THE EFFECT OF GENERAL ANAESTHETICS ON THE RESPONSE TO TETANIC STIMULUS IN MAN

BY

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SUMMARY

The effects of cyclopropane, diethyl ether, methoxyflurane and Ethrane anaesthesia on the response of the adductor pollicis muscle to tetanic stimulus were examined in eleven healthy patients undergoing elective surgery. During a control period of nitrous oxide anaesthesia, tetanus was well maintained when elicited by a stimulus frequency of 30 and 300 Hz. Following inhalation of a more potent agent, tetanus remained well maintained at 30 Hz, but fade was consistently observed during a stimulus of 300 Hz. These findings indicate that inhalational anaesthetic agents alter neuromuscular function, and that this should be taken into consideration when evaluating a neuromuscular block produced by tubocurarine.

The use of deep general anaesthesia has been and still is a useful way of providing surgical relaxation. It is generally stated that such relaxation does not represent a "curariform" effect of the drug, but results from inhibition of spinal reflex activity by the anaesthetic (Ngai, Hanks and Farhie, 1965; de Jong, Hershey and Wagman, 1967). However, there is also evidence that the inhalation agents have a direct effect on neuromuscular transmission. In vitro studies indicate that halothane and diethyl ether reduce the sensitivity of frog post-junctional membrane to acetylcholine, and thereby block neuromuscular transmission (Karis, Gissen and Nastuk, 1966; Gissen, Karis and Nastuk, 1966). When muscle twitch tension is evoked by indirect stimulation, halothane, methoxyflurane, and diethyl ether increase the blockade produced by tubocurarine in man (Katz, 1966; Katz and Gissen, 1967; Heisterkamp, Skovsted and Cohen, 1969). Finally, administration of very high concentrations of diethyl ether to man results in a measurable decrease in indirectly stimulated twitch tension (Katz, 1966).

This study was designed to detect any effects on neuromuscular transmission which might be manifested during clinical anaesthesia without neuromuscular blocking agents. The measure chosen was the response to varying frequencies of tetanic stimulus which Gissen and Katz (1969) have demonstrated to be a sensitive index of non-depolarizing neuromuscular block.

METHODS

Eleven healthy female patients, free of neuromuscular disease, were studied during surgery (table I). Informed consent for performance of the investigation was obtained from all participants. Anaesthesia was induced with a sleep dose of thiopentone, and initially maintained with nitrous oxide-oxygen. Neuromuscular blocking drugs were never administered. The arm was placed in a specially constructed armboard* and the contraction of the adductor pollicis muscle monitored with a force transducer (Grass FT-10). The output of the transducer was recorded with a Grass Model 5 polygraph and pen writer. Insulated needle electrodes (18 gauge Jelco IV catheters) were placed subcutaneously and the ulnar nerve stimulated supramaximally. Stimuli were delivered from a square-wave generator (American Electronics Laboratory No. 104-A) at a rate of 0.3 Hz with single pulses of 0.15 m.sec duration. In every patient, tetanic stimuli of 30 and 300 Hz were applied alternately, each for 5 seconds. This was repeated in the opposite

