THE ACTION OF G.29.505 ON THE RESPIRATION OF THE RABBIT

BY

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SUMMARY

G.29.505 was found to depress respiration in rabbits after an initial period of stimulation. When given shortly afterwards it augmented the respiratory depression produced by morphine but when administration was delayed there was in some animals an improvement in respiratory minute volume. It seemed that this response was not traceable to an effect of the solvent or suspending medium.

Most anaesthetists would agree that there is room for a more satisfactory intravenous anaesthetic than thiopentone. This drug is a powerful depressor both of blood pressure and of respiration. The compound G.29.505 was investigated in the laboratory by Thuillier and Domenjoz (1957), and appeared to offer some promise, particularly because of some tendency on its part to stimulate respiration. Frey and Hermann (1957), and later Henschel and Just (1957), confirmed that this respiratory stimulant effect occurred in the human subject. Swerdlow (1961) found that anaesthesia with G.29.505 terminated rapidly and left no hangover. Dundee and Hamilton (1960) showed that this drug lacked the anti-analgesic action of thiopentone and the barbiturates generally. All who have used the drug, however, have found that it tends to produce extensive thrombophlebitis in a small proportion of cases (Payne and Wright, 1962; Swerdlow, 1962). As this complication can involve obliteration of most of the veins in the limb into which the drug is injected, it must be regarded seriously, and before G.29.505 can find general acceptance it must be shown to possess very considerable advantages over thiopentone to outweigh the risk that it may provoke this complication.

It is the view of the author that prompt recovery and a lack of anti-analgesic action are not in themselves sufficient to justify a change-over. If, however, it could also be shown that the drug had substantially no effect on respiration it would add to its claim to be used more widely. With this in view the action of G.29.505 on the respiration of the rabbit was studied.

METHODS

Since the aim of this work was to elucidate the action of G.29.505 without other complicating factors and the drug to be tested was itself a general anaesthetic, no premedication or preliminary anaesthesia was employed. Drugs were given by intravenous injection into ear veins. Rabbits were employed. Changes in state of consciousness were assessed by the criteria used by Thuillier and Domenjoz (1957). These are:

**Stage O.** Position of rest and movement are normal; body righting reflexes acting on hindquarters are present.

**Stage I.** Animal lies on abdomen at rest; conspicuous ataxia during movement; spontaneous righting occurs when animal is placed on its side; extremities collapse due to force of gravity in spite of normal response to linear acceleration.

**Stage II.** Hindquarters remain in lateral position but righting occurs on stimulation. Labyrinthine righting reflexes, nystagmus on angular acceleration and body righting reflexes on anterior body part are all present.

**Stage III.** Animal lies on its side but the head is horizontal; incomplete righting on stimulation. Neck righting reflexes involving anterior part of the body, body righting reflexes involving the head, response of the head and horizontal nystagmus following angular acceleration are all maintained.

**Stage IV.** Righting reaction is absent (no response to painful stimulation). Nystagmus on angular acceleration and corneal reflexes are present.

**Stage V.** Reaction to pain (pinching of the paw, needle prick) and post-rotational nystagmus are present.
Stage VI. All reflexes, except knee-jerk, are absent.

These stages bear little relationship to the stages of anaesthesia recognized by anaesthetists. Indeed, only (V) and (VI) are degrees of narcosis likely to be clinically useful. Respiratory minute volume was measured with the aid of a Gaddum recorder (1941). This apparatus was calibrated against a depressed level water flowmeter on each occasion on which it was used. G.29.505, which is insoluble in water, is now available as a lecithin stabilized suspension. Except where the contrary is stated this solution was used throughout this study.

RESULTS

Relative potency.

The narcotic potency of G.29.505 was such that 20 mg/kg of this drug produced a level of narcosis comparable to that obtained from 40 mg/kg of thiopentone. The duration of action of 40 mg/kg of thiopentone was intermediate between that of 20 and 40 mg/kg of G.29.505. These results were obtained from crossover experiments in four rabbits (fig. 1).

