CLINICAL STUDIES OF INDUCTION AGENTS
VI: MISCELLANEOUS OBSERVATIONS WITH G.29.505

BY
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SUMMARY
Using G.29.505 the incidence of excitatory phenomena occurring after premedication with atropine and opiate was insignificantly different from that after atropine alone, whereas after hyoscine it was three times as high. Respiratory disturbances were significantly less frequent when an opiate was used with atropine than after atropine or hyoscine alone. G.29.505 was compared with nitrous oxide and oxygen for use in minor procedures. It did not prolong the time required, but was followed by a much higher incidence of brief but troublesome restlessness. Vein damage was much more frequent than after methohexitone or thiopentone.

Previous papers in this series have confirmed the findings of Continental workers that 2-methoxyl-4-allylphenoxyacetic acid—N, N-diethylamide (G.29.505) is an intravenous anaesthetic of considerable interest. Unfortunately, the advantages which this drug possesses over the rapidly acting barbiturates are more than outweighed by the high incidence of venous damage following its use.

In this paper the relationship is examined between the incidence of side effects accompanying the induction of anaesthesia with G.29.505, and the drugs used in premedication. A further study has been carried out to compare its usefulness as the sole anaesthetic for the performance of minor surgical operations in outpatients with that of the commonly used inhalation technique of nitrous oxide and oxygen, with or without volatile supplements (trichloroethylene or halothane) as required.

The results of a close examination, by three different observers, of damage to veins consequent on the use of various preparations and concentrations of G.29.505 are reported, and these are compared with the vein damage observed after the use of thiopentone and methohexitone.

INDUCTION CHARACTERISTICS WITH VARIOUS FORMS OF PREMEDICATION

Observations following the use of an induction dose of 4–4.5 mg/kg G.29.505 were made in a manner identical with that described by Dundee et al. (1961) for methohexitone. Each induction was graded according to the scheme devised by these authors. Three forms of premedication were used as indicated in table I. It can be seen that the three series are broadly comparable as regards the ages and weights of patients, and the doses of G.29.505 used for induction of anaesthesia. Data on blood pressure changes are not presented because previous work by Dundee and Rajagopalan (1962) showed that a fall in systolic blood pressure exceeding 20 mm Hg is infrequent with the doses of G.29.505 employed in the study.

There was no difference \( (\chi^2 = 3.24; P<0.10) \) between the incidence of excitatory phenomena with atropine and atropine-opiate premedication. On the other hand, the use of hyoscine was associated with an incidence more than three times as great as that with atropine alone, this increase being highly significant \( (\chi^2 = 38.17; P<0.001) \).

Premedication with atropine and an opiate was followed by the lowest incidence of respiratory disturbance, this being significantly less than after atropine alone \( (\chi^2 = 5.35; P<0.05) \) or hyoscine alone \( (\chi^2 = 4.88; P<0.05) \). Atropine was not superior to hyoscine in this respect \( (\chi^2 = 2.57; P<0.20) \).

There is a great similarity between the effects of premedication on the incidence of excitatory phenomena with G.29.505 and with methohexitone.
TABLE I
Incidence of induction complications with G.29.505 related to the form of premedication used.

