G.29.505: A COMPARISON WITH THIOPENTONE AND METHOHEXITONE*

BY

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SUMMARY

A brief account is given of the pharmacological properties of a new intravenous anaesthetic, G.29.505. In three series of 200 patients undergoing dental extractions, anaesthesia was induced respectively with G.29.505, thiopentone, and methohexitone, and maintained with nitrous oxide and oxygen. The time taken to settle the patient, the character of anaesthesia and recovery were noted, and the speed of recovery of consciousness and ambulation were recorded. It was found that G.29.505 had demonstrable advantages over thiopentone and methohexitone but it caused an unduly high incidence of venous thrombosis. Until the drug can be rendered non-irritant, methohexitone is considered the agent of choice for intravenous induction of anaesthesia for brief surgical procedures.

There has recently been developed a new non-barbiturate ultra short-acting intravenous anaesthetic—G.29.505. This drug is the diethylamide of 2 methoxy-4-allyl-phenoxyacetic acid. It is an oil which is almost insoluble in water but is soluble in most organic solvents. The preparation which is being investigated at present is an emulsion in 4 per cent lecithin with 5 per cent glucose.

Effects on the central nervous system.

In man the characteristic features of G.29.505 anaesthesia are the rapid onset and brief duration of anaesthesia and the rapid recovery. The dosage of G.29.505 has to be related to the body weight and in children a proportionately larger dose per kg body weight is required than in adults. During recovery of consciousness children frequently exhibit marked restlessness; in adults by contrast recovery is usually quiet. Postoperative "hangover" is rarely seen.

There is some evidence that in man G.29.505 produces a raising of the threshold of electrical excitation during anaesthesia. Bourret (1959) reported that in patients having electroconvulsive therapy it was necessary to increase current strength and duration to produce a convulsion when G.29.505 was used as the anaesthetic.

It has also been found that G.29.505 unlike the barbiturates does not have an anti-analgesic effect. Recent analgesimetry studies by Dundee and Hamilton (1961) have shown that sub-hypnotic doses of G.29.505 decrease sensitivity to somatic pain.

Effects on the respiratory system.

Intravenous administration of G.29.505 produces immediate respiratory stimulation which may be quite marked. This is followed by a period of up to half a minute respiratory depression or actual aspnoea. The hyperventilation commences suddenly about 20 seconds after commencement of injection, the minute volume being doubled or trebled. If repeated doses of G.29.505 are given in humans this respiratory stimulation recurs on every occasion. The degree of hyperventilation is reduced if a 2.5 per cent solution is employed (Corssen, personal communication, 1962).

Effects on the cardiovascular system.

In man, no fall in blood pressure or significant change in pulse rate can be demonstrated clinically, though there is sometimes a transient acceleration of the pulse as anaesthesia begins. By continuous recording from a cannula in the radial artery Payne (personal communication, 1962) has demonstrated a small immediate fall in blood pressure lasting not more than 10 or 20 seconds.

*Based on a paper delivered to the Annual General Meeting of the Association of Anaesthetists, Dublin, October 20, 1961.
and not usually exceeding 10–20 mm Hg. Payne also found that the changes in peripheral circulation during G.29.505 anaesthesia are comparable with those of any other anaesthetic.

Metabolism.

G.29.505 is rapidly broken down in the body by enzymatic processes whereby salts of acid amides are formed (Pulver, 1957). These quickly re-enter the circulation from tissues such as the brain and spinal cord, while amounts accumulated in fat depots are given up more slowly. No measurable quantities of unchanged G.29.505 are detectable in the blood during this phase but the presence of metabolites can be detected for several hours.

Results in man bear out this evidence of extremely rapid metabolism. The speed of recovery from clinical anaesthesia with G.29.505 has already been mentioned (Swerdlow, 1961b). Dundee and Hamilton (1961) during analgesiometry studies noted that G.29.505’s analgesic effect is also very transient. Even with large doses of G.29.505 the somatic response to pain had returned to normal after 20 to 35 minutes, whereas after comparable doses of thiopentone the time taken for response to somatic pain to return to normal is between 70 and 105 minutes.

