ARTERY-TO-MUSCLE ONSET TIME FOR NEUROMUSCULAR BLOCKING DRUGS

B. MINSAAS AND J. STOVNER

SUMMARY

Artery-to-muscle (A-M) onset time for five neuromuscular blocking agents was studied in 50 female patients under light endotracheal anaesthesia. Circulation to the right arm was occluded by a tourniquet and released 1 min after the injection i.v. into the left arm of a myoneural blocking drug. Muscle twitches were recorded in the right hand after stimulation of the ulnar nerve (1 Hz). After releasing the tourniquet the response to single twitches continued without decrease in height (latent onset time). The onset of gradual decreases in twitch height was noted, and the time until 90% depression of twitch height was measured (manifest onset time). The mean latent onset times were: pancuronium 31.9 s, tubocurarine 21 s, alcuronium 17.2 s, fazadinium 8.6 s and suxamethonium 4.8 s. Mean A-M latent onset time was significantly different for each drug (P < 0.005). Manifest A-M onset times were related to A-M latent onset times except for tubocurarine which exhibited a slower decline in twitch height. A-M latent onset time correlated well with the values for intravenous onset times reported in the literature.

The present study was undertaken to investigate the suitability of a method for the evaluation of the speed of onset of neuromuscular blocking drugs. Previously, such studies have been undertaken by measuring the time from the i.v. injection of the drug to the depression of the muscle twitch or the adequacy of tracheal intubation conditions. However, venous-arterial circulation time is variable (Harrison and Junius, 1972) and any evaluation of intubation conditions will always be subjective. The present method, proposed originally by Holst-Larsen (1976), eliminates inaccuracies as a result of the site and speed of injection and the venous-arterial circulation time. The neuromuscular blockers studied were pancuronium, tubocurarine, alcuronium, fazadinium and suxamethonium administered in doses used commonly for tracheal intubation.

PATIENTS AND METHODS

Fifty female patients were included in an open comparative study. Their ages varied between 28 and 50 yr and their weights from 49 to 75 kg. They were divided into five groups, one for each drug. The mean age and mean weight in each group and the mean drug doses are shown in table I. All patients were in good general health and about to undergo gynaecological operations for non-malignant conditions. Patients with cardiac, neurological or skeletal diseases were excluded. The patients were premedicated with pethidine 50–75 mg and atropine 0.6 mg. An indwelling catheter was inserted to a vein, usually on the back of the left hand, and connected to a continuous infusion of a Ringer acetate solution. Anaesthesia was induced with diazepam 5–10 mg i.v. followed by thiopentone 200–450 mg (mean dose 260 mg).

Between 2 and 3 min after the injection of thiopentone and with the eyelash reflex abolished, a tourniquet on the right arm was inflated beyond 200 mm Hg and the appropriate dose of neuromuscular blocking drug injected. Neuromuscular blocking drugs were administered via the left hand, randomly in the doses shown in table I. The ulnar nerve of the right arm was stimulated with a Block-Aid nerve stimulator (Burroughs Wellcome & Co., 1976), using skin surface electrodes. Maximum

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FIG. 1. Recording strips for the five drugs arranged according to the duration of A-M latent onset time. This period is marked L.

TABLE II. Mean artery-to-muscle (A-M) onset times for the five drugs with SEM and SD. P values for significance of differences between drugs are shown (t test). PANC = pancuronium; TUB = tubocurarine; ALC = alcuronium; FAZ = fazadinium; SUX = suxamethonium

