THE ANALGESIC ACTION AND NEURONAL MECHANISM OF PROPANIDID
(Human and Animal Studies)

TATSUSHI FUJITA, HIDEAKI ISHIKURA AND YASUHARU KITANI

SUMMARY

Subanaesthetic doses of propanidid, thiopentone and ketamine were given to volunteers at 30 min intervals. Change in the pain threshold values were observed by means of the earlobe algesimeter. The pain threshold value sharply rose 30 sec after propanidid 1 mg/kg but returned to control values in 2 min. With ketamine 0.1 mg/kg, the pain threshold rose in 2 min and the rise was maintained over 5 min. Thiopentone 0.5 mg/kg showed no significant change. Further, in order to clarify this analgesic effect, experiments were performed on both intact and cereau isolé rabbits to observe the effects of propanidid on the sensory pathways of the olfactory and visual systems. Propanidid had less inhibitory effect on the monosynaptic than on the polysynaptic reflex thus differing from the effects of barbiturates which inhibit both mono- and polysynaptic reflexes. Study of the recruiting response on the cortex after stimulation of the centre-median nucleus indicated that propanidid transiently inhibits the thalamocortical pathway. The neuronal mechanisms are evidence of the existence of an analgesic property of propanidid.

Thuillier and Domenjoz (1957) reported the results of pharmacological research on the substance, 2-methoxy, 4-allyl-phenoxyacetate-N, N-diethylamide (G.29 505), pointing out its characteristics as an anaesthetic having an ultra-short duration of action and a stimulant action on respiration. Further development, however, was suspended because of serious side-effects on the kidneys and the vascular system, mainly attributable to its solvent.

An eugenol derivative similar to G.29 505 is the active drug in propanidid, the solvent being the ionic surface active agent, cremophor EL which was later modified to ORPE in order to reduce histamine release.

Propanidid has an extremely short duration of anaesthetic action and has advantages over conventional intravenous anaesthetics. Dundee and Hamilton (1961) reported on the analgesic property of G.29 505 but the analgesic action of propanidid has not been confirmed. Dundee and Clarke (1965) demonstrated that there was a momentary analgesic effect after injection of subanaesthetic doses of propanidid, as shown by the response to somatic pain caused by pressure on the tibia, and an absence of the antanalgesic action such as can be observed after injection of barbiturates. Howells and associates (1964) could not confirm this clinically although Goldman and Kennedy (1964) suggested that propanidid might have some analgesic action. Fujita and colleagues (1968) reported that propanidid 8mg/kg injected intravenously, allayed pain caused by pinching the skin with Kocher forceps for a period of 60 to 120 sec. Kubota and associates (1968) reported that propanidid appeared to have some clinical useful analgesic effect because of the absence of reaction to tooth extraction. Thus, it is not difficult to suppose that propanidid has some analgesic action.

A comparative study was made of the analgesic effects of propanidid, thiopentone and ketamine in volunteers who were given subanaesthetic doses amounting to one-tenth of that required to induce sleep. Earlobe algesimetry (Siker, Wolfson and Stewart, 1966) was used.

In addition, the authors investigated the effects of propanidid on neuronal mechanisms in normal and spinal rabbits. In order to observe the effects of propanidid on sensory pathways, the olfactory and visual systems were studied. Following Hoffmeister and Wirth (1963) and Wirth and Hoffmeister (1964, 1965), TATSUSHI FUJITA, M.D., PH.D.; HIDEAKI ISHIKURA, M.D., PH.D.; YASUHARU KITANI, M.D.; Department of Anesthesiology, Gunma University Hospital, Maebashi, Gunma, Japan.
who attempted to investigate the specific effect of propanidid on the electroencephalogram at different stages of anaesthesia, experiments were conducted in cats whose spinal motor reflex was slightly depressed with chloralose-urethane. These authors reported that the effect of propanidid was not only, after a short period of inhibition, to enhance the monosynaptic patellar reflex but also to strengthen temporarily the polysynaptic reflex ipsilaterally. In contrast, hexobarbitone under the same conditions inhibited both the monosynaptic and polysynaptic reflexes. This implies a difference between the effects on neuronal mechanisms, of propanidid and barbiturates. Further, in order to clarify the question of the analgesic property of propanidid, its effects on the thalamocortical pathway were investigated by monitoring the recruiting response on the neocortex following electrical stimulation of the centre-median nucleus.

