The effect of halothane on experimental ischaemic muscle pain has been studied in 18 human volunteers. The submaximum effort tourniquet test was used in this investigation because it has been shown by previous workers to be a sensitive experimental test of analgesia. Two concentrations of halothane (0.25 and 0.35%) were compared with nitrous oxide (30%) in a controlled experiment. It was found that halothane 0.35% is of the same order of effectiveness as an analgesic as is nitrous oxide 30%. Halothane 0.25% appeared to have no analgesic action, and the possibility of a slight antanalgesic action at this concentration could not be eliminated. The practical effects of this finding are reviewed, and it is suggested that this finding taken with the work of other investigators indicates that halothane should be considered as an analgesic drug, and that the application of the term antanalgesic to this agent is misleading.

It is a widely held belief that halothane is antianalgesic (antanalgesic), that is that it causes increased sensitivity to pain. This belief is based primarily on the work of Dundee and Moore (1960). Using pre-tibial analgesimetry these workers not only failed to demonstrate an analgesic effect when 0.5% halothane in oxygen was being inhaled by volunteers, but also found, in patients who had been anaesthetized with the agent, an increased sensitivity to pain in the recovery period.

The possibility of an antanalgesic action of halothane has sometimes been linked with the clinical features of the drug. Thus, for example, it is frequently suggested that patients made unconscious with minimal concentrations of halothane are more likely to move in response to surgical stimulation than those who have been rendered unconscious with minimal concentrations of nitrous oxide.

This clinical observation is not direct evidence of an antanalgesic effect of halothane. Though degrees of analgesia are obviously recognized, analgesia must imply loss of conscious appreciation of pain, and the anaesthetized patient must have total analgesia if he be asleep. Evidence of an analgesic or antanalgesic effect of a drug deduced from its behaviour when used in the unconscious patient is only indirect, depending as it does on the supposed existence of a rough correlation between the ability of a drug to reduce response to surgical stimuli when used in anaesthesia, and the analgesic properties of the drug when given to the conscious patient.

Dundee, Nicholl and Black (1962) failed to confirm an antanalgesic effect of halothane, and even found slight analgesia when use of the agent was accompanied by drowsiness. There is already direct experimental evidence that halothane has an analgesic, rather than an antanalgesic, action on experimental pain. Robson, Davenport and Sugiyama (1965) found that both the tibial pressure pain and thermal pain thresholds fell when halothane (0.5%) was inhaled. Burns, Robson and Welt (1960) showed that halothane appeared to increase the established analgesic effect of nitrous oxide when tested with thermal analgesimetry, and Siker and colleagues (1967), using an ear lobe algesimeter, also found evidence of an increased threshold to pain with halothane.

Different experimental methods give different results and there is thus a conflict of evidence on an important feature of the clinical pharmacology of halothane; it was, therefore, decided to investigate the problem again using a totally different method of producing experimental pain from that used by previous investigators. A survey of the literature suggested that the submaximum effort tourniquet technique (Smith et al., 1966) was suitable. This is based on the production of ischaemic muscle pain in the arm using a tourniquet, and exercising the limb in a standard fashion after the tourniquet has been applied to accelerate the development and progress of the pain. Though somewhat demanding...
of experimental time, the technique has been ade-
quately validated previously (Smith et aL, 1966, 1968), and shown to be sensitive even to a ther-
apeutic dose of aspirin (600 mg) (Smith and Beecher, 1969).

METHODS

A total of 18 volunteers was used in this study, and each volunteer had to attend the laboratory on three occasions with an interval of one week between visits. Informed consent had been ob-
tained from each volunteer before he or she arrived at the laboratory; and on attendance at the laboratory for the first time the experimental pro-
cedure was again explained. Before beginning the experiment each volunteer was asked to practise with the hand exerciser, without a tourniquet on the arm. The dominant hand was used for this trial with the exerciser as the non-dominant hand was used in the actual experiment. In subsequent visits the experiment was again preceded by a brief practice with the exerciser (using the dominant hand) to refresh the volunteer’s memory of its use.