* Made by the Cardiovascular Clinical Research Center of the Hospital of the University of Pennsylvania.
<table>
<thead>
<tr>
<th>Age (yr.)</th>
<th>Height (cm)</th>
<th>Weight (kg)</th>
<th>Operation</th>
<th>Anaesthetic</th>
<th>Premedication (mg)</th>
<th>Respiration</th>
</tr>
</thead>
<tbody>
<tr>
<td>44</td>
<td>165</td>
<td>59</td>
<td>Total abdominal hysterectomy</td>
<td>Cyclopropane</td>
<td>Quinalbarbitone 100</td>
<td>Controlled</td>
</tr>
<tr>
<td>47</td>
<td>168</td>
<td>69</td>
<td>Dilatation and curettage</td>
<td>Cyclopropane</td>
<td>Quinalbarbitone 100</td>
<td>Spontaneous</td>
</tr>
<tr>
<td>28</td>
<td>152</td>
<td>59</td>
<td>Exploratory laparotomy</td>
<td>Cyclopropane-diethyl ether</td>
<td>Quinalbarbitone 100</td>
<td>Controlled</td>
</tr>
<tr>
<td>46</td>
<td>160</td>
<td>61</td>
<td>Vaginal hysterectomy</td>
<td>Diethyl ether</td>
<td>Quinalbarbitone 100</td>
<td>Spontaneous</td>
</tr>
<tr>
<td>45</td>
<td>165</td>
<td>59</td>
<td>Vaginal hysterectomy</td>
<td>Ethrane-nitrous oxide</td>
<td>Innovar 1.3 ml.</td>
<td>Spontaneous</td>
</tr>
<tr>
<td>40</td>
<td>183</td>
<td>79</td>
<td>Right inguinal herniorrhaphy</td>
<td>Ethrane-nitrous oxide</td>
<td>Pentobarbitone 100</td>
<td>Spontaneous</td>
</tr>
<tr>
<td>27</td>
<td>157</td>
<td>56</td>
<td>Ovarian cystectomy</td>
<td>Ethrane-nitrous oxide</td>
<td>Atropine 0.6</td>
<td>Spontaneous</td>
</tr>
<tr>
<td>32</td>
<td>160</td>
<td>53</td>
<td>Myomectomy</td>
<td>Methoxyflurane-nitrous oxide</td>
<td>Atropine 0.5</td>
<td>Controlled</td>
</tr>
<tr>
<td>37</td>
<td>175</td>
<td>73</td>
<td>Vaginal hysterectomy</td>
<td>Methoxyflurane-nitrous oxide</td>
<td>Quinalbarbitone 100</td>
<td>Controlled</td>
</tr>
<tr>
<td>24</td>
<td>168</td>
<td>63</td>
<td>Dilatation and curettage</td>
<td>Methoxyflurane-nitrous oxide</td>
<td>Atropine 0.4</td>
<td>Spontaneous</td>
</tr>
<tr>
<td>22</td>
<td>165</td>
<td>63</td>
<td>Dilatation and curettage</td>
<td>Methoxyflurane-nitrous oxide</td>
<td>Quinalbarbitone 100</td>
<td>Spontaneous</td>
</tr>
</tbody>
</table>

order at least 1 minute later. After suitable recordings had been obtained, anaesthesia was continued with the agents listed in table I. Respiration was controlled or spontaneous as deemed appropriate to the clinical situation. After a suitable depth of anaesthesia had been established, the response of the adductor pollicis muscle to twitch and tetanus was again measured.

RESULTS

Representative tracings of data obtained during this investigation are shown in figures 1 and 2. During anaesthesia with nitrous oxide-oxygen (control), tetanus was well maintained when stimuli of 30 and 300 Hz were applied. During the administration of cyclopropane, methoxyflurane, Ethrane, or diethyl ether, twitch tension was not decreased and tetanus was sustained when elicited by a stimulus of 30 Hz. In each of the patients examined, definite fade was evident when a 300 Hz tetanus was applied. Upon emergence from anaesthesia, tetanus was again well maintained at both 30 and 300 Hz.

DISCUSSION

In this investigation, the depth of anaesthesia chosen was one which would provide adequate surgical conditions without the use of neuromuscular blocking drugs. In some patients this dose permitted adequate spontaneous respiration, while in others controlled respiration was required (table I). Alveolar concentration was never constant, and knowledge of the anaesthetic concentration at the neuromuscular junction was uncertain. Thus, it was not possible to establish a relationship between anaesthetic depth and degree of fade. In this study, a comparison of different anaesthetics at equivalent doses was not feasible for the same reasons. Such information would be meaningful only in a steady state when anaesthetic concentration was known. However, it is clear that concentrations of anaesthesia used in ordinary clinical practice are capable of producing fade when a stimulus of 300 Hz is applied.

A previous study (Heisterkamp, Skovsted and Cohen, 1969) demonstrated that indirectly stimulated twitch tension was more profoundly affected by tubocurarine when methoxyflurane was inhaled than when anaesthesia was provided by nitrous oxide. Since these findings were unaffected by axillary block, it was suggested that a central effect of methoxyflurane (i.e., alteration of spinal reflex activity) was not implicated. It
Effect of Ethrane on mechanical response to tetanic stimulus. Fade is not observed during stimulus of 30 and 300 Hz during administration of nitrous oxide, and during stimulus of 30 Hz when Ethrane is inhaled. Profound fade is evident in response to a 300 Hz stimulus during the inhalation of Ethrane.