<table>
<thead>
<tr>
<th></th>
<th>PANC</th>
<th>TUB</th>
<th>ALC</th>
<th>FAZ</th>
<th>SUX</th>
</tr>
</thead>
<tbody>
<tr>
<td>LATENT A-M onset time (s)</td>
<td>31.9</td>
<td>21.0</td>
<td>17.2</td>
<td>8.6</td>
<td>4.8</td>
</tr>
<tr>
<td>Mean</td>
<td>±2.87</td>
<td>±1.26</td>
<td>±0.62</td>
<td>±0.38</td>
<td>±0.24</td>
</tr>
<tr>
<td>SEM</td>
<td>±4.11</td>
<td>±4.00</td>
<td>±1.95</td>
<td>±1.20</td>
<td>±0.75</td>
</tr>
<tr>
<td>P</td>
<td>&lt;0.0005</td>
<td>&lt;0.005</td>
<td>&lt;0.0005</td>
<td>&lt;0.0005</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>MANIFEST A-M onset time (s)</td>
<td>32.8</td>
<td>41.1</td>
<td>25.0</td>
<td>11.7</td>
<td>5.8</td>
</tr>
<tr>
<td>Mean</td>
<td>±1.79</td>
<td>±3.60</td>
<td>±2.84</td>
<td>±0.81</td>
<td>±0.56</td>
</tr>
<tr>
<td>SEM</td>
<td>±5.65</td>
<td>±11.37</td>
<td>±8.99</td>
<td>±2.56</td>
<td>±1.77</td>
</tr>
<tr>
<td>P</td>
<td>&lt;0.025</td>
<td>&lt;0.005</td>
<td>&lt;0.0005</td>
<td>&lt;0.0005</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>TOTAL A-M onset time (s)</td>
<td>64.7</td>
<td>61.1</td>
<td>42.2</td>
<td>20.3</td>
<td>10.6</td>
</tr>
<tr>
<td>Mean</td>
<td>±2.72</td>
<td>±3.60</td>
<td>±2.62</td>
<td>±1.08</td>
<td>±0.46</td>
</tr>
<tr>
<td>SEM</td>
<td>±8.61</td>
<td>±11.40</td>
<td>±8.30</td>
<td>±3.41</td>
<td>±1.02</td>
</tr>
<tr>
<td>P</td>
<td>n.s.</td>
<td>&lt;0.0005</td>
<td>&lt;0.0025</td>
<td>&lt;0.0005</td>
<td></td>
</tr>
</tbody>
</table>

RESULTS

Following the sudden release of the cuff pressure (time noted) single twitches continued for a period without alteration in twitch height. This was followed by a clearly defined change showing a gradual decrease in twitch height (fig. 1). The time from the release of the cuff pressure until the first change in twitch height was called the A-M latent onset time (line L in fig. 1). The period from the first evidence of any decrease in twitch height until 90% depression of twitch height was called the A-M manifest onset time. The A-M latent onset time plus the A-M manifest onset time equals the A-M total onset time (table II).

It can be seen that there were significant differences between the drugs studied with regard to A-M latent onset times and A-M manifest onset times.
although it will be observed that, whereas pancuronium had a longer A-M latent onset time than tubocurarine, it had a shorter A-M manifest onset time (table II). The opposite was true for tubocurarine which had a comparatively rapid A-M latent onset time and a slow and variable A-M manifest onset time. Thus, there was no significant difference in the A-M total onset time between these two drugs.

**DISCUSSION**

Since, in clinical practice, neuromuscular blocking agents are injected i.v., the time from the i.v. injection of the drug to full neuromuscular blockade is of importance. This period is made up, to a large extent, by the circulation time, which involves possible delays in the right heart, the lungs, the left heart and the vessels. Harrison and Junius (1972) showed that vein-to-artery circulation time was more than doubled in patients with circulatory failure. This variable was eliminated in our study by measuring the time from the release of the tourniquet to the various alterations in twitch height. By this method we found an A-M latent onset time unique for each drug, a feature which has not been described previously following the administration i.v. of alcuronium, tubocurarine or pancuronium (Harrison, 1972; Hey, 1973; Blackburn and Morgan, 1978).

One minute was chosen as the most appropriate period of occlusion of the circulation to the one arm after the injection i.v. of the drug; this was considered to be the minimum time necessary to allow even distribution of the injected drug in the circulation (Kalow, 1959). Thus on release of the tourniquet, "bolus" effects would be avoided.

