A CLINICAL STUDY OF INTRAVENOUS ANAESTHESIA WITH A EUGENOL DERIVATIVE, G.29.505

BY

D. A. WRIGHT AND J. P. PAYNE

Department of Anaesthesia, Postgraduate Medical School of London and Hammersmith Hospital, London

SUMMARY

A derivative of eugenol, G.29.505, was given intravenously to induce anaesthesia in 100 adult patients for operations ranging from minor gynaecological procedures to pneumonectomies and gastrectomies.

The drug when given in a 5 per cent solution produced rapid anaesthesia of short duration associated with a transient respiratory stimulation followed by a brief period of apnoea. No significant effects were observed on the rate and rhythm of the heart, on blood pressure, or on cardiac output. There was, however, an increase in skin blood flow as measured by digital plethysmography.

Thirty-three patients developed venous thrombosis around the site of injection and this incidence is too high to justify its use except in special circumstances.

In modern clinical practice the intravenous agent is generally regarded by patients and anaesthetists alike as the most convenient and the most satisfactory method of inducing anaesthesia, and thiopentone is the most widely used drug for this purpose. Its limitations and disadvantages, however, are well known and research has continued to find a more suitable drug especially for the elderly and for out-patients. Some years ago the steroid anaesthetic hydroxydione was introduced as an alternative to thiopentone (Laubach, P'An and Rudel, 1955; Murphy, Gaudagni and De Bon, 1955) but the delay in the onset of unconsciousness, among other factors, severely restricted its usefulness. More recently a eugenol derivative, 2-methoxy-4-allylphenoxycetic acid -N:N- diethylamide (G.29.505) has been investigated widely on the European continent (Frey and Herrmann, 1957; Henschel and Just, 1957; Boureau, 1959; Junod, 1959). These early reports of its use were encouraging, and accordingly a quantitative study of the action of the drug on the respiratory and cardiovascular system was undertaken in a series of patients undergoing surgery.

METHOD

One hundred adult patients of both sexes and all age groups, premedicated with atropine 0.6 mg, were given G.29.505 for the induction of anaesthesia for operations ranging from minor gynaecological procedures to pneumonectomies and gastrectomies. A 5 per cent solution of G.29.505 in a lecithin emulsion was used in most cases but in twenty patients the concentration was reduced to 2.5 per cent and in a further sixteen patients a 1 per cent solution was used. The drug was injected into a superficial vein on the forearm at a rate of 7.5 mg/sec in a dose ranging from 2 to 4 mg/kg. The time taken for unconsciousness to develop, together with any evidence of excitement, tremors or jactitations, was noted.

Because of technical difficulties, electroencephalographic, respiratory, cardiac and circulatory studies were not undertaken simultaneously; instead the patients were divided into groups and the various studies carried out independently. It was, however, possible to monitor the blood pressure and cardiac rate and rhythm in all patients.

Electroencephalographic recordings were obtained on one channel only from fronto-occipital leads using an Ediswan portable e.e.g. apparatus. A second channel was used to monitor cardiac rate and rhythm before and after induction of anaesthesia with G.29.505.

The rate and depth of ventilation and the res-
piratory minute volume were recorded throughout the induction of anaesthesia by means of a Benedict-Roth spirometer. Oxygen consumption was measured in a similar fashion.

Blood pressure was measured with a stethoscope and sphygmomanometer cuff or directly from the radial artery. For the latter purpose a polyethylene catheter was passed into the lumen of the artery by a technique based on that of Seldinger (1953) and Holmgren (1956) and described in detail elsewhere (Payne, 1962). Once in position it was connected through a transducer to a recording oscilloscope. The pulse rate was measured in one of three ways: by digital palpation, from the e.c.g., or from the blood pressure oscilloscope.

Cardiac output was determined by the dye-dilution technique described by Armstrong and Payne (1960) both before and after the injection of G.29.505.

Skin blood flow through the finger was measured by the method of digital plethysmography described by Melrose and his colleagues (1954).

The condition of the vein used for the injection of G.29.505 was observed until the patient was discharged from hospital.

In two patients undergoing pneumonectomy the lungs were examined in detail for evidence of pulmonary vascular pathology as described in cats (Payne and Wright, 1962).

RESULTS

Unconsciousness was produced in from 10 to 12 seconds in all patients by intravenous injection of G.29.505 in doses of 2 to 4 mg/kg. The initial excitement seen in cats (Payne and Wright, 1962) was not observed clinically but if the drug was injected rapidly tremors and jactitating movements similar to those seen with intravenous hexobarbitone (Dundee, 1956) were noted. The absence of excitement was confirmed by the electroencephalographic recordings made during induction. The e.e.g. patterns seen were typical of the induction of anaesthesia with any agent. Usually within about 10 to 20 seconds after the injection of G.29.505 the alpha rhythm began to recede and intermediate waves appeared, to be followed almost immediately by large delta waves at a rate of 2 to 3 per second. If no other anaesthetic agent was given alpha rhythm soon returned to become superimposed on the delta waves which quickly disappeared. Four patients given 2 mg/kg opened their eyes within 60 to 80 seconds of losing consciousness, but only one had any memory of the event postoperatively.