G.29.505 has been shown to pass rapidly through the placenta. The maternal blood level is an important factor in determining the concentration in the infant’s blood. Owing to rapid disintegration the level of G.29.505 in the maternal blood never reaches the levels attained by the thiobarbiturates. The level of G.29.505 in the infant’s blood is remarkably low and is much lower than with corresponding doses of thiobarbiturates (Simmer and Beck, 1960).

It has already been reported that, in a dose of 3–5 mg/kg in adults or 4–6 mg/kg in children, G.29.505 will provide anaesthesia for brief operations and procedures such as dental extractions, incision of abscess, manipulation, etc, (Swerdlow, 1961a), and that supplemented with nitrous oxide and oxygen it has many advantages in dental anaesthesia (Swerdlow, 1961b). The present paper describes a comparative trial of G.29.505 with thiopentone and methohexitone.

PRESENT STUDY

Technique.

All patients were weighed on entering the dental surgery. A stopwatch was started at the moment of commencing injection of the anaesthetic and the various measurements recorded below were noted. Immediately after injection of the intravenous agent administration of nitrous oxide with 5 per cent oxygen was commenced (using a McKesson apparatus) and the concentration of oxygen was increased to 10 per cent and usually to 15 per cent as quickly as conditions would allow. Where ten or more teeth were being extracted in adults a nasopharyngeal tube was employed. At the completion of extractions 100 per cent oxygen was administered for a few moments before removing the nasal mask. As soon as the patient was fit to walk (with support) he was conducted to the recovery room, where he was kept until judged fit to go home. No premedication was used.

Two hundred patients received each of the three intravenous agents supplemented by nitrous oxide and oxygen. The methohexitone series was commenced after the other two series had been started but otherwise the three drugs were used in random order and without selection.

General remarks.

Under thiopentone or methohexitone anaesthesia alone it is not possible to perform more than the briefest of surgical procedures unless a dose is used which results in undue delay in recovery of consciousness and ambulation. Hence it was not possible to compare G.29.505 with the two barbiturates given alone. In order to carry out a comparison of these three intravenous anaesthetics, therefore, all the patients in this study received nitrous oxide and oxygen to supplement the intravenous agent.

When thiopentone or methohexitone is used for induction in dental anaesthesia, a balance has to be struck between depth of anaesthesia and speed of recovery. If too little barbiturate is given, application of the nasal mask and settling under nitrous oxide are difficult; if too much is given recovery is unduly delayed. It was found in the present study that with thiopentone in adults a dose of 2–4 mg/kg and in children 3–5 mg/kg was optimal. With methohexitone the optimal
dosage was 0.8–1.1 mg/kg (i.e. 5–7 mg/stone) in adults and 0.9–1.2 mg/kg in children. The dosage of G.29.505 used was 2–4 mg/kg in adults and 3–6 mg/kg in children. Methohexitone was used in 1 per cent solution; thiopentone in 2½ per cent or 5 per cent solution. Throughout this work patients up to and including 15 years of age are classified as “children”.

Using an induction dose of 2 mg/kg thiopentone or 0.8 mg/kg methohexitone the patient not infrequently objected to the nasal mask being applied, and the subsequent settling with nitrous oxide and oxygen was often rather trying. Similarly, when a nasopharyngeal tube was employed it could be introduced immediately after injection of G.29.505 but this was more difficult and upsetting with the smaller doses of thiopentone or methohexitone. Patients who received thiopentone or methohexitone sometimes remembered application of the nasal mask but those who had G.29.505 rarely remembered this happening.

The surgical progress varied, of course, according to the difficulty of the extractions and the “resistance” of the patients, but it was our overall impression that patients were easier to manage with G.29.505 than with thiopentone or methohexitone; this is presumably related to the lack of anti-analgesic effect with G.29.505. Except for the period immediately after injection of the drugs, no clinical degrees of respiratory depression were noted.

