THE EFFECTS OF INTRAVENOUSLY ADMINISTERED DIHYDROCODEINE BITARTRATE IN ANAESTHETIZED MAN

BY

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In the past decade narcotic analgesics have been widely used to supplement thiopentone-nitrous oxide-oxygen anaesthesia. Pethidine (Neff, Mayer and Perales, 1947) and alphaprodine (Siker, Foldes, Pahk and Swerdlow, 1954) have been most frequently employed, but many other narcotics, e.g. levorphanol (Broman, Cullen and Wilkins, 1950) and anileridine (Riffin et al., 1958) have also been used. In the dosage necessary to produce adequate operating conditions, with small doses of thiopentone and muscle relaxants, these drugs frequently cause respiratory depression of variable intensity (Foldes et al., 1956). On the other hand, little or no circulatory changes have been observed when such techniques are employed (Foldes et al., 1957).

In view of the undesirable respiratory effects of narcotics when used for the supplementation of anaesthesia, the search has continued for a potent narcotic analgesic which would be free from this disadvantage. It has been reported that, in 30 mg subcutaneous doses, dihydrocodeine bitartrate produces relief of postoperative pain comparable with that given by 10 mg morphine, without causing appreciable respiratory depression (Gravenstein et al., 1956). Other investigators (Keats et al., 1957; Wallenstein et al., 1957) found that about 60 mg dihydrocodeine had the same analgesic potency as 10 mg morphine and that when used in this ratio the respiratory depression caused by the two analgesics was very similar (Seed et al., 1957). Eckenhoff and Helrich (1957) found relatively less respiratory depression after intramuscular injection of 50–60 mg dihydrocodeine than after comparable doses of other narcotic analgesics. In an earlier study one of us observed (Swerdlow, 1957) that the intravenous injection of 0.25 to 0.5 mg/kg dihydrocodeine bitartrate in patients anaesthetized with 8 mg/kg thiopentone sodium and nitrous oxide-oxygen produced less depression of respiration rate and minute volume than 0.6 mg/kg pethidine. However, in the course of these and other observations it became evident that relatively larger doses of dihydrocodeine than of pethidine are necessary to provide adequate analgesic supplementation of clinical anaesthesia. Consequently, a study was undertaken of the circulatory, respiratory and other effects of dihydrocodeine bitartrate in anaesthetized subjects.

PART I

MATERIAL AND METHOD

Circulatory and respiratory studies were carried out on 19 subjects, 9 males and 10 females. Their ages ranged from 19 to 52 years; the average age was 31 years. All were relatively fit patients who were to be operated on for minor surgical conditions which did not affect their general health. They were premedicated with 8–11 mg morphine and 0.6 mg atropine injected subcutaneously 45–60 minutes before the start of anaesthesia. In the anaesthetic room the patients were lightly anaesthetized with thiopentone sodium and nitrous oxide-oxygen according to a previously described technique (Foldes et al., 1952). When the level of anaesthesia became stabilized pulse rate, blood pressure, respiratory rate and respiratory minute volume were deter-

*Minute volume was measured with a Bennett ventilation meter inserted in the circle absorption system.
mined. These measurements were used as control values. Following this, at zero time, 1.5 mg/kg dihydrocodeine bitartrate was injected intravenously in 30 seconds. All measurements were repeated at 3, 6, 10 and 15 minutes after the injection of dihydrocodeine. Tidal volume was calculated from respiratory rate and minute volume. In addition to these objective measurements observations were made on the presence or absence of skin changes attributable to histamine release, and of central nervous system stimulation (e.g. awakening, movement of extremities, coughing, etc.).

The respiratory changes were expressed as per cent of control values, and the absolute values of the circulatory changes were recorded.

**RESULTS**

The observations made on the respiratory and circulatory changes are summarized in tables I and II respectively. It is evident from table I that the injection of 1.5 mg/kg dihydrocodeine caused a statistically significant (p<0.001) decrease of the respiratory rate. This decrease was 20.5 per cent 3 minutes after the injection of the drug and reached its maximum (35.9 per cent) at 15 minutes. There was a compensatory increase in the tidal volume which amounted to 5 per cent at 3 minutes and reached its maximum (55.8 per cent) at 15 minutes. The tidal volume changes were statistically significant from 6 minutes onwards. There was a moderate, but not significant, decrease in minute volume in the first 10 minutes but by 15 minutes after the drug administration the minute volume had returned to control level.

In contrast to the relatively minor changes in the respiratory parameters, marked circulatory changes were present throughout the 15-minute observation period. There was a statistically significant (p<0.001) increase of the pulse rate and decrease of both the systolic and diastolic blood pressure. The circulatory changes were most marked at 3 minutes when the average increase in pulse rate was 26 per cent, and the average systolic and diastolic blood pressure decreased by 47 and 52 per cent respectively. The circulatory measurements tended to return towards normal with time but were still significantly different from control values at the end of the 15-minute observation period.

**Side Effects**

Of the 19 patients included in the respiratory and circulatory study 16 showed signs suggestive of histamine release immediately following the intravenous injection of dihydrocodeine. These signs, noted earlier by Swerdlow (1957), included wealing along the course of the vein into which the injection was made, generalized "goose pimples", and marked reddening of the face, neck and upper part of chest. Seven of the 19 patients coughed after injection of dihydrocodeine and 13 showed various signs of transient central nervous system stimulation.