METHOD

Algesimetry.

The subjects were healthy volunteers, seven male and two female aged 22–30. There were five doctors, three medical students and one nurse. However, one of them experienced transitory sickness after propanidid and the experimental results of this subject have been excluded. Experiments were conducted with the volunteers lying on a couch in a recovery room in which the temperature and humidity were maintained at 25°C ± 1°C and 55% ± 5% respectively. An automatic monitoring recorder was applied to each subject to measure pulse, arterial pressure and respiratory rates continuously. The earlobe terminal of the algesimeter (Siker, Wolfson and Stewart, 1966) was fixed lightly on the right earlobe while the “stop” terminal was operated by the volunteer’s left hand (fig. 1). An inductorium varied its capacitance by a clock-work motor and provided an electric pulse of 60 Hz of alternating current on the earlobe. Initially a sensation of vibration is felt altering to pinprick as the voltage is gradually raised.

The drugs used were propanidid 1 mg/kg, thiopentone 0.5 mg/kg and ketamine 0.1 mg/kg, (each amount being 1/10 of the minimum sleep dose), each diluted to 0.1 ml/kg with physiological saline and administered in random order by the double blind method. An infusion of physiological saline was first set up in a right elbow vein of the subject and then each drug was injected in precisely

Fig. 1. Application of Siker’s earlobe algesimeter to the right earlobe of a volunteer.

30 sec via the rubber part of the infusion set. The threshold value of the pain was measured 30 sec, 1 min, 2 min, 3 min, 4 min and 10 min after injection. Base line values had been previously determined by application of the stimulus at one minute intervals for 30 min. The subject was required to press the “stop” button as soon as he or she felt the first sensation of pain, the reading at that point being termed the minimum pain threshold (m.p.t.). The stimulus was increased until it became unbearable, the reading at that point being the maximal tolerable pain (M.T.P.). Subjects were not informed of those readings. About 30 min later, the second agent was administered and the procedure repeated, the third drug being given 30 min after the second and the procedure again repeated. Care was taken that the order of administration of the drugs differed in all the volunteers.

Animal experiments.

Adult rabbits weighing 2.2–2.5 kg had endotracheal cannulation performed through a tracheostomy under ether anaesthesia. Two groups of five rabbits
ANALGESIC ACTION AND NEURONAL MECHANISM OF PROPANIDID 811

were studied for the response to stimulation of the olfactory and visual tracts and a further two rabbits were investigated for stimulation of centre-median nucleus, being conditioned in cerveau isolé, using the method of Bueno, Bost and Himwich (1968). The head was fixed using a device designed by the Tokyo University Brain Research Institute the animal being immobilized by gallamine with artificial ventilation. After removal of the overlying skull, the dura was opened to expose the brain. A silver needle electrode, 1 mm in diameter, was placed on the olfactory bulb, and coaxial electrodes, 0.5 mm in diameter, inserted in the amygdala. In the other group of five rabbits electrodes were inserted into both the corpus geniculatum and the cortical visual area according to the map of Sawyer, Green and Everett (1954).

The position of the tip of electrode in the amygdala was guided by the discharge arising from the lesion in the nucleus caused by the needle tip. At the end of the experiment, formalin was injected via the carotid artery to fix the brain in order to confirm the location of the electrode.

A 7-10 mm length of nasal bone was ablated from the nasion to the proboscis, taking care that the mucous membrane was not damaged, and then the coaxial electrode was located where the largest amplitude of induced electric potential was recorded. Thereafter the electrode was fixed for electrical stimulation of the olfactory mucosa. Rectangular pulses were used to stimulate the olfactory mucosa. In the group of rabbits in which the visual evoked response was studied the retina was stimulated by flashes of light using a photic stimulator (Nihon Koden MSP-3). The recruiting response was obtained from the motor cortex caused by stimulation of the centre-median nucleus on the left side with low frequency (6Hz, 4V) in two rabbits being conditioned in cerveau isolé in order to preclude ascending impulses through the reticular formation. As a control the right motor cortex and hippocampal discharges were monitored simultaneously. The electrical potentials from the amygdala, the olfactory bulb, the corpus geniculatum laterale and the cortical visual area were amplified by a CR combined-type amplifier and recorded on an oscilloscope.