Immediately after the loss of consciousness there was a marked increase in the tidal volume associated with a smaller increase in the rate of breathing (fig. 1). This was followed within a minute by a short period of apnoea (30 to 90 sec), the duration of which appeared to be related to the dose employed. After the period of apnoea both the tidal and minute volumes returned to more normal levels for the duration of anaesthesia. A quantitative analysis of the respiratory change in five patients is set out in table I.

Oxygen consumption during the control period immediately before induction averaged 325 ml/min in a group of five patients and this fell by more than 30 per cent to 205 ml/min once anaesthesia was established. The details are shown in table II.

The effect of G.29.505 on pulse rate was equivocal and no specific pattern was apparent. Abnormalities in rhythm were noted in only two of the 100 patients to whom the drug was given; a transient A-V nodal rhythm lasted for a few seconds in one patient and there was an equally transient appearance of unifocal ventricular extrasystoles in the other.

In most patients the blood pressure did not change by more than 20 mm Hg and the greatest fall observed was 30 mm Hg. When a fall did occur it developed rapidly after the intravenous injection and lasted less than 1 minute (fig. 2).

Cardiac output was measured in five patients before and after the injection of G.29.505. The average output fell from 8.9 l. to 6.9 l./min, a reduction of approximately 22 per cent. The figures obtained for individual determinations are shown in table III.

Table IV shows the effect of G.29.505 on peripheral blood flow as indicated by skin plethysmography. In each instance the blood flow was increased; from a mean figure of 14 ml/100 ml tissue/min it rose more than fourfold to 64 ml. A typical recording is demonstrated in figure 3.

The incidence of venous thrombosis at the site of injection of G.29.505 was unaffected by the
Fig. 1
Showing the effect of an intravenous injection of G.29.505 on ventilation. The initial respiratory stimulation starts about 20 sec after the injection and lasts for approximately 30 sec. It is followed by a period of apnoea, the duration of which appears to be related to the dose of drug employed.

Table 1
Ventilatory changes associated with intravenous injection of G.29.505.

<table>
<thead>
<tr>
<th>Patient's initials</th>
<th>Frequency</th>
<th>Average tidal volume (ml)</th>
<th>Maximum tidal volume (ml)</th>
<th>Minute volume (l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>O.L.</td>
<td>A</td>
<td>17</td>
<td>675</td>
<td>11.5</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>20</td>
<td>1100</td>
<td>22.0</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>21</td>
<td>225</td>
<td>4.75</td>
</tr>
<tr>
<td>P.W.</td>
<td>A</td>
<td>14</td>
<td>355</td>
<td>5.0</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>24</td>
<td>1120</td>
<td>27.0</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>16</td>
<td>335</td>
<td>5.4</td>
</tr>
<tr>
<td>P.C.</td>
<td>A</td>
<td>16</td>
<td>340</td>
<td>5.5</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>20</td>
<td>750</td>
<td>15.0</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>18</td>
<td>195</td>
<td>3.5</td>
</tr>
<tr>
<td>N.K.</td>
<td>A</td>
<td>15</td>
<td>465</td>
<td>7.0</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>20</td>
<td>980</td>
<td>19.6</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>14</td>
<td>193</td>
<td>2.7</td>
</tr>
<tr>
<td>R.P.</td>
<td>A</td>
<td>12</td>
<td>475</td>
<td>5.6</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>16</td>
<td>950</td>
<td>15.6</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>16</td>
<td>280</td>
<td>4.5</td>
</tr>
</tbody>
</table>

DIGITAL BLOOD FLOWS

CONTROL

---

**TABLE II**

<table>
<thead>
<tr>
<th>Patient's initials</th>
<th>C.C.</th>
<th>N.K.</th>
<th>F.L.</th>
<th>F.W.</th>
<th>A.N.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before</td>
<td>G.29.505</td>
<td>360</td>
<td>350</td>
<td>260</td>
<td>430</td>
</tr>
<tr>
<td>After</td>
<td>G.29.505</td>
<td>200</td>
<td>215</td>
<td>200</td>
<td>225</td>
</tr>
</tbody>
</table>

**TABLE III**

<table>
<thead>
<tr>
<th>Patient's initials</th>
<th>T.B.</th>
<th>W.L.</th>
<th>T.H.</th>
<th>C.R.</th>
<th>J.T.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before</td>
<td>G.29.505</td>
<td>10.7</td>
<td>5.26</td>
<td>13.5</td>
<td>8.67</td>
</tr>
<tr>
<td>After</td>
<td>G.29.505</td>
<td>8.9</td>
<td>5.81</td>
<td>7.75</td>
<td>6.86</td>
</tr>
</tbody>
</table>

---

**FIG. 2**

Showing arterial blood pressure response, measured directly from the radial artery, when G.29.505 is given intravenously.