<table>
<thead>
<tr>
<th></th>
<th>Atropine 0.6 mg</th>
<th>Opiate*—- atropine</th>
<th>Hyoscine 0.4 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of cases</td>
<td>577</td>
<td>270</td>
<td>184</td>
</tr>
<tr>
<td>Average age (years)</td>
<td>34.8</td>
<td>33.7</td>
<td>31.6</td>
</tr>
<tr>
<td>Average weight (kg)</td>
<td>62.6</td>
<td>59.9</td>
<td>59.8</td>
</tr>
<tr>
<td>Average induction dose (mg/kg)</td>
<td>4.28</td>
<td>4.32</td>
<td>4.03</td>
</tr>
<tr>
<td>Percentage incidence</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Excitatory phenomena</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tremor</td>
<td>1.6</td>
<td>0.4</td>
<td>3.3</td>
</tr>
<tr>
<td>Muscle movement</td>
<td>15.8</td>
<td>10.7</td>
<td>54.9</td>
</tr>
<tr>
<td>Nil</td>
<td>83.0</td>
<td>88.9</td>
<td>44.6</td>
</tr>
<tr>
<td>Respiratory upset</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough/hiccough</td>
<td>17.3</td>
<td>10.4</td>
<td>21.2</td>
</tr>
<tr>
<td>Laryngospasm</td>
<td>1.0</td>
<td>1.1</td>
<td>4.3</td>
</tr>
<tr>
<td>Nil</td>
<td>82.0</td>
<td>88.5</td>
<td>76.6</td>
</tr>
<tr>
<td>Marked respiratory depression</td>
<td>3.3</td>
<td>2.6</td>
<td>4.4</td>
</tr>
<tr>
<td>Induction grades</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>64.8</td>
<td>78.1</td>
<td>28.8</td>
</tr>
<tr>
<td>2a</td>
<td>22.4</td>
<td>16.2</td>
<td>44.6</td>
</tr>
<tr>
<td>2b</td>
<td>11.6</td>
<td>5.3</td>
<td>25.5</td>
</tr>
<tr>
<td>3</td>
<td>1.2</td>
<td>0.4</td>
<td>1.1</td>
</tr>
</tbody>
</table>

* Morphine 10 mg or pethidine 50–100 mg with atropine 0.6 mg.

(Dundee et al., 1961). This may be correlated with the analgesic (opiate) or antanalgesic (hyoscine) action of the premedication. For reasons which will be apparent later, a more detailed examination of this relationship is inadvisable.

Reference to table I shows that, setting aside trivial induction complications (grade 2a), more than one quarter of the administrations were frankly unsatisfactory (grades 2b and 3), when hyoscine was used as premedication compared with 12.8 per cent and 5.7 per cent with atropine, and atropine-opiate respectively. This difference between hyoscine and other forms of premedication is significant at the 0.1 per cent level. From this it would appear that, if other difficulties with the drug are overcome so that it comes into general use, premedication with hyoscine alone is not recommended.

OUTPATIENT STUDY
This study was carried out on patients scheduled for minor operations, such as incision and drainage of abscesses and manipulation of fractures.

When G.29.505 was used alone the technique was as follows:

The area of operation was prepared and the surgeon was ready to incise before the drug was given. Surgery was carried out at the second breath of hyperventilation. Supplementary doses were given when necessary.

Inhalation anaesthesia was induced with a high flow of nitrous oxide and oxygen and with this technique the wound was not cleaned up until the patient was unconscious.

In both series the time was noted from the commencement of administration to
(a) the end of operation;
(b) the moment when the patient opened his eyes; and
(c) to the time when the patient was considered to be fully orientated.

The follow-up of the incidence of emetic sequelae was limited to about 30 minutes after the end of the operation.

Table II shows the findings which reveal a significantly higher incidence of unsatisfactory administrations (grades 2b and 3) with the gaseous technique. All the average times with G.29.505 are significantly shorter (P<0.001) than with the inhalation method. Despite the statistical finding it is doubtful if the difference between the two techniques, as regards the average time elapsing until the patients were fully orientated, is of clinical significance. In fact, an impression of a more rapid awakening from inhalation anaesthesia is easily gained because of the shorter average time from the completion of the operation (2.6 min) as compared with G.29.505 (5.4 min). Allowing for initial skin toilet, it is reasonable to conclude that the use of G.29.505 does not prolong the time taken...
Observations on outpatient cases: comparison of G.29.505 as the sole agent, with nitrous oxide and oxygen supplemented as required.