After the animals regained consciousness completely from anaesthesia, the authors investigated the potentials on continuous stimulation before and after 100 mg/min of 5% propanidid, injected via the ear vein.

In order to prevent vibration of the brain caused by artificial ventilation and pulsation of vessels, and also short circuit of the electrode on the olfactory bulb caused by outflow of the cerebrospinal fluid during recording, cerebrospinal fluid was removed through opening of the cisterna magna. The surface of the exposed brain was covered with fluid paraffin, warmed to body temperature so as to prevent its drying.

RESULTS

Algesimetry on volunteers

On vital signs.

After injection of each drug all the subjects felt pleasantly drowsy, but this sensation passed off in 30 sec to 2 min after propanidid, 30 sec to 5 min after thiopentone, and 1 to 7 min after ketamine. However, with each drug all subjects maintained full consciousness. There was no change in the arterial pressure, except in four subjects in whom injection of ketamine caused a rise of 5% to 10%. Heart rate and respiratory rate were unaffected. One subject felt sick after propanidid and the experiment was abandoned as previously mentioned.

On pain threshold

The average pre-drug value of m.p.t. was 2.13±0.18 V and M.T.P. was 2.96±0.11 V before thiopentone, 1.93±0.20 V and 2.91±0.25 V before propanidid and 1.95±0.13 V and 3.12±0.31 V before ketamine as shown in table I (fig. 2). These values denoted that the average pre-drug values for minimum pain threshold and maximal tolerable pain were not significantly different among the drug groups.

After thiopentone, there was a slight upward tendency in both threshold values reaching a peak at 3 min after injection, but there was no significant statistical difference from the control values in either case.

After propanidid, both m.p.t. and M.T.P. rose to the highest points 30 sec after injection, these elevations being significantly different from the initial threshold value (P<0.05). However, in 2 min they recovered almost to the baseline values.

After ketamine, both m.p.t. and M.T.P. were significantly elevated at 2 min. These significant rises were still sustained at 5 min.

Neuronal mechanism of propanidid

Inhibition of synapses in the olfactory pathway.

Propanidid caused complete inhibition of potentials evoked in the amygdala, the terminal nucleus,
TABLE I. Pain threshold expressed in volts (mean and SE) after subanaesthetic doses of thiopentone, propanidid and ketamine (average of 8 volunteers).

<table>
<thead>
<tr>
<th></th>
<th>control</th>
<th>30'</th>
<th>1'</th>
<th>2'</th>
<th>3'</th>
<th>4'</th>
<th>5'</th>
<th>10'</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thiopentone</td>
<td>2.13</td>
<td>2.41</td>
<td>2.49</td>
<td>2.55</td>
<td>2.77</td>
<td>2.52</td>
<td>2.50</td>
<td>2.26</td>
</tr>
<tr>
<td></td>
<td>±0.18</td>
<td>±0.23</td>
<td>±0.23</td>
<td>±0.30</td>
<td>±0.40</td>
<td>±0.15</td>
<td>±0.15</td>
<td>±0.23</td>
</tr>
<tr>
<td>Propanidid</td>
<td>1.93</td>
<td>2.89*</td>
<td>2.76*</td>
<td>2.41</td>
<td>2.25</td>
<td>2.15</td>
<td>2.15</td>
<td>2.21</td>
</tr>
<tr>
<td></td>
<td>±0.20</td>
<td>±0.34</td>
<td>±0.35</td>
<td>±0.41</td>
<td>±0.34</td>
<td>±0.26</td>
<td>±0.22</td>
<td></td>
</tr>
<tr>
<td>Ketamine</td>
<td>1.95</td>
<td>2.33</td>
<td>3.02*</td>
<td>3.12**</td>
<td>2.85*</td>
<td>2.83*</td>
<td>2.72*</td>
<td>2.65</td>
</tr>
<tr>
<td></td>
<td>±0.13</td>
<td>±0.36</td>
<td>±0.40</td>
<td>±0.36</td>
<td>±0.36</td>
<td>±0.33</td>
<td>±0.28</td>
<td>±0.28</td>
</tr>
</tbody>
</table>