**FIG. 3**

Showing the effect of intravenous G.29.505 on skin blood flow measured by digital plethysmography. In this instance there is an approximately threefold increase in blood flow.
TABLE IV
Peripheral blood flow in ml/100 ml tissue/min before and after the intravenous injection of G.29.505.

<table>
<thead>
<tr>
<th>Solution</th>
<th>Patient's initials</th>
<th>F.S.</th>
<th>A.W.</th>
<th>J.B.</th>
<th>A.F.</th>
<th>N.K.</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.0%</td>
<td>Before</td>
<td>20</td>
<td>24</td>
<td>4</td>
<td>10</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>After</td>
<td>63</td>
<td>66</td>
<td>22</td>
<td>150</td>
<td>22</td>
</tr>
</tbody>
</table>

TABLE V
Incidence of thrombosis and thrombophlebitis.

<table>
<thead>
<tr>
<th>Solution</th>
<th>No. of patients</th>
<th>No reaction</th>
<th>Thrombosis</th>
<th>Thrombophlebitis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M. F. Total</td>
<td>M. F. 6.39</td>
<td>M. F. 6.10</td>
<td>M. F. 0.3</td>
</tr>
<tr>
<td>5.0%</td>
<td>12 52 64</td>
<td>6 39 6</td>
<td>6 10 0</td>
<td>3</td>
</tr>
<tr>
<td>2.5%</td>
<td>5   15 20</td>
<td>2 10 2</td>
<td>2 4 1</td>
<td>1</td>
</tr>
<tr>
<td>1.0%</td>
<td>7   9 16</td>
<td>4 6 3</td>
<td>3 3 0</td>
<td>0</td>
</tr>
</tbody>
</table>

concentration of drug employed but it was higher in men than in women (table V). Twelve of the twenty-four male patients to whom the drug was given developed venous thrombosis and, of these, one developed a painful thrombophlebitis. Among the female patients thrombosis occurred in twenty-one (28 per cent), four of which progressed to a painful thrombophlebitis. The thrombosis always appeared within 24 hours of the injection and resolved spontaneously. In those patients with thrombophlebitis conservative treatment with heat and rest brought resolution.

Of the two lungs sent for section the diffuse spread of carcinoma throughout one lung made comment on any other aspect impossible. The second lung showed no abnormality that could be attributed to the administration of G.29.505.

DISCUSSION

It has been confirmed that G.29.505 produces anaesthesia rapidly without initial excitement in man when given intravenously. The duration of unconsciousness is brief and recovery occurs within a few minutes if anaesthesia is not supplemented by some other means.

The most striking feature of the onset of anaesthesia was the development of hyperventilation which was succeeded usually within 30 seconds by a period of apnoea. The fact that hyperventilation occurred after consciousness was lost supports the view that the respiratory stimulation is central in origin and unrelated to any direct action of the drug on the pulmonary vascular bed as appears to be the case in the cat (Payne and Wright, 1962). The absence of any incriminating evidence when the lungs were examined histologically, together with the absence of any such reports from the many thousands of anaesthetics given with G.29.505, further suggests that pulmonary vascular disturbances are unlikely with G.29.505 in man.

According to Frey and Herrmann (1957) and Junod (1959) the related apnoea is due to the washing out of carbon dioxide from the lungs during the period of hyperventilation. This contention, however, cannot be upheld because not only was the duration of apnoea often out of proportion to the amount of hyperpnoea but sometimes apnoea developed without any preceding hyperventilation. Moreover the pattern of events after the injection of G.29.505 qualitatively resembles that obtained when thiopentone is given intravenously and it has never been claimed that thiopentone apnoea is due to carbon dioxide wash-out, and further the sequence of initial stimulation followed by depression is sufficiently familiar in pharmacology to exclude the need for a more specific explanation.

A fall in oxygen consumption after the induction of anaesthesia was to be expected but no great accuracy can be claimed because of the changes in the amount of carbon dioxide present in the alveoli brought about by varying ventilation.

Apart from the short duration of anaesthesia the most obvious advantage of G.29.505 was the absence of any pronounced circulatory effects. Although a fall in blood pressure of 40 mm Hg or more has been reported in 33 per cent of 100 patients who were given a rapid intravenous in-
jection of thiopentone (Stephen et al., 1953), after G.29.505 the blood pressure was unchanged in most instances. When a fall did occur it was both slight and transient and at no time did it exceed 30 mm Hg.