Patients and Nature of Operations

Distribution of patients.

On the whole the distributions of the patients on whom each drug was used are reasonably similar as regards sex, age, weight, and mean number of teeth extracted. The exception was in the children who received methohexitone. This group exhibited a higher proportion of males, a lower average number of teeth extracted, a higher proportion of older children, and (as would be expected) a higher average weight than in the children who received thiopentone or G.29.505. Table I shows the distribution of the patients according to age and intravenous agent administered.

Table II analyzes the number of teeth extracted in the patients receiving each of the three drugs.

Observations

Significance of results.

In the tables which follow, the degree of significance of difference found is indicated under column 1 as shown:

N.S. = Not significant at 5% level.

+ = Significant at 5% level.

++ = Significant at 1% level.

+++ = Significant at 0.1% level.

Column 2 gives the results of a test to determine which drugs show a significant difference from the others.

In column 2 the drugs are entered in order of magnitude of the mean, that with the smallest

Table I

Number and age of patients.

<table>
<thead>
<tr>
<th>Age</th>
<th>G.29.505</th>
<th>Thiopentone</th>
<th>Methohexitone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-10 years</td>
<td>38</td>
<td>41</td>
<td>35</td>
</tr>
<tr>
<td>11-15 years</td>
<td>31</td>
<td>34</td>
<td>44</td>
</tr>
<tr>
<td>Total children</td>
<td>69</td>
<td>75</td>
<td>79</td>
</tr>
<tr>
<td>Adults:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>16-29 years</td>
<td>48</td>
<td>46</td>
<td>47</td>
</tr>
<tr>
<td>30-39 years</td>
<td>53</td>
<td>45</td>
<td>45</td>
</tr>
<tr>
<td>&gt; 39 years</td>
<td>28</td>
<td>34</td>
<td>28</td>
</tr>
<tr>
<td>Not stated</td>
<td>2</td>
<td>—</td>
<td>1</td>
</tr>
<tr>
<td>Total adults</td>
<td>131</td>
<td>125</td>
<td>121</td>
</tr>
<tr>
<td>Grand total</td>
<td>200</td>
<td>200</td>
<td>200</td>
</tr>
</tbody>
</table>
G.29.505: A COMPARISON WITH THIOPENTONE AND METHOHEXITONE

TABLE II

Number of teeth extracted.

<table>
<thead>
<tr>
<th>Number of teeth extracted</th>
<th>G.29.505</th>
<th>Thiopentone</th>
<th>Methohexitone</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of cases</td>
<td>Mean No. of teeth</td>
<td>No. of cases</td>
</tr>
<tr>
<td>Children:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-10</td>
<td>69</td>
<td>5.5</td>
<td>75</td>
</tr>
<tr>
<td>11-20</td>
<td>37</td>
<td>15.5</td>
<td>29</td>
</tr>
<tr>
<td>&gt; 20</td>
<td>21</td>
<td>23.1</td>
<td>16</td>
</tr>
<tr>
<td>Adults:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-10</td>
<td>73</td>
<td>4.4</td>
<td>80</td>
</tr>
<tr>
<td>11-20</td>
<td>37</td>
<td>15.5</td>
<td>29</td>
</tr>
<tr>
<td>&gt; 20</td>
<td>21</td>
<td>23.1</td>
<td>16</td>
</tr>
</tbody>
</table>

The mean being on the left. The significance or otherwise (at the 5 per cent level) of the differences between the three drugs is indicated by using italic characters for those letters whose mean values do not differ significantly. Thus G TM indicates that G.29.505 (with the smallest mean) differs significantly from thiopentone and methohexitone and that the latter two drugs are not significantly different from each other.

Dosage.

Table III shows the overall mean dosages of the three drugs, the child and adult doses being given separately. With each drug the induction dose proved inadequate in a small number of patients. In compiling this table, doses which proved insufficient to produce complete unconsciousness were omitted.