Action on respiration.

It was confirmed that the immediate effect of injecting G.29.505 into conscious rabbits was a brief increase in depth of respiration (fig. 2). This was followed by a period of apnoea lasting some 20 sec, and thereafter the respiratory exchange of each animal was stabilized at a level lower than its normal. The reductions in the minute volume produced by 20 mg/kg and 40 mg/kg of G.29.505 were comparable to those produced by 40 mg/kg of thiopentone, though the latter drug produced more slowing of respiration (table I). The time courses of the mean changes produced are shown in figures 3 and 4 for four animals.

Action on the morphinized animal.

Thuillier and Domenjoz (1958) had shown that G.29.505 increased the depth and minute volume of respiration in morphinized rabbits. This experiment was repeated. It was found that the intravenous injection of G.29.505 in doses of 10 mg/kg produced an intensification of the respiratory depression produced by 8 mg/kg of morphine given intravenously some 5 to 10 minutes previously. The same experiment was repeated with 10 mg/kg of thiopentone instead of 10 mg/kg of G.29.505, and again respiratory depression was intensified. As the intravenous anaesthetic thial-barbitone (Kemithal) had been reported as a respiratory stimulant (Gordon and Gibbons, 1946) the experiment was again performed this time with 20 mg/kg of this drug, an amount which is approximately equipotent with 10 mg/kg of thiopentone. Respiratory depression was again
The effect of G.29.505 and thiopentone on the respiratory rate of the rabbit.

The effect of G.29.505, thiopentone and thalbarbitone on the respiratory displacement of the morphinized rabbit. (The narcotic drug was given within 10 minutes of the morphine.)

The effect of G.29.505 on the respiratory displacement of the morphinized rabbit to show the difference when the drug was given 30 minutes after the morphine.
intensified to the same extent as with 10 mg/kg of G.29.505 but to a lesser extent than with thiopentone (table II; fig. 5). Changes in respiratory rate and minute volume ran parallel.

Delayed injection of G.29.505.

Some 30 minutes had elapsed in the experiments of Thuillier and Domenjoz between the injection of morphine and G.29.505. A similar experiment was performed in which rabbits were given 8 mg/kg of morphine intravenously. This was followed half an hour later by G.29.505 in doses of 10 mg/kg or 20 mg/kg. The respiratory depression which developed in this group was much less serious and in some animals the minute volume was actually improved (fig. 6). The same experiment was repeated with 20 mg/kg of thiobarbitone given half an hour after the morphine. With this drug much more marked intensification of respiratory depression occurred than with 10 mg/kg G.29.505 (table II).

It seemed that the preparation of G.29.505 used in these experiments might be influencing the result. G.29.505 was therefore given to recently morphinized rabbits in the original benzoate glycol solution. When this was injected shortly after the morphine the same result was obtained

**Table I**

The effect of G.29.505 and thiopentone on the rabbit's respiration (cross-over experiment).

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose (mg/kg)</th>
<th>No. of animals</th>
<th>Minimum respiratory rate (per cent control) after</th>
<th>Minimum respiratory volume (per cent control) after</th>
</tr>
</thead>
<tbody>
<tr>
<td>G.29.505</td>
<td>20</td>
<td>4</td>
<td>39 (33-46)</td>
<td>50 (28-76)</td>
</tr>
<tr>
<td>G.29.505</td>
<td>40</td>
<td>4</td>
<td>33 (21-43)</td>
<td>60 (37-67)</td>
</tr>
<tr>
<td>Thiopentone</td>
<td>40</td>
<td>4</td>
<td>26 (21-33)</td>
<td>64 (43-85)</td>
</tr>
</tbody>
</table>

**Table II**

The effect of intravenous anaesthetics on the respiration of the morphinized rabbit. Two sets of cross-over results. (All figures are percentages of control value before morphine 8 mg/kg).

