a pressure of 250 mm Hg. It was deflated 5 min later. In the vecuronium group, the rate of onset did not differ in both arms and mean maximum block was 95 (sd 4 % in the tourniquet arm, which was not different from 99 (2 % in the perfused arm. In the suxamethonium group, the presence of a tourniquet decreased the rate of onset by 66 %. Maximum block was only 74 (20 % in the tourniquet arm compared with 97 (5 % in the perfused arm (P < 0.05). The difference in maximum neuromuscular block between arms was 4 (3 % in the vecuronium group and 22 (17 % in the suxamethonium group (P < 0.01). We conclude that during onset, neuromuscular block continued to increase in spite of interruption of blood flow, and this increase was greater with vecuronium than with suxamethonium. These results suggest that redistribution of free molecules of drug from extra-junctional to junctional areas is one of the factors governing onset of action of neuromuscular blocking drugs. (Br. J. Anaesth. 1995; 75: 436–440)

Key words

Onset of neuromuscular block is determined by the rate at which blocker molecules reach the neuromuscular junction and this in turn is thought to depend to a large extent on circulatory factors, which influence the interval between injection of the drug in a peripheral vein and its arrival at the neuromuscular junction [1–3]. Cardiac output has been recognized as a factor modifying onset time of depolarizing and non-depolarizing agents [4, 5]. In dogs, onset time was found to be inversely related to muscle blood flow [6]. In humans, the role of muscle blood flow is likely to explain the faster onset of respiratory muscles compared with peripheral muscles [7].

If muscle blood flow were the only determinant of onset time, interruption of circulation to muscle would be expected to affect intensity of paralysis, and block should remain constant in a muscle with absent blood supply. The application of a tourniquet to interrupt blood flow has been used during recovery after systemic injection of atracurium [8]. In spite of the lack of circulation in the arm, recovery was found to continue, although more slowly in the isolated than in the perfused arm. The finding was explained by Hoffman degradation and ester hydrolysis in the non-perfused arm. Presumably, the findings could have been different for a drug which did not depend on the same type of metabolism. The effect of a tourniquet during onset has not been evaluated in humans.

The purpose of this study was to measure onset of neuromuscular block in an arm with a tourniquet inflated during onset, compared with a normally perfused arm. To determine if the results depended on the mechanism of action of the blocker used, we studied two groups of patients, one receiving vecuronium and the other suxamethonium.

Patients and methods
We studied 20 adult patients undergoing general, vascular or gynaecological surgery. The study was approved by the Ethics Committee of the institution and informed written consent was obtained from each patient. They were between 20 and 65 yr of age and within 25 % of normal body weight. All patients were devoid of renal, hepatic or neuromuscular disease and were not receiving any drug known or suspected to interfere with neuromuscular transmission.
On arrival in the operating room, ECG, pulse oximetry and arterial pressure were monitored non-invasively. A tourniquet cuff was placed around the arm opposite to the extremity where the venous cannula was sited. Surface electrodes were applied near the ulnar nerve at both wrists and over the first dorsal interosseous. The electromyographic response was recorded with two Datex NMT 221 monitors (Helsinki, Finland). After induction of anaesthesia, supramaximal single twitch stimulation (40–70 mA) was applied to both ulnar nerves at the wrists every 10 s. To maintain skin temperature within the normal range, both arms were wrapped with blankets.

Anaesthesia was induced with fentanyl 1.5–3 \( \mu \text{g kg}^{-1} \) and thiopentone 4–6 mg kg\(^{-1} \), and maintained with 50–60 % nitrous oxide in oxygen. Additional doses of fentanyl or thiopentone were given as needed. After a stable EMG response was obtained, patients received either vecuronium 0.1 mg kg\(^{-1} \) (\( n = 10 \)) or suxamethonium 1 mg kg\(^{-1} \) (\( n = 10 \)) by random allocation over 20 s. When neuromuscular block was 20 % (i.e. twitch height was 80 % of control), the tourniquet was inflated to a pressure of 250 mm Hg. This pressure was reached within 5 s. The tourniquet was deflated 5 min later. Tracheal intubation was performed when maximum neuromuscular block was attained. Isoflurane 1 % inspired was added after tourniquet deflation. The lungs were ventilated to maintain end-tidal carbon dioxide partial pressure within the range 4.8–5.3 kPa. The EMG response was recorded until twitch recovery was at least 25 % in both arms. At that point, anaesthetic management was left to the anaesthetist’s discretion.

The following measurements were made: (1) time between beginning of injection of the blocker and tourniquet inflation; (2) maximum block in each arm; (3) time to maximum block, defined as the interval from beginning of injection until the first of three consecutive equal twitches; (4) maximum rate of onset, defined as the largest decrease in twitch height over 20 s per unit time; and (5) duration of action, defined as time from injection to 25 % recovery.

Data are presented as mean (sd). Comparisons between arms in the same patient were made using the Wilcoxon test. The difference in maximum block between arms was compared between the vecuronium and suxamethonium groups using the Mann–Whitney test. Twitch height was compared between arms using ANOVA for repeated measures. \( P < 0.05 \) was considered to indicate statistically significant differences.