After practice with the hand exerciser, the volunteer lay on a couch and the cuff of an aneroid sphyg-
momanometer was wrapped round the upper arm on the non-dominant side without being inflated. An anaesthetic facepiece was then applied to the subject, and one of the experimental gas mixtures adminis-
tered by means of a circuit incorporating a Ruben valve. After the patient had started to inhale the mixture no further conversation took place between the volunteer and the experimenters, instructions being given by means of a tape-recorder. The volunteer continued to inhale from the piece throughout the rest of the experiment.

Ten minutes after the facepiece had been applied the volunteer was asked to raise the non-dominant arm for half a minute. The arm was then exsanguin-
ated using an Esmarch bandage, and the cuff of the sphygmomanometer was inflated to a pressure of 240 mm Hg. The Esmarch bandage was then removed, with adjustments of the sphygmomanometer to maintain the pressure in the cuff.

Immediately after the arm had been rendered ischaemic in this way the exerciser was placed in the hand and, following commands recorded on tape, the volunteer squeezed the handles (in time with a recorded buzzer) 20 times. The duration of approxi-
mation of the handles of the exerciser was timed to be 2 sec with 2 sec rest between squeezes, though volunteers were not eliminated from the trial for small departures from the appointed pattern. When the squeezes had been completed the exerciser was removed.

At irregular but predetermined intervals the tape-
recorded voice asked the volunteer to grade the pain he felt in four stereotyped categories, viz. 0 none, 1 slight, 2 moderately distressing, 3 very distressing, and 4 unbearable. As soon as grade 4 was reported the cuff was immediately deflated (the pressure in the cuff being checked first).

The times used to grade pain in minutes after completion of the use of the hand exerciser were 0, 1, 4, 7, 11, 13.5, 15, 19, 22.5, 26, 28.5, 31, 34.5, 37.5, 41, 43.5, 46.5, 50.5, 52.5, 56.5 and 60. These are the same intervals as those used by Smith and col-
leagues (1966). At each of these times the recorded question “Will you please describe the degree of pain?” appeared on the tape and the volunteer replied by giving grade 0 to 4.

The volunteers almost always graded pain pro-
gressively as time went on, from grades 0 to 1, 1 to 2, and so on. On some occasions, however, the volun-
tee came back to a previous grade (for example, from grade 3 to grade 2 then back to grade 3). In these circumstances the time to the first complaint of pain of grade 3 was used in the results. On one occasion the volunteer’s complaint jumped (from grade 1 to grade 3); here a time to develop pain of grade 2 was arbitrarily assigned to a time half way between the last complaint of pain of grade 1 and the (first) complaint of pain of grade 3.

Two investigators were in attendance during each experiment. One held the mask on the volunteer’s face; this investigator was not aware which gas mix-
ture was being delivered. The other was hidden behind a screen; this investigator maintained the gas mixtures and recorded the replies to the ques-
tions about grading pain.

The gas mixture.

In the first series of experiments each volunteer was subjected to inhalation of nitrous oxide 30%, halothane 0.25% and air (as a control). When the results from this had been studied a second series was instituted using halothane 0.35% instead of halothane 0.25%, the nitrous oxide and control experiments being kept as before.

In both of these series the order in which a volun-
teer had each experiment was decided on a random basis. In case there might be an improved pain tolerance with successive experiments it was arranged that the same number of volunteers had each experi-
ment first: thus in both series the number having
the control experiment first, the nitrous oxide experiment first, and the halothane experiment first should have been three in all cases. In the second series, however, one volunteer was eliminated from the experiment, as is described later; this resulted in there being two volunteers in this series who received halothane first, at the expense of one less receiving air first.

To make it impossible for the volunteer (or the experimenter administering the mixture) to detect halothane or nitrous oxide by smell, a little Eau de Cologne, vaporized with a Halox vaporizer, was added to the circuit for 3 minutes at the beginning of the experiment. The Eau de Cologne used was essentially a mixture of ethyl alcohol (about 80%) with water and a small amount of aromatic oil. It appeared to be completely effective in disguising smell; only minute amounts of the scent were volatilized.