<table>
<thead>
<tr>
<th>Drug</th>
<th>No. of animals</th>
<th>Dose (mg/kg)</th>
<th>Interval after morphine (min.)</th>
<th>Respiratory rate (per cent control) Before</th>
<th>After</th>
<th>Respiratory minute volume (per cent control) Before</th>
<th>After</th>
</tr>
</thead>
<tbody>
<tr>
<td>G.29.505</td>
<td>4</td>
<td>10</td>
<td>30</td>
<td>45 (28-67)</td>
<td>35 (19-43)</td>
<td>68 (55-97)</td>
<td>41 (28-48)</td>
</tr>
<tr>
<td>G.29.505</td>
<td>4</td>
<td>10</td>
<td>10</td>
<td>53 (42-70)</td>
<td>24 (0-36)</td>
<td>53 (35-60)</td>
<td>29 (0-46)</td>
</tr>
<tr>
<td>Thiopentone</td>
<td>4</td>
<td>10</td>
<td>10</td>
<td>50 (36-62)</td>
<td>12 (0-37)</td>
<td>57 (45-70)</td>
<td>14 (0-32)</td>
</tr>
<tr>
<td>Thialbarbitone</td>
<td>4</td>
<td>20</td>
<td>10</td>
<td>55 (49-67)</td>
<td>21 (0-32)</td>
<td>52 (41-59)</td>
<td>30 (0-60)</td>
</tr>
<tr>
<td>G.29.505</td>
<td>4</td>
<td>20</td>
<td>10</td>
<td>41 (25-52)</td>
<td>18 (0-38)</td>
<td>47 (36-63)</td>
<td>20 (0-50)</td>
</tr>
<tr>
<td>Thialbarbitone</td>
<td>3†</td>
<td>20</td>
<td>30</td>
<td>48 (37-60)</td>
<td>2 (0-3)</td>
<td>65 (52-76)</td>
<td>3 (0-6)</td>
</tr>
<tr>
<td>G.29.505</td>
<td>3†</td>
<td>10</td>
<td>30</td>
<td>33 (13-46)</td>
<td>25 (4-44)</td>
<td>51 (32-66)</td>
<td>29 (10-36)</td>
</tr>
</tbody>
</table>

* Propylene glycol benzoate solution. † Fresh cross-over experiment.
as with the emulsion, namely an intensification of respiratory depression. When, however, the glycol benzoate solution of the drug was injected 30 minutes after morphine had been given the animals did not develop increased respiratory depression (table II).

Effect of solvents, etc.

It seemed possible that the stimulation of respiration produced by the injection of preparations of G.29.505 might not be due to the drug itself but produced by the somewhat acid sodium benzoate or by the effect of fatty emboli on the pulmonary circulation when the emulsion was used. Animals which had previously been morphinized were therefore given 25 per cent sodium benzoate, 12 per cent propylene glycol and the lecithin emulsion, without any active drug. There was no change in rate or depth of respiration (table III). It therefore seemed that the respiratory effects observed were probably directly due to the G.29.505 and should not be related to the solvent or suspending medium.

DISCUSSION

The compound G.29.505 represents an entirely new approach to the production of intravenous anaesthesia. Its other pharmacological properties have been investigated fully by other workers and it has been shown to be substantially without hypotensive action and to lack the anti-analgesic effect of the barbiturates. On the reverse side it has an unpleasant tendency to cause venous thrombosis. The present study has demonstrated that the drug in itself produces substantially the same effects on respiration as does thiopentone. It differs, however, in that when it is given to an animal some 30 minutes after a fairly large dose of morphine it produces much less reduction in respiratory minute volume and rate or even improves them. This property could be of importance in clinical anaesthesia when a patient is premedicated with an opiate drug and is subsequently put to sleep with an intravenous agent. Since G.29.505 has so much less respiratory depressant action, it might seem preferable for this purpose. In current anaesthetic practice, however, some 90 per cent of the patients who receive an induction dose of thiopentone are immediately paralyzed by a relaxant and ventilated artificially, as a preliminary to tracheal intubation, so that the primary effect of the intravenous agent on respiration is of secondary importance. It is therefore the author's view that the respiratory advantages of G.29.505 are not sufficient to outweigh its drawbacks and particularly the adverse effect it has on veins.