Minimum pain threshold (M.T.P)

<p>| | | | | | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Thiopentone</td>
<td>2.96</td>
<td>3.23</td>
<td>3.28</td>
<td>3.23</td>
<td>3.28</td>
<td>3.18</td>
<td>3.30</td>
</tr>
<tr>
<td></td>
<td>±0.11</td>
<td>±0.25</td>
<td>±0.25</td>
<td>±0.23</td>
<td>±0.17</td>
<td>±0.18</td>
<td>±0.21</td>
</tr>
<tr>
<td>Propanidid</td>
<td>1.91</td>
<td>3.96*</td>
<td>3.60</td>
<td>3.60</td>
<td>3.03</td>
<td>3.05</td>
<td>3.00</td>
</tr>
<tr>
<td></td>
<td>±0.25</td>
<td>±0.45</td>
<td>±0.38</td>
<td>±0.33</td>
<td>±0.33</td>
<td>±0.33</td>
<td>±0.26</td>
</tr>
<tr>
<td>Ketamine</td>
<td>3.12</td>
<td>3.37</td>
<td>3.93</td>
<td>4.10*</td>
<td>3.90</td>
<td>4.05*</td>
<td>4.20**</td>
</tr>
<tr>
<td></td>
<td>±0.31</td>
<td>±0.14</td>
<td>±0.48</td>
<td>±0.45</td>
<td>±0.41</td>
<td>±0.44</td>
<td>±0.35</td>
</tr>
</tbody>
</table>

Maximal tolerable pain (M.T.P.)

* P < 0.05 compared with the control value
** P < 0.01 compared with the control value
(No star mark means statistically non-significant)

by olfactory stimulation from 1 to 2 min and sometimes up to 4 min. In contrast, potentials evoked in the olfactory bulb were depressed by a maximum of about 50% during the same period. Figure 3 shows a representative tracing and figure 4 depicts the different degrees of inhibition based on the results of several experiments in five rabbits.

Inhibition of synapses in the visual pathway.

The potentials evoked by stimulation of the retina by flashes of light were recorded from both the nucleus geniculatum laterale, an intermediate nucleus, and the cortical visual area, the terminal nucleus. There was again less inhibition of the primary monosynaptic response in the specific pathway one to two min after propanidid than of the secondary polysynaptic response through the non-specific pathway (fig. 5).

Recruiting response.

The recruiting response which arises in the ipsilateral cortex as a result of a low-frequency stimulation applied to the non-specific thalamic nucleus,
especially to the centre-median nucleus, disappeared after propanidid and this indicates suppression of the universal activator system as well as the reticular formation. Propanidid caused complete disappearance of the response in 2.5 min. There was gradual restoration of the response to control amplitudes in 19 to 21 min (fig. 6).

Figure 6 shows records from the left motor cortical area, the left centre-median nucleus being stimulated, and from the right motor cortical area which served as the control. Discharges from the hippocampus were monitored in order to verify the state of consciousness; these discharges disappeared from 1 to 10 min after injection of propanidid. As in the cerveau isolé preparation the action of the ascending reticular activating system was obtunded, this inhibition shows that propanidid has a direct action on the non-specific thalamic pathway.

DISCUSSION

Hardy, Wolff and Goodell (1947) undertook studies of pain using the radiant heat method. This method has yielded conflicting results in the hands of other workers and has been used to a limited extent. Harris and Blockus (1952) using the method of electrical stimulation of tooth pulp affirmed that the analgesic
property of a drug could be defined as that which could raise pain threshold more than no treatment or the application of a placebo.

Robson, Davenport and Sugiyama (1965) showed that the superficial pain threshold to a thermal stimulus and the pain threshold to tibial pressure diverged in subjects given low doses of thiopentone.