Results

There were no differences between groups in age, sex, ASA status, height or weight (table 1).

Tourniquet inflation was performed at the same level of twitch depression in the two groups (table 2). In spite of tourniquet inflation, neuromuscular block continued to increase in the isolated arm (figs 1, 2). In the vecuronium group, maximum rate of onset and maximum block did not differ between the tourniquet arm and the perfused arm (table 2). Nevertheless, the time to obtain maximum block was increased in the tourniquet arm. Application of the tourniquet had a different effect in the suxamethonium group. Neuromuscular block continued to progress in the tourniquet arm, but the increase was less than in the vecuronium group (fig. 2, table 2). The maximum rate of onset in the tourniquet arm was 33 % that in the perfused arm and maximal block was only 74 (20 % compared with 97 (5 %) \( P < 0.05 \) vs the perfused arm). As in the vecuronium group, the time to obtain maximal block was greater in the tourniquet arm (table 2).

In the suxamethonium group, offset began to occur while the tourniquet was inflated (fig. 2). After deflation, recovery continued without any difference in rate. In the vecuronium group, no recovery was observed before deflation of the tourniquet and, when circulation was re-established, either the block had already reached 100 % before deflation and no change was observed, or the block increased to 100 % in all of the remaining patients.

Recovery was different in the two groups. With suxamethonium, twitch depression in the tourniquet arm did not reach 75 % in four patients, and therefore time to 25 % recovery could not be determined. The time between injection of the blocker and 25 % twitch recovery was markedly decreased in the tourniquet arm for the six remaining patients (6.4 (1.9) min \( \text{vs} \) 10.0 (1.9) min; \( P < 0.05 \)). In the vecuronium group, the effect of the tourniquet on recovery was different and mean recovery time did not differ between arms (56 (19) min in the tourniquet arm, 61 (26) min in the perfused arm).

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<th>Table 1</th>
<th>Patient characteristics (mean (so or range) or number)</th>
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<td>Vecuronium</td>
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<td></td>
<td>(( n = 10 ))</td>
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<tr>
<td>Age (yr)</td>
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<td>Sex (M/F)</td>
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<tr>
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<th>Table 2</th>
<th>Onset characteristics after vecuronium and suxamethonium (mean (sd)). Significant differences (( P &lt; 0.05 )): *between groups; † between arms in the same group</th>
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<td>Vecuronium</td>
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<tr>
<td></td>
<td>Twitch height at tourniquet inflation (% )</td>
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<td>21 (13)</td>
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<td>Maximal block (% )</td>
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<td>Maximum rate of onset (% s(^{-1} ))</td>
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\( P < 0.05 \) by random allocation over 20 s. When circulation was re-established, either the block had already reached 100 % before deflation and no change was observed, or the block increased to 100 % in all of the remaining patients.

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Discussion

We found that interruption of arterial blood flow by means of a tourniquet did not stop onset of block. In this respect, vecuronium and suxamethonium behaved differently. Inflation of a tourniquet had less effect on the onset of vecuronium block.

The tourniquet has been used to study recovery and draw inferences on mode of action of neuromuscular blockers [9, 10]. In these studies, the drug was injected in the isolated forearm. In another study a tourniquet was inflated to assess recovery after systemic injection of atracurium [8]. The present study differed from these investigations in the role of the tourniquet. Administration of the blocker was systemic, not in the isolated arm, and inflation was during onset, not during recovery.

The doses of blockers were chosen to achieve adequate neuromuscular block for intubation, and were approximately equipotent. Maximum block in the perfused arm was 100% in all patients except for one in the suxamethonium group. Onset time was 2.0 (0.9) min in the suxamethonium group and 4.2 (1.1) min in the vecuronium group, comparable with the findings of others [11–14]. The onset time in the suxamethonium group may seem large. However, onset time has been reported to be greater when the block is measured with electromyographic rather than mechanical response [15]. Moreover, onset time was shown to be greater when the stimulation applied was single twitch rather than train-of-four [11]. Also, it was shown recently that short periods of control stimulation were associated with longer onset times [16]: this was the case in our study, control stimulation lasting approximately 1 min. Finally, suxamethonium was given slowly (over 20 s) to decrease the chances of failing to inflate the tourniquet at 20% block. A slow rate of injection of the blocker is known to increase onset time [17]. All of these factors contributed to increase the onset time.

The tourniquet was inflated at 20% block (i.e. twitch height was 80% of control) when it was obvious that block had started. This was a compromise between inflating too early when no paralysis was detected and no evidence of drug action was present, and inflating too late when full paralysis might occur during tourniquet inflation or shortly after. This was a concern, especially with suxamethonium. We chose not to inflate the tourniquet at a fixed time after injection, because the amount of drug arriving at the junction is likely to be different for both agents, which have different kinetics.