The halothane was administered by a Draeger Vapor vaporizer. The concentrations actually delivered were subsequently checked using atomic absorption. The halothane was delivered to the volunteer in air (supplied by a cylinder) and the nitrous oxide in air enriched with oxygen (to give a total concentration of oxygen of 20%).

The hand exerciser.

A hand exerciser (fig. 1) was constructed by the Department of Bio-Engineering, University of Liverpool. It was designed on similar lines to the more satisfactory of two versions described by Smith and colleagues (1966). The excursion distance was 4.36 cm, and the force required to approximate the handle was 7.5 kg. To help the volunteer to use the exerciser the handles were wired so that when they were approximated a red light went on and when they were completely relaxed a green light went on.

Volunteers.

A total of 19 volunteers was used but results from only 18 are presented. It had been arranged before the experiments had been started that any volunteer who could not tolerate the tourniquet for 5 minutes from its application should be eliminated from the trial. In practice one volunteer was eliminated for this reason.

All the volunteers were psychology students, dental students, or dental or medical practitioners. Their ages were between 18 and 48 years (mean 26). Weights varied from about 60 kg to 98 kg (mean 80). In the first group (that is the group receiving 0.25% halothane) there were 5 males and 4 females;
in the second group (that is the group receiving 0.35% halothane) all the volunteers were males.

It will be noted that there is wide individual variation in the values among the volunteers (fig. 2). This leads to a considerable difference in the control values obtained for series 1 and those from the other group of volunteers in series 2. Nevertheless, it will be noted, each subject acts as his own control.

RESULTS
The results are shown in table I and in the histogram (fig. 2). The table shows the mean times taken for the volunteers to complain of the four grades of pain (grades 1 to 4; slight to unbearable) in each of the three experimental situations (control, nitrous oxide, halothane) for both series 1 and series 2 (i.e. using 0.25% and 0.35% halothane respectively).

Analysis of variance was used to study these results, and underneath the mean times for each experimental situation in both series in table I is given the difference in the mean values which is required to achieve a statistically significant result at the usual confidence level (P<0.05).

In the first series of experiments statistically significant differences were found when comparing nitrous oxide with control for grade 4 ("unbearable") pain (P<0.01) and for grade 2 ("moderately distressing") pain (P<0.05). There is also a difference between nitrous oxide and halothane for "unbearable" and "moderately distressing" pain (P<0.01 and P<0.02 respectively).

Thus in the first series of experiments, using
THE ANALGESIC EFFECT OF HALOTHANE

Table I. The mean time in minutes taken to reach each of the four grades of pain as shown for the control, halothane and nitrous oxide experiments in both series. Under these times is shown the difference which would be required between each of the mean values for them to be significantly different at the usual confidence level.

<table>
<thead>
<tr>
<th></th>
<th>Series 1 (n=9)</th>
<th></th>
<th>Series 2 (n=9)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>Halothane 0.25%</td>
<td>N₂O</td>
</tr>
<tr>
<td><strong>Unbearable (Grade 4)</strong></td>
<td>Mean time (min)</td>
<td>19.5</td>
<td>19.4</td>
</tr>
<tr>
<td>Difference required between mean values for significance at P&lt;0.05 level</td>
<td>4.3</td>
<td>1.2</td>
<td>1.4</td>
</tr>
<tr>
<td><strong>Very distressing (Grade 3)</strong></td>
<td>Mean time (min)</td>
<td>12.4</td>
<td>9.9</td>
</tr>
<tr>
<td>Difference required between mean values for significance at P&lt;0.05 level</td>
<td>4.1</td>
<td>6.1</td>
<td>7.9</td>
</tr>
<tr>
<td><strong>Moderately distressing (Grade 2)</strong></td>
<td>Mean time (min)</td>
<td>5.1</td>
<td>3.7</td>
</tr>
<tr>
<td>Difference required between mean values for significance at P&lt;0.05 level</td>
<td>3.2</td>
<td>4.8</td>
<td>5.9</td>
</tr>
<tr>
<td><strong>Slight (Grade 1)</strong></td>
<td>Mean time (min)</td>
<td>0.6</td>
<td>1.5</td>
</tr>
<tr>
<td>Difference required between mean values for significance at P&lt;0.05 level</td>
<td>3.2</td>
<td>1.8</td>
<td>1.8</td>
</tr>
</tbody>
</table>

