CLINICAL STUDIES OF INDUCTION AGENTS
XI: THE INFLUENCE OF SOME INTRAVENOUS ANAESTHETICS ON THE
RESPIRATORY EFFECTS AND SEQUELAE OF SUXAMETHONIUM

BY
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SUMMARY
Suxamethonium 25 mg was injected intravenously after induction of anaesthesia with
equipotent doses of thiopentone, thialbarbitone, methohexitone, FBA.1420 and
G.29.505. The duration of apnoea and of respiratory depression was measured and
found to be significantly greater after the two eugenol derivatives than after the bar-
biturates. The incidence of postoperative muscle pains was found to be significantly
lower after methohexitone, and after the eugenol derivatives, than after thiopentone
and thialbarbitone. The possible mechanisms of these findings may include a direct
action of the eugenol derivatives on voluntary muscle.

Interest has recently been shown in the use of
phenoxyacetic amines (eugenol derivatives) as
agents for intravenous anaesthesia. The German
preparation FBA.1420* has been the subject of
favourable reports (Dundee and Clarke, 1964;
Howells et al., 1964).

One of the advantages of this drug is that the
recovery of consciousness is more rapid than after
equipotent doses of thiopentone. For this reason
a preliminary trial was carried out in which
FBA.1420 was employed, with suxamethonium,
for anaesthesia for bronchoscopy in out-patients.
The impression was gained that the duration of
apnoea and respiratory depression was greater
than when thiopentone or methohexitone re-
placed FBA.1420. It appeared a possibility that
the risk of consciousness being regained before
full muscular activity was greater with FBA.1420
than with other drugs.

This paper reports a clinical investigation of
the possible relationship between intravenous in-
duction agents and the effects of suxamethonium
on respiration. Three intravenous barbiturates
were used: thiopentone, thialbarbitone and
methohexitone. The effects of these drugs were
compared with FBA.1420 and with G.29.505 (an-
other eugenol derivative).

METHODS
The patients were women undergoing minor
gynaecological operations, mainly cervical dil-
ations and uterine curettage. Premedication
consisted of atropine 0.6 mg. The intravenous
agents were given on a weight basis in what was
thought to be equipotent doses. In the relaxant
series suxamethonium 25 mg, which had been
stored in a refrigerator until the morning of use,
was given immediately after the induction agent
and anaesthesia was maintained with nitrous
oxide and oxygen. All durations were measured
from the time of injection of suxamethonium
and the following endpoints noted:
time of onset of apnoea (if the patient became
apnoeic);
time of first return of respiration (referred to
as duration of apnoea);
time of return of clinically adequate respira-
tion (referred to as duration of respiratory
depression).

During the period of apnoea and respiratory
depression the chest was inflated, but care was
taken not to over-ventilate. No supplementary
doses of the intravenous anaesthetic agent were
given during the period of apnoea, but after
respiration had partially returned additional

*This drug is now also referred to as propanidid.
doses of the drug were given if anaesthesia appeared to be inadequate. The control series differed only in that no suxamethonium was given.

In a few patients anaesthetized with FBA.1420 in whom there was prolonged respiratory depression, an attempt was made to determine the nature of the myoneural block with a Medelec nerve stimulator (Wylie and Churchill-Davidson, 1960) or injection of edrophonium 5 mg.

Table I shows that all groups of patients, both in the relaxant and the control series, were broadly comparable. The difference between total intravenous dose in the relaxant and in the control series arises from the method of calculation. In the relaxant series total dose was measured up to the return of adequate respiration and in the control series it was measured up to the end of the procedure.

All anaesthetics were given by, and the observations made by, the first two authors. The operations were carried out in the morning and the patients were allowed out of bed on the same evening. Each patient was seen on the first, second and third day after operation and asked in general terms how she felt. If there was a complaint about muscle pains these were classified as moderate or severe. Pains only mentioned on specific questioning were classed as mild.

Thiopentone and FBA.1420 were used concurrently at the start of the trial. After fifty cases with each of these the differences found were so great that further series, each of fifty cases, were anaesthetized using thialbarbitone and methohexitone. FBA.1420 was used in a further fifty cases (in which supplementary doses were purposely restricted). The last twenty-five patients in the study were anaesthetized with G.29.505 and, with this drug, limitation of supplies restricted the number of patients and supplementary dosage.

RESULTS

Respiratory effects.