The time required for tourniquet inflation was less than 5 s. One presumes that immediately after inflation, there was still some blood flow from the arterial to the venous side of the circulation, at least until pressure equilibration. It is difficult to determine the exact duration of this post-tourniquet intravascular transfer, but it was probably a small effect which lasted only a few seconds because of the small quantity of blood in the arterial tree. Thus, if these new molecules continued to reach the muscle over 5–10 s, the tourniquet did not exert a complete effect before 10–15 s. Even if the data from the first 15 s are ignored, the results do not differ. In any event, the delay between tourniquet inflation and interruption of circulation was the same in both groups and cannot explain the difference between the two drugs tested.

Ischaemia of the arm, although very short, might be suspected to induce local pH modifications or hypoxia, which in turn would modify the action of blockers. This issue has already been studied. After 20 min of tourniquet inflation in patients receiving atracurium, peripheral venous pH remained within
Onset of block of suxamethonium and vecuronium after tourniquet inflation

the physiological range (i.e. 7.34–7.42), and there was no difference between the two arms [8]. In the same study, the EMG response was not affected by tourniquet inflation for 20 min in the absence of neuromuscular blockers. In the present study, the tourniquet was inflated for only 5 min. Thus hypoxia and acidosis were unlikely to play a role here.

The different findings between drugs cannot be explained by the unique elimination pathway of suxamethonium. As the isolated arm contained a certain amount of plasma, metabolism of suxamethonium was presumed to occur. Thus recovery began in the isolated arm of the patients in the suxamethonium group (fig. 2). However, the recovery rate during tourniquet inflation was less (6 % per unit) than in the perfused arm (16 % per min). Thus if metabolism of suxamethonium were important in the isolated arm, neuromuscular block should have been greater in the isolated arm. The opposite was observed, indicating that other factors, such as perfusion, played a more important role. Furthermore, if the difference in elimination process explained part of or all the differences observed between suxamethonium and vecuronium, it would not explain why neuromuscular block continued to increase in the vecuronium group.

Recovery was expected to be shorter in the tourniquet arm, because it received fewer blocker molecules, being isolated at a time when plasma concentrations were still high. This was observed in the suxamethonium group. However, the results in the vecuronium group were variable, leading to absence of difference between mean recovery times. This was probably related to inter-individual variations, to the relatively small sample of this study and to the short period of tourniquet inflation (5 min) compared with the prolonged effect of the drug (more than 50 min).

There is a possible explanation for these results. If paralysis continues to progress, in spite of interruption of blood flow and thus with no new blocker molecules coming from the bloodstream, new blocker molecules must arrive at the junction from extra-junctional areas. Diffusion of molecules from the extracellular fluid surrounding the junction is the most likely mechanism. According to animal studies, 75 % of receptors have to be occupied before neuromuscular block is apparent with non-depolarizing agents, and approximately 90 % of receptors have to be bound before complete neuromuscular block [18]. In addition, the density of acetylcholine receptors is extremely high at the end-plate. Consequently, most of the drug molecules at the junction are bound. For example, it has been estimated that for tubocurarine, only one molecule is free for every 300 bound [19]. Although some of the molecules are presumably bound to non-receptor proteins in the non-junctional areas, a larger concentration of free molecules is likely to be present. However, to reach junctional receptors, drug molecules have to enter the narrow synaptic cleft. Thus, diffusion is slow and difficult. This concept has been termed “buffered diffusion” [19]. After arrival in the synaptic cleft, non-depolarizing agents bind receptors rapidly [20]. Consequently, between the junction and the surrounding areas there should be a high concentration gradient promoting transfer of drug to the synaptic cleft. After interruption of blood flow, there probably is a redistribution from these surrounding areas to the junction because the high gradient of concentration continues to promote this transfer. This phenomenon could explain the increase in paralysis after interruption of blood flow to the muscle. Suxamethonium would probably not have to bind a large number of receptors to be effective [21]. Also, this drug has a low affinity for receptors. There should be a higher concentration of free molecules within the synaptic cleft. Thus the concentration gradient of free molecules between the junction and the surrounding areas would be less important, limiting the extent of diffusion.

Whatever the explanation, the consequences of our findings may not be limited to the artificial situation of tourniquet inflation. Onset of action of neuromuscular blockers may be regarded as the sum of two components: (1) circulation to muscle and (2) non-circulatory factors. This last effect has a time course of a few minutes, and for vecuronium appears to be quantitatively important. This may explain why some non-depolarizing agents have a long onset time. In spite of a short half-life as a result of its fast degradation by plasma cholinesterase, mivacurium has a much longer onset time than suxamethonium [22]. Rocuronium, another new non-depolarizing agent, has a relatively short onset time [23]: this is probably because of its low potency, which implies that more free molecules are present at the neuromuscular junction, thus there is a smaller concentration gradient between junctional and extra-junctional areas. Onset of action of blockers occurs in two steps: the time for molecules to pass from the injection site to muscle, and the time for molecules to redistribute from non-junctional areas to the neuromuscular junction. We suggest that the relative importance of these steps differs between different blockers. For vecuronium, diffusion seems to be important as complete interruption of perfusion did not alter significantly the time course of neuromuscular block. This phenomenon, which may be a consequence of “buffered diffusion”, and appears to be more important for non-depolarizing agents, may place intrinsic limits on the speed of onset of action of non-depolarizing agents.

References