<table>
<thead>
<tr>
<th>Anaesthetic technique</th>
<th>G.29.505</th>
<th>Nitrous oxide and oxygen with supplement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of cases</td>
<td>106</td>
<td>53</td>
</tr>
<tr>
<td>Average age (years)</td>
<td>33.8 (18-59)</td>
<td>31.7 (13-84)</td>
</tr>
<tr>
<td>Average weight (kg)</td>
<td>63.2 (50-88)</td>
<td>59.8 (43-95)</td>
</tr>
<tr>
<td>Average dosage (mg/kg)</td>
<td>3.87 ± 0.015</td>
<td>4.23 ± 0.093</td>
</tr>
<tr>
<td>Induction</td>
<td>81.1</td>
<td>73.6</td>
</tr>
<tr>
<td>Total</td>
<td>14.3</td>
<td>15.1</td>
</tr>
<tr>
<td>% incidence of induction grades</td>
<td>2.8</td>
<td>1.9</td>
</tr>
<tr>
<td>(a) End of operation</td>
<td>2.12 ± 0.103</td>
<td>7.89 ± 0.386</td>
</tr>
<tr>
<td>(b) Patient opens eyes</td>
<td>4.85 ± 0.206</td>
<td>8.34 ± 0.505</td>
</tr>
<tr>
<td>(c) Patient is fully orientated</td>
<td>7.52 ± 0.365</td>
<td>10.57 ± 0.743</td>
</tr>
<tr>
<td>% incidence of sequelae</td>
<td>4.7</td>
<td>9.4</td>
</tr>
<tr>
<td>Nausea</td>
<td>4.7</td>
<td>3.8</td>
</tr>
<tr>
<td>Vomiting</td>
<td>17.0</td>
<td>1.9</td>
</tr>
<tr>
<td>Slight restlessness</td>
<td>7.5</td>
<td>1.9</td>
</tr>
</tbody>
</table>

for an outpatient to have a minor operation. Its use is, however, followed by a much higher incidence of restlessness (P < 0.001), which, although of brief duration, may be very troublesome for a few minutes.

**Damage to veins.**

At an early stage in the clinical trial of G.29.505 it became obvious that vein damage occurred much more frequently than after injection of thiopentone and that this damage could sometimes be quite disturbing in degree. The form of venous damage most commonly noted was that of localized thrombosis or of thickening of the vessel wall. Such alterations in veins were sometimes accompanied by pain and tenderness but this was frequently not the case. Often when a patient had no spontaneous complaint about the injection site, inspection revealed thrombosis of the vein. Occasionally pain and tenderness were noted without obvious thrombosis.

To obtain confirmation of this impression of a high incidence of vein damage, three observers examined the injection sites of three different groups of patients on the first and second post-operative day (table III). An incidence below 20 per cent was not found in any series. Diluting G.29.505 with an equal volume of water did not appear to affect the incidence (54 per cent of 41 cases). Suggestive evidence was obtained that the incidence of vein damage might be higher with increase in size of the dose used. This possibility was not examined further because no useful clinical application seemed likely to follow. The effect of flushing the vein with saline after completion of injection of G.29.505 also proved disappointing in reducing the incidence of vein damage (22 per cent of 32 cases).

<table>
<thead>
<tr>
<th>Observer</th>
<th>A</th>
<th>B</th>
<th>C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients in series</td>
<td>58</td>
<td>163</td>
<td>125</td>
</tr>
<tr>
<td>Vein damage (Nos.)</td>
<td>22</td>
<td>51</td>
<td>28</td>
</tr>
<tr>
<td>Vein damage (%)</td>
<td>38</td>
<td>31</td>
<td>22</td>
</tr>
</tbody>
</table>

**TABLE III**

Incidence of venous damage found by three observers when injection sites were examined on the first and second days after administration of 5 per cent G.29.505.
Table IV shows the results obtained in patients whose injection sites were examined after injection of thiopentone or methohexitone and these can be compared with the incidence following all the injections of G.29.505. Although the incidence following the injection of barbiturate is higher than common experience would suggest, it is evident that when vein damage is carefully looked for it is very much less commonly encountered than when it is sought after G.29.505 injection. None of the patients receiving barbiturate had extensive thrombotic damage, whereas this was frequent enough with G.29.505 to be regarded as a serious drawback to its use.

ACKNOWLEDGMENTS

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REFERENCES