The ratio (in adults) of potency between methohexitone and thiopentone is 3.4:1. The ratio of the equivalent clinical doses of G.29.505 to methohexitone is 3.9:1 and of G.29.505 to thiopentone 1.1:1.

Time of commencement of extractions.

The interval between injection of the intravenous drug and commencement of extractions indicates the time taken to settle the patient for dental surgery. The average time from commencement of injection of the anaesthetic to commencement of extractions varied with the number of teeth being extracted and with the drug employed for induction. The details are given in Table IV together with the statistical significance of the differences.

Recovery.

The mean times for the interval between removing the nasal mask and full recovery of consciousness are shown in Table V. In adults the time for recovery of full consciousness was similar with thiopentone, methohexitone and G.29.505. In children, however, recovery was significantly quicker when methohexitone was used for induction and also the time to waking was more consistently low than with the other two drugs. However, the children who received methohexi-
Waking time.

<table>
<thead>
<tr>
<th>Group and number of teeth extracted</th>
<th>Mean waking time (min)</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>G.29.505</td>
<td>Thiopentone</td>
</tr>
<tr>
<td>Children</td>
<td>2.01</td>
<td>2.00</td>
</tr>
<tr>
<td>Adults</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-10</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 20</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

For explanation of significance see text.

Vomiting.

The incidence of nausea, retching and vomiting is shown in table VII. No explanation can be offered for the reversal of the nausea:vomiting ratio with thiopentone.

It must be pointed out that the nitrous oxide and oxygen administered with the intravenous agent will be partly responsible for the nausea and vomiting. Bodman, Morton and Thomas (1960) found that the incidence of vomiting in unpremedicated patients undergoing minor procedures under nitrous oxide oxygen alone ranged from 5.4 per cent for short procedures to 40.8 per cent for anaesthetics lasting over 6 minutes.

Venous thrombosis.

Unfortunately, G.29.505 has one serious drawback. In an appreciable proportion of cases it gives rise to venous thrombosis and thrombo-phlebitis. In the present 200 patients who received G.29.505 there have been twelve instances of this, but there may well have been

<table>
<thead>
<tr>
<th>Group and number of teeth extracted</th>
<th>Mean time (min)</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>G.29.505</td>
<td>Thiopentone</td>
</tr>
<tr>
<td>Children</td>
<td>18.69</td>
<td>24.64</td>
</tr>
<tr>
<td>Adults</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-10</td>
<td>14.44</td>
<td>16.63</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 20</td>
<td>13.66</td>
<td>27.66</td>
</tr>
</tbody>
</table>

For explanation of significance see text.

<table>
<thead>
<tr>
<th>Age Group</th>
<th>G.29.505 Nausea</th>
<th>G.29.505 Vomiting</th>
<th>Thiopentone Nausea</th>
<th>Thiopentone Vomiting</th>
<th>Methohexitone Nausea</th>
<th>Methohexitone Vomiting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children</td>
<td>11.9</td>
<td>4.4</td>
<td>4.1</td>
<td>18.9</td>
<td>17.5</td>
<td>3.8</td>
</tr>
<tr>
<td>Adults</td>
<td>6.7</td>
<td>4.5</td>
<td>3.9</td>
<td>10.2</td>
<td>8.3</td>
<td>3.3</td>
</tr>
</tbody>
</table>
other mild localized thromboses which did not cause any incapacity and which patients did not report. Of the twelve thromboses reported, two were severe with swelling of arm and forearm, tenderness up the vein, and tenderness of axillary and/or epitrochlear glands, and necessitated loss of time from work. Four were of moderate severity and extent. The remaining six were localized to the site of injection. All cleared up readily with conservative treatment. No instance of venous thrombosis has been encountered in young children; the youngest patient with thrombophlebitis was 15 years old. None of the patients given thiopentone or methohexitone reported thrombophlebitis and one thiopentone patient only reported localized thrombosis.