Tracings from two patients. Neither shows fade when stimulated at 300 Hz during the control period. Both are unable to sustain tetanus during a stimulus of 300 Hz during the inhalation of either methoxyflurane or cyclopropane; no fade is observed when the stimulus was 30 Hz.
was concluded that enhancement by methoxyflurane of the action of tubocurarine represented an interaction of tubocurarine and the anaesthetic at the neuromuscular junction.

Data obtained in the present study demonstrate a direct effect of the potent inhalation anaesthetics on the mechanical response of muscle to tetanic stimulus. The mechanisms responsible for failure to sustain tension during a tetanus of 300 Hz are not immediately apparent. The anaesthetics may block neuromuscular transmission by reducing the sensitivity of the post-junctional membrane to acetylcholine as has been suggested by Karis, Gissen and Nastuk (1966) and Gissen, Karis and Nastuk (1966). Both neuromuscular blocking drugs (Epstein, Jackson and Wyte, 1969) and inhalation agents (Epstein and Jackson, 1969) are known to affect the neuromuscular refractory period. The increase in the neuromuscular refractory period produced by inhalation agents could explain these findings. In addition, changes in muscular contractility (Sabawala and Dillon, 1958) could result in the observed response.

Although the mechanisms responsible for these peripheral effects of anaesthetics remain to be elucidated, one can enumerate the factors responsible for the muscular relaxation which accompanies surgical anaesthesia. Relaxation results mainly from suppression of spinal reflex activity which produces a diminished neural output from the central nervous system (Ngai, Hanks and Farhie, 1965; de Jong, Hershey and Wagman, 1967). In addition, the peripheral action of the anaesthetics acts to decrease the effectiveness of neuromuscular function should a train of stimuli be delivered from the central nervous system. The latter may well explain the enhanced neuromuscular blockade produced by tubocurarine in the presence of a potent inhalation agent.

Finally, knowledge of the effect of inhalation agents on indirectly stimulated muscle contraction is important in monitoring during clinical anaesthesia. If high frequency tetanus is used as a gauge for judging the adequacy of reversal of the effect of tubocurarine (Gissen and Katz, 1969) one may be misled if anaesthesia was still being maintained with a potent inhalation agent. In such a case, fade during high frequency tetanus might represent the effect of the inhalational agent rather than that of tubocurarine.
DIE WIRKUNG VON MITTELN ZUR ALLGEMEINNARKOSE HINSICHTLICH DER REAKTION AUF TETANISCHE REIZE BEIM MENSCHEN

ZUSAMMENFASSUNG
Es wurde die Wirkung von Cyclopropan-, Dihyethyläther-, Methoxyfluoran- und Ethran-Narkose hinsichtlich der Reaktion des Adductorpollinis Muskels auf tetanische Reizung bei elf gesunden Patienten untersucht, die sich einer Operation unterzogen. Während einer Kontrollperiode mit Stickoxydulnarkose liess sich durch eine Reizfrequenz von 30 und 300 Hz Tetanus leicht erhalten. Nach der Inhalation eines stärkeren Mittels wurde Tetanus leicht bei 30 Hz erhalten, bei einem Reiz von 300 Hz jedoch wurde regelmäßig ein Nachlassen beobachtet. Diese Beobachtungen zeigen, dass Inhalationsnarkotika die neuromuskuläre Funktion verändern, und dass dies in Betracht gezogen werden sollte, wenn ein durch Tubocurarin hervorgerufener neuromuskulärer Block bewertet werden soll.

CORRESPONDENCE

SEVERE RESPIRATORY DEPRESSION AFTER PENTAZOCINE ADMINISTRATION: TWO CASE REPORTS

Sir,—Pentazocine with its strong analgesic action, freedom from severe undesirable side effects and lack of addiction potential, has made it a promising substitute for the opium alkaloids.

The extensive literature on the use of this drug persuaded us to use it without restraint.