The fact that premedication and apprehension of the operation may cause a rise in cardiac output (Prime and Gray, 1952) probably explains the rather high initial outputs obtained in the majority of patients listed in table III. The decrease in output which followed most inductions was not excessive and, indeed, the trend previously reported (Payne, Gardiner and Verner, 1959; Löf, Verner and Payne, 1960), of high outputs falling and low outputs rising once anaesthesia was induced, seemed to be again operative.

The fourfold increase in skin blood flow with G.29.505 is similar to the increase in forearm blood flow described by Prime and Gray (1952) after the injection of thiopentone and attributed to a depressant effect of that drug on the vasomotor centre. Such an explanation, however, is unlikely in the case of G.29.505 since the blood pressure was largely unaltered and in the presence of an associated fall in cardiac output it must be assumed that the increase in skin blood flow occurs at the expense of blood flow elsewhere in the body at a site yet to be determined.

The most serious disadvantage of G.29.505 was the high incidence of venous thrombosis that followed its use. Thirty-three per cent of all patients given the drug developed this complication which, though less than the 40 per cent thrombosis rate with hydroxydione (Robertson and Williams, 1961), still compares very unfavourably with the low incidence associated with thiopentone.

A reduction in the strength of the G.29.505 solution from 5 per cent to 1 per cent did not prevent the occurrence of thrombosis. Of special interest is the observation that the reaction was nearly twice as common in men as in women and that the relationship apparently does not hold for thrombophlebitis which occurred in both sexes almost equally. The significance of the latter observation is, however, difficult to determine because of the small number of patients involved.

Before such a high incidence of venous thrombosis could be clinically acceptable, the advantages offered would have to be greatly in excess of those obtainable by other means. While there can be no doubt that the brevity of action, the respiratory stimulation and the absence of any significant circulatory disturbances are considerable assets of G.29.505, they are not sufficiently great to justify its use in its present form except in special circumstances. The possibility exists, however, that the solvent and not the active ingredient of the solution is the cause of the thrombosis; thus, if a more satisfactory solvent can be found, G.29.505 may yet establish itself in routine use.

ACKNOWLEDGMENTS

We are grateful to our nursing and surgical colleagues for their tolerance and understanding during the course of this investigation.

We are indebted to Professor C. V. Harrison for the histological reports, to Mr. R. W. G. Tennant for technical assistance, to Miss Diana Bryant and to Mr. C. R. Brecknall and his staff for the illustrations, and to Dr. P. Birkett of Geigy Pharmaceuticals Limited for advice and supplies of G.29.505.

REFERENCES


**SUMMARY**

Un dérivé de l'eugenol: G.29.505, fut administré par voie endo-veineuse pour induire l'anesthésie chez cent malades adultes pour des interventions allant d'interventions gynécologiques mineures à des pneumectomies et à des gastrectomies.

Le médicament, administré dans une solution à 5 pour cent, produisit une anesthésie rapide de courte durée associée à une stimulation respiratoire passagère, suivie d'une courte période d'apnée. On n'observa pas d'effets secondaires significatifs sur la fréquence et le rythme du cœur, sur la pression sanguine et le débit cardiaque. Il y eut cependant une augmentation de la circulation sanguine de la peau, mesurée à l'aide de la pléthysmographie digitale.

Trente-trois malades eurent une thrombose veineuse autour du lieu d'injection et cette fréquence est trop élevée pour justifier son emploi sauf dans des circonstances spéciales.

**ZUSAMMENFASSUNG**

Zwecks Herbeiführung der Narkose im Zusammenhang mit verschiedenen, von kleinen gynäkologischen Eingriffen bis zu Pneumektomien und Magenresektionen reichenden Operationen wurde bei hundert erwachsenen Patienten ein Abkömmling des Eugenols (Versuchsbezeichnung 29.505) intravenös gespritzt.

Bei Anwendung einer 5%igen Lösung konnte mit dem Pharmakon eine rasch einsetzende Narkose erzeugt werden, die von kurzer Dauer war und mit einer vorübergehenden respiratorischen Anregung einherging, auf die eine kurze apnoische Phase folgte. In bezug auf die Pulfsfrequenz und den Herzrhythmus sowie auf Blutdruck und auf Herzminutenvolumen wurden keine signifikanten Wirkungen beobachtet; hingegen ergab die fingerplethysmographische Untersuchung eine Vermehrung der kutanen Blutdurchströmung.

Bei dreiunddreißig Patienten entstand rings um die Injektionsstelle eine Venenthrombose. Dies ist nun allerdings ein zu hoher Prozentsatz, als daß die Anwendung des Mittels—aufier unter ganz besonderen Umständen—gerechtfertigt erschiene.