Table II contains the relevant data on the respiratory effects of suxamethonium in the five series. It can be seen that the effects of suxamethonium were more marked when anaesthesia was induced with FBA.1420 or with G.29.505 than with any of the three barbiturates. Statistical comparisons were limited to the percentage of patients who were apnoeic, the average duration of apnoea in these cases, and the average duration of inadequate respiration in all patients. There were no significant differences (P>0.05) between any of the barbiturate series with respect to these observations, nor was there any difference between the series in which anaesthesia was induced with FBA.1420 and G.29.505. The respiratory effects of suxamethonium in the FBA.1420 series were different in all respects from those in the barbiturate series at a 1 per cent significance level, except when methohexitone was used, in which case the percentage of apnoeic cases only differed at the 2½ per cent level.

The durations of apnoea and respiratory depression following the injection of G.29.505 were significantly different from those following any of the barbiturates. The difference between the percentage of patients having apnoea, however, did not reach the 5 per cent level of signi-
ficance because of the smaller number of cases in the G.29.505 series. When the results of the barbiturate groups of patients were pooled there was significantly less respiratory depression when compared with the pooled results of the eugenol series.

When there was a complete cessation of respiration the onset of apnoea occurred, on the average, between 35 and 40 seconds after injection. This aspect of the respiratory effects of suxamethonium showed no difference between drugs, and will not be discussed further.

There are factors other than the nature of the drugs which could cause these differences. FBA.1420, being shorter acting than any of the barbiturates, more frequent and greater supplementary doses may have been needed which could have affected duration of respiratory depression. In the second series of fifty patients anaesthetized with FBA.1420, the incremental doses, when required, were kept very small without significantly affecting the average duration of respiratory depression (table III).

Table IV shows that the average dose given to the patients in whom apnoea or respiratory depression was shortest, differed little from the corresponding average for those in whom the durations were longest. This indicates that, for the range of dosage used, there is no relationship between dose and duration of any practical importance with regard to apnoea or respiratory depression. There were too few cases in the G.29.505 group to consider in this analysis.

Patients who became apnoeic showed a longer duration of respiratory depression than the non-apnoeic cases, and the results for each of the intravenous agents were similar in this respect.

Of six persons who were given edrophonium 5 mg, three showed a marked immediate improvement in respiration, suggesting the presence of a non-depolarizing block, while the other three showed no response to the injection. A sustained tetanus was found on application of a stimulus of 50 impulses/sec to the ulnar nerve in six out of ten patients, suggesting the presence of a depolarizing block. The tetanus was not sustained in the

<table>
<thead>
<tr>
<th>Drug</th>
<th>Percentage of patients apnoeic</th>
<th>Average duration of apnoea (sec)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Apnoeic cases only</td>
<td>All cases</td>
</tr>
<tr>
<td>Thiopentone</td>
<td>68</td>
<td>85 ± 13.0</td>
</tr>
<tr>
<td>Thialbarbitone</td>
<td>60</td>
<td>109 ± 8.9</td>
</tr>
<tr>
<td>Methohexitone</td>
<td>72</td>
<td>115 ± 11.2</td>
</tr>
<tr>
<td>FBA.1420</td>
<td>87</td>
<td>154 ± 8.2</td>
</tr>
<tr>
<td>G.29.505</td>
<td>88</td>
<td>163 ± 16.6</td>
</tr>
<tr>
<td>Total barbiturates</td>
<td>67</td>
<td>103 ± 5.4</td>
</tr>
<tr>
<td>Total eugenols</td>
<td>87</td>
<td>155 ± 9.1</td>
</tr>
</tbody>
</table>

Table III

Comparison of first and second groups of fifty patients in whom FBA.1420 was used, with respect to dosage and mean duration of respiratory depression.

<table>
<thead>
<tr>
<th>Dose (mg/kg)</th>
<th>No. given supplementary dose</th>
<th>Average initial</th>
<th>Average supplementary to those given any</th>
<th>Average duration of respiratory depression (sec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>First 50</td>
<td>41</td>
<td>4.05</td>
<td>1.31</td>
<td>277 ± 16.6</td>
</tr>
<tr>
<td>Second 50</td>
<td>30</td>
<td>4.07</td>
<td>1.13</td>
<td>257 ± 10.1</td>
</tr>
</tbody>
</table>
TABLE IV
Relationship between duration of apnoea and initial doses, and respiratory depression and total doses of drugs used.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Average initial dose (mg/kg)</th>
<th>Average total dose (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patients with no apnoea</td>
<td>Longest* apnoea</td>
</tr>
<tr>
<td>Thiopentone</td>
<td>3.99</td>
<td>3.81</td>
</tr>
<tr>
<td>Thialbarbitone</td>
<td>7.79</td>
<td>7.83</td>
</tr>
<tr>
<td>Methohexitone</td>
<td>1.59</td>
<td>1.51</td>
</tr>
<tr>
<td>FBA.1420</td>
<td>3.98</td>
<td>4.18</td>
</tr>
</tbody>
</table>

* Average of six patients with longest or shortest apnoea or respiratory depression.