In the last six months we have observed only mild side actions such as nausea, dizziness, tremor and sedation. Recently, however, we have observed two cases of severe respiratory depression. Since we have not encountered in the literature a report of a similar complication we thought that we should draw attention to this potential serious side effect of this drug.

CASE NO. 1. A 70-year-old male suffering from severe rheumatoid arthritis was admitted for operation on the right knee joint. The patient had been on cortisone therapy for the last 10 years. This treatment had been discontinued 3 months prior to his admission. On examination the only abnormal findings were mild emphysema and evidence of mild myocardial ischaemia on the e.c.g.

The patient was premedicated at 10 a.m. with pethidine hydrochloride 50 mg and atropine sulphate 0.5 mg. Anaesthesia was induced at 10.30 a.m. with thiopentone 250 mg (5 per cent); intubation of the trachea was performed following succinylcholine 70 mg and anaesthesia was maintained with nitrous oxide and oxygen and methoxyfluran. Operation lasted 90 minutes. At the time of incision an additional 100 mg of 5 per cent thiopentone was administered and another 30 mg of pethidine was given halfway through the operation. Throughout the operation the condition of the patient remained satisfactory. The estimated loss of blood was about 400 ml which was replaced with fresh whole blood.

At the end of the procedure 100 mg of solu-cortef was given intravenously. The patient was taken to his room at 12.45 p.m. in excellent condition.

At 3.30 p.m. I was summoned to the hospital by the house officer because the patient had lapsed into coma. On arrival I found the patient unconscious and not responding to painful stimuli. He was mildly cyanotic. His extremities were cold and clammy and he was sweating profusely. The pulse rate was 150 b.p.m. with a systolic blood pressure of 80 mm Hg. We were impressed by the shallow and slow rate of respiration, i.e. 10 per min. An e.c.g. was taken which revealed no changes when compared with the one taken preoperatively.

The patient was immediately ventilated with a face mask and 100 per cent oxygen. He was also digitalized and given another 100 mg solu-cortef intravenously.

After about 1 hour of artificial ventilation his condition started to improve, the pulse rate diminished and the blood pressure rose. The cyanosis disappeared and the skin gradually became dry again. A short time later the patient regained consciousness and his breathing improved so that only nasally administered oxygen was required.

Within 3 hours from the initiation of the therapy the patient had completely recovered. The rest of his postoperative course was uneventful.

After questioning the nurses and the house officer it was discovered that the patient had received pentazocine 30 mg at about 2.15 p.m. at the instruction of the orthopaedic surgeon. Within 30 minutes of the injection the state described above made its appearance.

CASE NO. 2. A 70-year-old woman suffering from an inoperable tumour of the spine, presumably a metastasis from a cancer of the uterus which was removed 2 years previously, complained of an intractable pain alleviated only by injections of morphine or pethidine.

The surgeon who treated this patient advised the use of pentazocine in order to avoid addiction to morphia. The first injection of pentazocine 30 mg was given at 5 p.m. on October 20, 1968. Half an hour later the patient became comatose, her blood pressure fell to 70 mm Hg, her respiration became shallow, and the extremities were cyanotic.

We visited the patient at 6 p.m. and started anti-shock treatment and oxygen administration with a face mask. Her general condition improved gradually and she regained consciousness at 1 a.m. the next day.

We believe that in both cases the shock was caused by respiratory depression.

Following the injection of pentazocine both patients developed characteristically shallow and slow respiration. This was followed by hypoxia and carbon dioxide retention which resulted in respiratory acidosis and coma.

The only mild side effects of pentazocine described in the literature are hypnosis, changes of mood, nervousness, restlessness, headache, indifference, and paresis. Severe respiratory depression has not been reported as far as we know, but a reduction in respiratory frequency is mentioned as occurring in 1 per cent of cases and is considered of no consequence, being supplemented by an increase in the tidal volume.

Nevertheless these two clinical observations suggest that a stronger action of pentazocine on the respiratory centre is possible in elderly people. These two patients may have exhibited an idiosyncrasy to this drug which produced a generalized system reaction. We believe that this drug should be given with caution in elderly or debilitated patients and that further investigation on the action of pentazocine is indicated.

S. C. RIGAS, Athens