The i.v. onset time should equal the A-M latent onset time plus the 30 s found as an average vein-to-artery circulation time by Harrison and Junius (1972). Blackburn and Morgan (1978) have determined, in patients with normal circulations, the times from the i.v. administration of a drug until the production of a 25% depression of twitch height with four of the neuromuscular blockers we have used. With these four drugs our A-M latent onset times plus 30 s came within 10% of the i.v. onset times found by Blackburn and Morgan (1978). This shows that artery-to-muscle latent onset time is a valid indicator of the speed of onset of a neuromuscular blocker.

A-M latent onset time must represent the time for the relaxant to (a) gain access to the receptors; (b) occupy the receptors sufficiently for blockade to occur. So far we can only speculate on the role played by each of these processes. For suxamethonium, however, we must presume that the value (4.8 s) found for this drug represented access time.
only, because the drug is principally an agonist acting instantaneously with the receptors. The 4.8 s found in our study is extremely close to the 4 s onset time found for acetylcholine itself after injection to the brachial artery in humans (Grob, Johns and Harvey, 1956).

If the artery-to-muscle latent onset time represents mainly access to the receptors by diffusion, certain physicochemical factors should be of importance. No correlation, however, could be found between latent onset time and the square root of the molecular weight, although this last factor is thought to determine speed of diffusion along a concentration gradient. Information on protein binding is available only for suxamethonium, pancuronium and tubocurarine (Cohen, Brewer and Smith, 1967; Dal Santo, 1968; Thompson, 1976). Of these drugs the last two are protein bound and have the longest onset times while the first is free and has the shortest onset time.

Receptor occupancy by non-depolarizing drugs was shown by Waud and Waud (1975) to have a safety margin of 75–90% for the transmission of single twitches. Paton (1961), in his kinetic theory, proposed that the speed of action of neuromuscular blockers reflected their rate of receptor occupancy. In 1967, however, Waud applied neuromuscular blocking drugs directly to the receptors in animals and found that they acted as if access was the only rate-limiting factor. In a later review (Waud, 1968), however, he admits that the rate of combination with the receptor provides a satisfactory explanation for the speed of onset of drugs. This explains why the speed of onset is inversely related to potency. This postulate agrees only partly with our results. Pancuronium, the most potent myoneural blocking drug on the market, has the longest A-M latent onset time. Alcuronium, on the other hand, is more potent than tubocurarine but has a shorter A-M latent onset time and does not fit into the postulate.

In 1973 Feldman showed that depolarizers, such as suxamethonium, lost their effect on the human hand muscles in 1–2 min compared with 15–20 min for the non-depolarizers. It is possible that the non-depolarizers have a stronger affinity for the receptors which manifests itself as a slow onset and a slow dissociation rate whereas the opposite is the case for depolarizers.

REFERENCES


PERIODE D'INVASION ARTERE-MUSCLE DE CINQ AGENTS DE BLOCAGE NEUROMUSCULAIRE

RESUME
La période d'invasion artère-muscle (A–M) de cinq agents de blocage neuromusculaire a été étudiée sur cinquante femmes subissant une intervention sous anesthésie endotrachéale légère. La circulation du bras droit a été arrêtée par un tourniquet, puis relâchée une minute après l'injection intraveineuse d'un agent de blocage musculo-nerveux dans le bras gauche. Des contractions du muscle ont été enregistrées dans la main droite après stimulation du nerf ulnaire (1 Hz). Après avoir relâché le tourniquet, la réaction aux contractions isolées s'est poursuivie sans diminution de l'intensité (départ de réaction latente). On a noté le début des diminutions graduelles de l'intensité des contractions et on a chronométré le temps nécessaire pour atteindre 90% de la diminution de l'intensité des contractions (départ manifeste de la réaction). Les temps latents moyens nécessaires au départ de la réaction ont été les suivants: pancuronium 31,9 s, tubocurarine 21 s., alcuronium 17,2 s., fazadinium 8,6 s et suxamethonium 4,8 s. Le temps latent moyen nécessaire au départ de la réaction A–M a été nettement différent pour chaque agent (P < 0,005). Les
temps de manifestation nécessaires au départ de la réaction A-M ont été reliés aux temps latents moyens nécessaires au départ de la réaction A-M sauf pour la tubocurarine, qui a accusé une baisse plus lente dans l'intensité de la contraction. Les temps latents nécessaires au départ de la réaction A-M ont été en bonne corrélation avec les valeurs des périodes d'invasion intraveineuse signalées dans la documentation.