DISCUSSION

No previous comparison of G.29.505 with barbiturates has been reported. A number of workers have, however, carried out comparative studies of thiopentone and methohexitone. Most of these investigations showed no significant difference in "waking" time with the two drugs but a marked difference in "going home" time. Redish et al. (1958), who noted the time at which the Romberg test became negative, found that this also was earlier with methohexitone. It must be noted that the use of nitrous oxide and oxygen in addition to the intravenous agents will influence the recovery times, but it will have a bigger effect on the waking time than on the going home time.

The relative potency of thiopentone and methohexitone has been studied by various workers. Egbert, Oech and Eckenhoff (1959) found in volunteers that the average dose of thiopentone required to produce unconsciousness was about two and a half times that of methohexitone, while Redish et al. (1958) consider that methohexitone is three times as potent as thiopentone. Other investigators have found that the plasma concentration of thiopentone to produce a given level of anaesthesia (using e.g. control of anaesthetic depth) was about twice that required with methohexitone (reported by Coleman and Green, 1960). The ratio of the dosage of the two drugs required for induction of anaesthesia found in the present work is similar to that of previous reports.

Apnoea and respiratory depression have been reported with methohexitone by a number of workers. Wyant and Chang (1959) and Wyant, Dobkin and Aasheim (1957) found a high incidence of apnoea with methohexitone, while Taylor and Stoelting (1960) reported apnoea of up to 3 minutes duration with this drug. On the other hand, Coleman and Green (1960), who employed methohexitone in dental anaesthesia under similar conditions to those of the present study, report an absence of marked respiratory depression. The lack of apnoea in the present work and in that of Coleman and Green may be accounted for by the smaller dosage used and by the omission of premedication. It has been shown that apnoea and respiratory depression will be more obvious when opiate premedication has been employed (Eckenhoff and Helrich, 1958) or when large doses of barbiturates are employed (Dobkin and Wyant, 1957; Swerdlow, 1958).

Other "respiratory disturbances" have also been reported with methohexitone. Stoelting (1957) found one instance of coughing and one of laryngospasm with methohexitone in 285 patients, but in a later and much larger series (Taylor and Stoelting, 1960) a 3 per cent incidence of hiccough was noted following induction, while coughing occurred in 1 per cent and laryngeal spasm in a slightly lower proportion of patients. Dundee and Moore (1961), who compared 4 mg/kg thiopentone (5 per cent solution) with 1.6 mg/kg methohexitone (2 per cent solution), found a significantly higher inci-
idence of coughing, hiccough and laryngeal spasm after methohexitone.

Under the essentially clinical conditions of the present study it was not possible to study blood pressure changes. Redish et al. (1958) found a significant rise in systolic and diastolic blood pressure during induction with thiopentone and a less marked rise in diastolic pressure with methohexitone. During recovery a significant fall in blood pressure occurred with both drugs. Dundee and Moore (1961) found that thiopentone caused a markedly higher incidence of hypotension than an equivalent dose of methohexitone. Taylor and Stoelting (1960) also reported an appreciable but transient fall in blood pressure with methohexitone.

The dosage of methohexitone used in the present work is similar to that used in dental anaesthesia by Coleman and Green (1960) and by Harris and Goldman (1960). The former workers found that 84 per cent of patients could go home within 20 minutes of injection of the anaesthetic. They do not state the number of teeth extracted nor the time taken for extraction. It would appear that the average number of extractions was less than in the present work.

It is difficult to find data regarding the incidence of venous thrombosis with thiopentone and methohexitone in the literature. Dundee and Moore (1961) report venous thrombosis in 6 out of 100 patients given thiopentone and in 5 out of 100 given methohexitone. Taylor and Stoelting (1960) found no instance of thrombophlebitis in 3,340 patients to whom methohexitone was administered. It is obvious, however, that severe or even moderate thrombophlebitis is uncommon with these agents. The new drug, G.29.505 has the advantage over the other two of lack of anti-analgiesic effect, lack of cardiovascular depressant effects, and of early recovery of full co-ordination. It has for the time being the disadvantage of causing a clinically unacceptable incidence of venous irritation.