0.25% halothane, there was sound evidence that the experimental method showed that nitrous oxide 30% had an analgesic action. There was no evidence that halothane at this concentration had an analgesic action, but no statistically acceptable evidence that halothane had an antanalgesic effect, though it should be noted that it took longer for the volunteers to complain of pain of grades 2 and 3 in the control group than in the halothane group.

In the second series of experiments there was a significant difference between nitrous oxide and control and for halothane and control for both “unbearable” (grade 4) and “moderately distressing” (grade 2) pain (P<0.05 in all four cases). There was no difference between halothane 0.35% and nitrous oxide large enough to be considered statistically significant in this series.

In the second series there is thus experimental evidence that both nitrous oxide (30%) and halothane (0.35%) have an analgesic action. Examination of figure 2 indicates that this appears to be quantitatively similar.

**DISCUSSION**

There are several difficulties to be considered in the present investigation. Though the volunteers were unable to tell the difference between nitrous oxide and halothane because the Eau de Cologne masked the smell they were usually able to tell when a central nervous depressant was being administered. It is arguable that the analgesic effects which the experiment purports to have demonstrated were really manifestations of a placebo reaction.

This seems to be very unlikely. Halothane 0.25% was also readily identified as a central nervous depressant by the volunteers, and yet halothane at this concentration appeared to make little or no difference from the control. Nevertheless this possibility must remain as a flaw in the argument, though it is a flaw which is common to all investigations of this type. In the present state of knowledge it is not correctable.

It would also clearly be desirable for the volunteer to have been on his own and not have had someone in the room in which the investigation was taking place. There remains the possibility that the investigator holding the facepiece might influence the patient in some way. The investigator holding the facepiece, however, was quite unable to tell which of the mixtures was being administered except on one occasion when a volunteer became very drowsy and it was obvious that a central depressant drug was being administered.

It is also possible that the administration of an analgesic drug before muscular activity is undertaken may diminish the amount of exertion which the volunteer makes subsequently or may change its character. It was for this reason that Smith and colleagues (1966) when investigating the effects of morphine gave the drug intravenously after the
hand exercise had been completed. It was feared, however, that if this were done in this investigation and inhalation commenced only after the hand exerciser had been used an analgesic action might be missed before more or less constant blood levels of inhalational agent were attained. All that can be said on this point is that there was certainly no obvious evidence that the method of using the exerciser changed after inhalational agents had been used.

The submaximum effort tourniquet technique has advantages. First it is very sensitive (Smith and Beecher, 1969). Secondly it is possible that ischaemic muscle pain is more like pathological pain than are other types of experimental pain (Smith et al., 1966). This, of course, is a proposition not susceptible to proof; but it is probable that ischaemic pain is more like wound pain or fracture pain than is pain caused by heating the skin. The whole question of experimental pain and pathological pain with their various psychological concomitants is clearly beyond the scope of the present discussion.

The results presented here show little or no evidence of an antanalgesic effect of halothane, though there is perhaps a suggestion of this in the first series. The basic finding is that halothane 0.35% appeared to be as effective an analgesic as nitrous oxide 30%, though perhaps with less effect on slight pain.

This analgesic effect is not likely to last for long after a general anaesthetic has been administered with halothane. One of the virtues of halothane is its speedy reduction in concentration in the body. The ideals of quick recovery and good postoperative analgesia cannot be satisfactorily provided by one agent.

Despite this it might be expected that for some minutes after recovery from a halothane anaesthetic there would be a significant degree of analgesia. As, in the clinical situation, this is often a time in which the patient has several painful manoeuvres performed on him (e.g., being lifted off the operating table) it might be expected that this analgesic action would be useful.

ACKNOWLEDGEMENTS

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We are also grateful to those volunteers who bravely returned for what was an unpleasant experiment.

REFERENCES