TABLE V
Per cent incidence of muscle pains during first two days after operation.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Severe</th>
<th>Moderate</th>
<th>Mild</th>
<th>Nil</th>
<th>Control series, all grades</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thiopentone</td>
<td>10</td>
<td>22</td>
<td>34</td>
<td>34</td>
<td>2</td>
</tr>
<tr>
<td>Thialbarbitone</td>
<td>10</td>
<td>22</td>
<td>32</td>
<td>36</td>
<td>4</td>
</tr>
<tr>
<td>Methohexitone</td>
<td>4</td>
<td>8</td>
<td>26</td>
<td>62</td>
<td>6</td>
</tr>
<tr>
<td>FBA.1420</td>
<td>4</td>
<td>6</td>
<td>18</td>
<td>72</td>
<td>4</td>
</tr>
<tr>
<td>G.29.505</td>
<td>4</td>
<td>12</td>
<td>16</td>
<td>68</td>
<td></td>
</tr>
</tbody>
</table>

TABLE VI
Relationship between respiratory effects of suxamethonium and the occurrence of after pains.

<table>
<thead>
<tr>
<th>Observation</th>
<th>Percentage of patients without apnoea</th>
<th>Average duration of apnoea</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Muscle pain: Absent Present</td>
<td>Absent Slight Moderate Severe</td>
</tr>
<tr>
<td>Thiopentone and thialbarbitone</td>
<td>34 35</td>
<td>66 68 57 43</td>
</tr>
<tr>
<td>Methohexitone</td>
<td>29 26</td>
<td>87 79 79 60</td>
</tr>
<tr>
<td>FBA.1420</td>
<td>15 7</td>
<td>132 151 103 134</td>
</tr>
<tr>
<td>G.29.505</td>
<td>18 0</td>
<td>126 205 163 120</td>
</tr>
</tbody>
</table>

Other four cases. The limited data throws no light on the mechanism of the prolonged respiratory depression when suxamethonium is given after FBA.1420.

Muscle pains.

Table V leaves no doubt that, irrespective of the induction agents, the 25 mg dose of suxamethonium causes a high incidence of postoperative muscle pains. The overall incidence following thiopentone or thialbarbitone differed from that of FBA.1420 at a 1 per cent level of significance and from G.29.505 at a 5 per cent level. There were no significant differences between the incidence of pains following the two eugenol derivatives or between those following FBA.1420 and methohexitone. The oxybarbiturate (methohexitone), however, was followed by a much lower incidence (P<0.05) than either thiobarbiturate (thiopentone and thialbarbitone).

Attempts were made to correlate the incidence and severity of muscle pains with that of fasciculations, but the occurrence of fasciculations was very difficult to evaluate in some cases because of confusion with the excitatory effects of the induction agent. With each drug the percentage of
Fig. 1

Spirogram (reading from right to left), breathing oxygen, during the injection of three doses of FBA.1420.
patients having muscle pain was higher for those in whom fasciculations were observed than those in whom they were not, but the unreliability of the observation precludes any significance being attached to this finding.

As can be seen in table VI, there is no obvious relationship between the severity of muscle pain and the incidence or duration of apnoea. No significant relationship could be found between the incidence of muscle pains and dose of the individual drugs and, for the sake of brevity, detailed figures are not given.

Muscle pains, when they occurred, were most frequently found in the neck and shoulder girdle followed by the subcostal and upper abdominal areas. A proportion of patients complained of pains all over the upper half of the body. There was no obvious difference between the sites of pains and the different anaesthetics (table VII).

### DISCUSSION

While realizing the limitations of accuracy of the method employed for measuring the duration of action of suxamethonium, these results show that the representatives of the two groups of intravenous anaesthetics—the barbiturates and eugenol derivatives—are followed by significantly different respiratory effects after the same dose of this relaxant. The more prolonged action associated with FBA.1420 and G.29.505 suggests that these phenoxyacetic acid amines in some way "potentiate" suxamethonium. There is no data to show how this happens or whether these two agents have any direct effect on either the motor endplate or the muscle itself, or not.

The possibility of a central depressant action of the eugenol derivatives must be considered. Induction doses of both drugs used in this study usually cause marked hyperventilation followed by transient apnoea. Figure 1 illustrates a typical finding with FBA.1420, which very closely resembles the findings of Swerdlow (1961) with G.29.505. The absence of any prolonged respiratory depression in figure 1 is against this hypothesis.