The earlobe algesimeter, originally described in 1954 by Siker, Swerdlow and Foldes and modified in 1965 (Siker, Wolfson and Stewart), is convenient for the measurement of the pain threshold value because the subject is able to press the “stop” button while conscious and therefore it is possible to compare the analgesic effects of drugs given in subanaesthetic doses. The pain threshold may differ from person to person depending upon the resistance, inductance and capacitance of each earlobe, but immediately before the experiment, the readings were of a similar order to those reported by Siker, Wolfson and Stewart (1966) in their description of method. In 16 volunteers Siker and his colleagues found a mean value of 2.12 ± 0.77 V without significant change over a period of 140 min. From the authors’ pre-drug measurements on Japanese subjects, the thresholds obtained here were almost the same. In this experiment propanidid was used in an amount equal to one tenth of the minimum sleeping dose, and had minimal effect on consciousness apart from a feeling of slight sleepiness which did not interfere with the subject’s capacity to operate the “stop” button.

It is possible that the doses of the drugs employed were not equipotent. Problems arising from the excretion and accumulation of the drugs were minimized in this experiment by varying the order of administration and by taking care to ensure that unless the threshold value had reverted to the control value, the experiment did not continue.

In the case of propanidid, the pain threshold values of both m.p.t. and M.T.P. showed a characteristic pattern of rising to the highest point 30 sec after injection and returning to the baseline level in 2 min and nearly to the control level in 4 min. No antanalgesia was demonstrated. If elevation of pain threshold value could be equated with the clinical rise in the pain threshold value, one could say that analgesic effects appeared 30 sec after injection. This agrees with clinical experience that the analgesic action of propanidid is of rapid onset and short duration.

In the case of ketamine, the pain threshold value rose 2 to 5 min after injection. As expected from the characteristics of the drug, its effect lasted longer and was greater than that of propanidid. Thiopentone did not cause a significant rise in the threshold value nor was there evidence of antanalgesia. It will be recalled that Robson, Davenport and Sugiyama (1965) demonstrated that the threshold to thermal pain rose after thiopentone whilst threshold to tibial pressure pain decreased.

Duke-Elder (1968) introduced the idea of a “just noticeable difference” (JND) on visual sensation where the strength of light can be distinguished in gradations. This can be applied to classify the relationship between intensity of pain and increase in strength of stimulus in linear fashion. The present authors used two end points with a gradual increase in stimulus, the minimum pain threshold (m.p.t.) corresponding to “1 JND”, and the point of the maximal tolerable pain (M.T.P.), the changes in voltage between these two points being measured. Dundee and Moore (1960) recommended this discriminated evaluation of pain, using the first appreciation of pain and then unbearable pain, in order to preclude any disturbance of consciousness induced by anaesthetics even though given in subanaesthetic dose. The algesimetre is so designed that 05-20 V can be applied to the earlobe, and the subjects were considered capable of discerning the intensity of pain as the voltage was gradually increased. Both values for m.t.p. and M.T.P. should be estimated simultaneously to determine the effect of amounts of anaesthetics which might affect consciousness even to a limited degree, thus excluding interference with the discrimination procedure.

Hoffmeister and Wirth (1963) compared the effects of propanidid and hexobarbitone on the electroencephalogram. They concluded that the pattern was similar with both agents, the only difference being the time course. The duration of anaesthesia with hexobarbitone was prolonged by the addition of chlorpromazine, and similar prolongation of anaesthesia was also observed with propanidid. This suggests that propanidid primarily inhibits the cortex and to a lesser degree the reticular formation. Further Hoffmeister and Wirth (1963) studied the effect of reserpine in prolonging anaesthesia and reported that it did not prolong propanidid anaesthesia but did prolong barbiturate anaesthesia. This may be explained on the basis that because propanidid causes less inhibition of the reticular formation, the effect of reserpine on cortical depression does not prolong anaesthesia.

In order to clarify the characteristics of the neuro-
nal effects of propanidid and its relation to the analgesic effects, the authors present evidence of the inhibition of synapses in the sensory pathway of the olfactory and visual systems. Responses in the olfactory bulb and the amygdala caused by electrical stimulation of the olfactory mucosa denoted incomplete inhibition of the monosynaptic pathway but complete inhibition of the polysynaptic pathway by propanidid. This agreed with the other results, as obtained in the corpus geniculatum laterale and in the cortical visual area in response to retinal stimulation, where the inhibition of the primary response in the specific pathway was less, but the secondary, polysynaptic responses were clearly inhibited. These findings explain the clinical observation that the analgesic effect of propanidid is short lived.