From the pharmacological point of view, two points require to be considered. First, no primary respiratory stimulation occurred when the solvents or suspending agents for G.29.505 were injected into the morphinized rabbit nor did any of these show any subsequent tendency to reverse morphine depression. It would therefore seem that the changes observed after the administration of G.29.505 are peculiar to the drug itself and not the result of the activity of the vehicle. Further, since the lecithin emulsion did not produce the tachypnoea or hyperpnoea which is the characteristic response of an experimental animal to acute pulmonary emboli (Halmagyi and Colebatch, 1961), it is unlikely that the changes in breathing were developed as a result of impaction of the

<table>
<thead>
<tr>
<th>Drug</th>
<th>No. of animals</th>
<th>Dose (mg/kg)</th>
<th>Interval after morphine (min)</th>
<th>Respiratory rate (per cent control) Before</th>
<th>After</th>
<th>Respiratory minute volume (per cent control) Before</th>
<th>After</th>
</tr>
</thead>
<tbody>
<tr>
<td>25% sodium benzoate</td>
<td>2</td>
<td>0.30</td>
<td>5</td>
<td>31 (29-32)</td>
<td>31</td>
<td>35 (23-46)</td>
<td>42</td>
</tr>
<tr>
<td>12% propylene glycol</td>
<td>4</td>
<td>0.17</td>
<td>7</td>
<td>29 (15-43)</td>
<td>30</td>
<td>41 (30-55)</td>
<td>41</td>
</tr>
<tr>
<td>Emulsion</td>
<td>3</td>
<td>0.12</td>
<td>30</td>
<td>24 (17-34)</td>
<td>26</td>
<td>44 (25-64)</td>
<td>44</td>
</tr>
</tbody>
</table>

TABLE III
The effect of solvents and suspending medium on the respiration of morphinized rabbits. Morphine given 30 minutes previously. (Figures in the table are percentages of control value before morphine.)
particles of the emulsion in the lungs. It is, of course, possible that the G.29.505 came out of solution in particulate form between the site of injection and the lungs and thus caused multiple small pulmonary emboli and therefore hyperpnoea. This, however, does not explain why the respiratory depressant effect of G.29.505 should be so much less in evidence 30 minutes after morphinization while that of thialbarbitone should still be serious. On the whole it seems probable that the respiratory changes produced by G.29.505 are due to a direct action of the drug and not to a secondary side effect, traceable to the action of the suspended emulsion. Payne and Wright (1962) reached a similar conclusion, but believed that the solvent—in this case presumably the glycol benzocate mixture—could produce pulmonary oedema. It is in any case unlikely that suitably emulsified fat should produce pulmonary disturbances, since preparations for intravenous injection are available for nutritional purposes (Meyer et al., 1957; Kaplan, Strauss and Yuceaglu, 1960).

It is exceedingly difficult to visualize the mechanism whereby G.29.505 produces much less severe respiratory depression when given 30 min. after morphine than when it is given sooner. Simple spontaneous recovery from morphinization is not the explanation. Table III shows that the degree of respiratory depression in the rabbits 30 minutes after morphine was not appreciably less than that 7 minutes after this drug. The only apparent difference between the two groups of animals is that those in which there was the longer interval between the morphine and G.29.505 had presumably accumulated more carbon dioxide. It is therefore possible that G.29.505 temporarily increases the sensitivity of the respiratory centre to carbon dioxide. This might also explain the early hyperpnoea which follows the injection of the drug. It would explain, too, if this effect becomes more pronounced with rising dosage why the later respiratory depressant effect of G.29.505 increases relatively little with the amount given.

**REFERENCES**