The frequency and severity of muscle pains following suxamethonium varies with the age and sex of the patient, and the nature of the operation which will determine the time and amount of postoperative ambulation. All these factors have been controlled as far as clinically possible in this investigation and the early ambulation probably accounts for the high incidence of muscle pains (Churchill-Davidson, 1954). No explanation can be offered for the significantly lower incidence of these pains after FBA.1420 or G.29.505, as compared with the incidence after the barbiturates. This difference, coupled with the increased respiratory depression, suggests a direct effect on the muscle rather than a central action.

### ACKNOWLEDGMENTS

Thanks are due to Dr. D. Whitfield and Farbenfabriken Bayer AG, for generous supplies of FBA.1420 and for defraying part of the cost of the investigation; Imperial Chemical Industries Limited for thialbarbitone; and Geigy Pharmaceuticals Limited for G.29.505. We are also indebted to the gynaecological staff of Musgrave Park Hospital, Balmoral, for their co-operation in this study.

### REFERENCES


ETUDE CLINIQUE DES AGENTS INDUCTEURS XI: L’INFLUENCE DE QUELQUES ANESTHÉSIQUES INTRAVEINEUX SUR LES EFFETS RESPIRATOIRES ET LES SÉQUELLES DU SUXAMÉTHONIUM

SOMMAIRE

Injection intraveineuse de 25 mg de suxaméthonium après induction de l’anesthésie avec des doses équivalentes de thiopentone, de thialbarbitione, de méthohexitone, de FBA.1420 et de G.29.505. On a pu constater que la durée de l’apnée et de la dépression respiratoire était nettement plus importante après application des deux dérivés de l’ Eugénol qu’après les barbituriques. La fréquence des douleurs musculaires post-opératoires était nettement plus réduite après méthohexitone et après les dérivés de l’eugénol qu’après la thiopentone et la thialbarbitione. Parmi les mécanismes susceptibles d’expliquer ces résultats il y a probablement une action directe des dérivés de l’eugénol sur la musculature striée.

BOOK REVIEW


One of the senior neurosurgeons in Professor Tönnis’s Cologne unit has produced a thorough monograph dealing with “Central respiratory disturbances in head injuries and brain tumours”. In the first twenty-six pages similar animal and clinical studies are reviewed, and the gaps in knowledge are emphasized. The subsequent material relates to 370 quantitative analyses in 180 in-patients of various types, (e.g., 43 head injuries, 69 tumours, 7 aneurysms and 10 normal controls). The investigations included arterial Pco₂, arterial oxygen saturation, and extensive spirometry producing kymograph records of actual respiratory movements, assessments of respiratory equivalents by relating oxygen uptake to minute volume, and analyses of respiratory centre sensitivities to increased carbon dioxide partial pressures. Of the numerous technical problems, particular mention is made of premature termination of recordings in the presence of excessive secretions, of the improbability of carrying out “acute” investigations at the roadside, and of the deliberate assumption that lung function and the remaining metabolic functions were normal.

Several important principles are put on a sound scientific basis. Clinical assessment in the ordinary sense is an unreliable guide to actual events. In particular, when compared with the actual oxygen uptake, the respiratory minute volume may be too low or uneconomically exaggerated, and even in patients without any apparent disturbances of rate of air flow serious disturbances may be present and it is these disturbances which will produce abruptly the well-recognized “unexpected” disasters.

If very promptly initiated, correct treatment will reverse some severe disorders. The efficacy of a tracheostomy is vividly proved—even in cases without any obvious distress—but there is also a major warning. Tracheostomy in patients with a very high Pco₂ may produce such an abrupt reduction in carbon dioxide levels that fatal respiratory and circulatory disturbances will occur.

Paradoxically the damaged respiratory centres are often hypersensitive to carbon dioxide. If this is the case, “decerebrate rigidity”, and hypocapnia with its attendant reduction in cerebral blood flow and peripheral vasoconstriction, are usually marked. Sedation (including general anaesthesia on occasion) is then not ordered as a risk, but as an essential therapeutic measure which produces dramatic improvement. On the other hand, sedatives are risky if the centres are hyposensitive.

The monograph is in German, and this is a pity for the solely English speaking doctor because he will not be able to benefit maximally from the great volume of valuable information. On the other hand, there is a five-page summary in English and an eighteen-page bibliography, and the numerous visual aids would reward study undertaken with the aid of a dictionary.

A. G. MacIntyre