ACKNOWLEDGMENTS

I am indebted to Mr. H. D. Levy, L.D.S., for his cooperation, and to Mrs. J. M. Warren, R.N.N., and Mrs. D. Moore, S.R.N., for assistance. My thanks are also due to Mr. R. H. Daw, B.Sc., F.F.S., for the statistical analysis, Dr. J. P. Birkett of Geigy Pharmaceutical Co. Limited, for generous supplies of G.29.505 and for much useful advice and help and to Miss B. Howland for secretarial assistance. Finally, I am grateful to Eli Lilly & Co. for providing supplies of methohexitone (Brevital).

REFERENCES


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SOMMAIRE
Compte-rendu bref des propriétés pharmacologiques de ce nouveau produit. Chez trois séries de patients devant subir des avulsions de dents, l'anesthésie fut produits soit par le G.29.505, soit par thiopentone soit par méthohexitone et maintenue ensuite avec de l'oxyde nitreux et de l'oxygène. Le temps nécessaire pour apaiser le patient, le caractère de l'anesthésie et du retour à l'état normal furent notés ainsi que la rapidité du rétablissement de l'état de conscience et de la capacité de marcher. Il fut constaté que le G.29.505 présente des avantages manifestes par comparaison avec le thiopentone et le méthohexitone, mais qu'il provoquait un nombre excessif de thrombose veineuse. En attendant qu'on parvienne à rendre le nouveau produit non-irritant, le méthohexitone est considéré comme la substance de choix pour l'obtention d'anesthésies par voie intra-veineuse pour des interventions chirurgicales brèves.

ZUSAMMENFASSUNG

BOOK REVIEW

Veterinary Anaesthesia and Analgesia (5th edition).
By J. G. Wright and L. W. Hall. Published by Baillière, Tindall and Cox, London. Pp. 408; 119 illustrations. Price 37s. 6d.

Since its first edition in 1941, Wright's Veterinary Anaesthesia has been the standard book of reference for veterinary surgeons administering anaesthetics in general practice and the standard textbook for veterinary students. The practical guidance this small book has always offered has been invaluable on many occasions.

During the last decade, considerable advances have been made in the practice of veterinary anaesthetic and analgesic techniques and the modern approach to the subject is given an introduction in this new 5th edition, now under the joint authorship of Professor J. G. Wright and Dr. L. W. Hall. It is, therefore, a very welcome and important publication for the veterinary profession.

Generally accepted principles of anaesthetic practice will, of course, be well known to anaesthetists of the medical profession. Each species of animal, however, presents special anaesthetic problems associated with differences in anatomical and physiological make-up and with varying pharmacological responses to anaesthetic agents and ancillary drugs. Medical anaesthetists often anaesthetize animals for purposes of anaesthetic and/or surgical researches, and an increasing number of species are being used in this way. The animals dealt with in this book are, horses, cattle, sheep, goats, pigs, dogs and cats. The first chapter, entitled "General Considerations", describes some of the problems each of these present, when considering selection of an anaesthetic technique.

The first section of this book describes techniques of local, regional and spinal analgesia. The section dealing with general anaesthesia is introduced by a chapter on premedication and basal narcosis. The pharmacological actions of various drugs employed and relevant aspects of physiology are discussed. One chapter is devoted to the relaxation of skeletal muscles and another to anaesthesia for intrathoracic surgery, including cardiac surgery, and a technique for hypothermia in the dog. The final chapter deals with some accidents and emergencies which may be encountered.

Specialist anaesthetists should not expect too much from this book, since it is small and cannot be expected to cover completely the whole subject of anaesthesia in animals even as it is at present understood. Nevertheless, it contains a great deal of useful information for all who wish to anaesthetize animals.

B. M. Q. Weaver