Compared with the inhibition of both monosynaptic and polysynaptic reflexes caused by barbiturates (Young and Robles, 1968), the inhibition of the reticular activating system is less with propanidid. This also explains its characteristic of causing less disturbance of homeostatic mechanisms and of allowing quick restoration of consciousness, and its lack of hangover effect. This is also evident from the patterns of the recruiting responses on the cortex by stimulation of the centre-median nucleus though it could not be concluded that propanidid has an analgesic effect without experiments on the ventro-postero lateral nucleus.

Tachibana (personal communication, 1968) has demonstrated brief depression of the ventro-postero lateral nucleus by propanidid on cats.

The action of propanidid as an analgesic drug appears to differ from that of thiopentone for the latter inhibits both monosynaptic and polysynaptic systems equally. Robson, Davenport and Sugiyama (1965) demonstrated in volunteers that thiopentone raised the thermal pain threshold. The sensations of pain, temperature and light touch depend upon the integrity of spinothalamic tracts, while touch and kinesthesia are concerned with the medial lemniscal system. Thus the lowering of threshold to pressure on the tibia that they demonstrated after thiopentone was of a different modality. This differentiation is produced by presynaptic inhibition in the spinal cord. As is clear from the recruiting response of the cortex to low-frequency stimulation of the centremedian nucleus, a non-specific system, the inhibitory effects on the ascending reticular formation are less. Therefore, this means less inhibition of inhibitory effects of the gate control. The authors, however, could not confirm it in this experiment on volunteers, because of the difference of doses given to volunteers (1 mg/kg) and the rabbits (25 mg/kg).

Dundee and Clarke (1965) using subanaesthetic doses of propanidid (50 mg to 200 mg; about 1 mg/kg to 3 mg/kg) in volunteers found that the analgesic trend increased with increase in dose.

In regard to the analgesic mechanism of ketamine, Miyasaka and Domino (1968) reported that it inhibited the recruiting response in the cat at a stage when the reticular formation was intact. This action differs from that of barbiturates because it is well accepted that barbiturates depress neocortical activity initially whilst the reticular formation is being activated (King, 1956). The analgesic effect of subanaesthetic doses of ketamine can be explained by inhibition of the non-specific thalamoneocortical system. Thus different neuronal mechanisms may be responsible for the analgesic effects of ketamine and propanidid.

ACKNOWLEDGEMENT

The authors thank Dr E. S. Siker for his kind donation of an algesimeter.

REFERENCES


L'ACCION ANALGESICA Y MECANISMO NEURONAL DEL PROPANIDID ALGESMETRIA DEL LOBULO DE LA OREJA EN VOLUNTARIOS HUMANOS Y SU MECANISMO NEURONAL POR EXPERIMENTO EN CONEJOS

RESUMEN
Fueron administradas dosis subanestésicas de propanidid, thiopentona y cetamina a voluntarios con intervalos de 30 min. Los cambios en los valores umbrales para el dolor fueron observados por medio del algesimetro del lóbulo de la oreja. El valor umbral para el dolor ascendió rápidamente 30 seg después de 1 mg/kg de propanidid, pero volvió a los valores de control en 2 min. Con 0,1 mg/kg de cetamina, el umbral para el dolor aumentó en 2 min y este aumento se mantuvo durante 5 min. 0,5 mg/kg de tiopentona no mostraron cambio. Con objeto de clarificar este efecto analgésico también fueron llevados a cabo experimentos en conejos intocados y desecrerebrados para observar los efectos del propanidid sobre las vías sensoriales de los sistemas olfatorios y visuales. El propanidid tuvo un efecto menos inhibitorio sobre el reflejo monosináptico que sobre el reflejo polisináptico, diferenciando así de los efectos de los barbituratos, los cuales inhiben tanto los reflejos monosinápticos como los polisinápticos. El estudio de la respuesta de recubrimiento en la corneja después de la estimulación del núcleo centro-médiano indicó que el propanidid inhibe transitoriamente la vía talamocortical. Estos mecanismos neuronales constituyen una prueba de la existencia de una propiedad analgésica en el propanidid.