**ZUSAMMENFASSUNG**

Die Arterie-bis-Muskel-Wirkungseintrittszeit bei fünf neuromuskulären Blockierungsdrogen wurde bei 50 Patientinnen unter leichter endotrachealer Anästhesie studiert. Die Zirkulation zum rechten Arm wurde durch einen Knebel unterbunden, der 1 min nach der Injektion intravenös in den linken Arm einer myoneuralen Blockierungsdroge gelöst wurde. Die Muskelzuckungen in der rechten Hand wurden nach Stimulierung (1 Hz) des Ulnarnervs aufgezeichnet. Nach Lösung des Knebels ging die Reaktion auf Einzelzuckungen ohne Verminderung an Höhe (latente Eintrittszeit) weiter. Der Eintritt gradueller Verminderungen der Zuckungshöhe wurde festgestellt, und die Dauer bis zur 90%igen Unterdrückung der Zuckungshöhe (offensichtliche Eintrittszeit) weiter. Der Eintritt gradueller Verminderungen der Zuckungshöhe wurde festgestellt, und die Dauer bis zur 90%igen Unterdrückung der Zuckungshöhe (offensichtliche Eintrittszeit) weiter. Die mittleren latenten Eintrittszeiten waren: Pancuronium 31,9 s, Tubocurarin 21 s, Alcuronium 17,2 s, Fazadinium 8,6 s und Suxamethonium 4,8 s. Die mittlere Arterie-bis-Muskel-Wirkungseintrittszeit (latent) war für jede Droge deutlich verschieden ($P<0,005$). Die offensichtlichen A-M-Wirkungseintrittszeiten waren auf die latente A-M-Wirkungseintrittszeit abgestimmt, ausser bei Tubocurarin, das einen langsameren Abstieg der Zuckhöhe zeigte. Die latente A-M-Wirkungseintrittszeit war gut auf die Werte für intravenöse Eintrittszeiten abgestimmt, wie sie in der Literatur zu finden sind.

**SUMMARY**

Se llevó a cabo un estudio del principio del efecto arteria-a-músculo (AM) de cinco agentes bloqueadores neuromusculares en 50 pacientes femininas bajo anestesia endotraqueal ligera. Se observó la iniciación en el brazo derecho mediante un torquínete y se soltó 1 min después de la inyección i.v. en el brazo izquierdo de una substancia bloqueadora mioneural. Se registraron los críAMPamientos espasmódicos musculares en la mano derecha después de estimular al nervio ulnar (1 Hz). Una vez soltado el torquínete, la respuesta a críAMPamientos únicos siguió sin disminuir en su altura (tiempo de iniciación latente). Se observó la iniciación de disminuciones progresivas de la altura del críAMPamiento y se midió el tiempo hasta que la altura hubiera bajado en un 90% (tiempo de iniciación manifestado). Los tiempos medios de iniciación latente fueron: pancuronio (31,9 s), tubocurarina (21 s), alcuronio (17,2 s), fazadinio (8,6 s) et suxametonio 4,8 s). El tiempo de iniciación latente promedio (AM) difirió significativamente para cada droga ($P<0,005$). Los tiempos de iniciación manifestados (AM) se relacionaban a los tiempos de iniciación latente (AM), salvo en el caso de la tubocurarina que demostró un descenso más lento de la altura del críAMPamiento. El tiempo de iniciación latente (AM) se correlacionaba bien con los valores de los tiempos de iniciación intravenosos indicados en la folletería.