**PART II**

**METHOD OF EVALUATION OF ANALGESIC POTENCY**

In 7 of the 19 patients included in the studies described surgical incision was made within a few minutes of the end of the experimental measurements (i.e. 18–26 minutes after administration of 1.5 mg/kg dihydrocodeine). Analgesia was satisfactory in only 3 of the 7 patients; the others resented the skin incision and required supplementary doses of dihydrocodeine or of thiopentone before it was possible to proceed with the operation.

In 35 patients dihydrocodeine was used as an analgesic supplement to anaesthesia consisting of a sleep dose of thiopentone followed by nitrous oxide-oxygen (6L:2L) and when necessary small doses of muscle relaxants. These 35 patients were undergoing a variety of operations including appendicectomy, herniorrhaphy, partial gastrectomy and orthopaedic surgery. An initial dose of 20 mg dihydrocodeine was usually employed followed by supplementary doses of 10–20 mg. Despite preliminary spraying of the cords with a local analgesic and the use of an analgesic cream on the endotracheal tube, the patients frequently demonstrated a persistent objection to the presence of the tube. It was found much easier to maintain smooth and satisfactory anaesthesia with regular, adequate respirations if an endotracheal tube was not employed.

Postoperative recovery of consciousness was rapid, the cough reflex being uniformly present at the termination of surgery and in most cases patients were capable of answering simple questions within 5 minutes of discontinuing the
### Table I

*The effects of Dihydrocodeine Tartrate on Respiratory Rate, Tidal Volume and Minute Volume expressed in per cent of Control Values.*

<table>
<thead>
<tr>
<th>Time in minutes after administration</th>
<th>Respiratory rate</th>
<th>Tidal volume</th>
<th>Minute volume</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>St. error</td>
<td>Mean</td>
</tr>
<tr>
<td>0</td>
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<td>—</td>
<td>100.0</td>
</tr>
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<td>79.4</td>
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<td>74.1</td>
<td>4.1</td>
<td>118.7</td>
</tr>
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<td>67.4</td>
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</tr>
<tr>
<td>15</td>
<td>64.1</td>
<td>4.3</td>
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</table>

### Table II

*The effects of Dihydrocodeine Tartrate on Pulse and Blood Pressure.*

<table>
<thead>
<tr>
<th>Time in minutes after administration</th>
<th>Pulse rate</th>
<th>Systolic pressure</th>
<th>Diastolic pressure</th>
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<td></td>
<td>Mean</td>
<td>St. error</td>
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administration of nitrous oxide and oxygen. The respiration rate tended to be rather rapid throughout anaesthesia and there was commonly an increase in pulse rate, but the blood pressure did not show any regular trend.

No marked ill effects were noted on careful follow-up in any of the patients in this study. In one patient, however, a diffuse rash developed over the whole body, without any apparent cause, 2 hours after appendicectomy. The rash disappeared promptly on antihistamine treatment.

**DISCUSSION**

The respiratory changes observed after intravenous injection of dihydrocodeine were less marked than those caused by comparable intravenous doses of other analgesics (Foldes et al., 1957); this was also reported by Eckenhoff et al. (1957), who administered dihydrocodeine by the intramuscular route. Unlike other narcotic analgesics which cause maximal respiratory depression within 2–5 minutes after intravenous administration, dihydrocodeine caused a slowing of the respiratory rate which did not reach its nadir until 15 minutes after its administration. We have no definite explanation for this unusual phenomenon, but it may have resulted from breath-holding due to lightness of anaesthesia with dihydrocodeine. As with other analgesics the compensatory increase in tidal volume became progressively greater throughout the observation period and minute volume had returned to control level by the end of 15 minutes. In contrast to this the circulatory effects of large intravenous doses of dihydrocodeine were more pronounced and persistent than those seen after comparable doses of other narcotic analgesics.

Of the 19 patients in whom respiratory and circulatory changes were followed closely, the lowest systolic blood pressure could not be measured in 3, nor the diastolic blood pressure in 9 patients. Return of blood pressure to control values was slow and the systolic pressure was 70 or less in 5 of the 19 patients. The intravenous administration of antihistaminics had no effect on the hypotension but the blood pressure responded promptly to intravenous methoxamine. Considering that these dramatic circulatory changes occurred in relatively young and fit individuals it is evident that the intravenous administration of a large dose of dihydrocodeine might have disastrous consequences in anaesthetized patients with known or latent myocardial insufficiency. Other disturbing findings were the high incidence of signs and symptoms suggestive of histamine release and central nervous system stimulation. Besides the skin changes described, bronchiolar spasm was encountered in 2 patients and an asthmatic type of breathing with prolonged expiratory phase in several others. The incidence and intensity of signs of central nervous system stimulation were also alarming. These effects, seldom seen with other narcotic analgesics, were described for dihydrocodeine in 1934 by Eddy and Small.

Based on its ability to relieve postoperative pain (Keats et al., 1957) or chronic pain caused by cancer (Wallenstein et al., 1957), 60 mg and 68 mg dihydrocodeine respectively were reported to be equivalent to 10 mg of morphine. Assuming the generally accepted 10:1 ratio between the analgesic potency of morphine and pethidine, 68 mg dihydrocodeine should be equivalent to 100 mg of pethidine. The analgesic potency of 1.5 mg/kg dihydrocodeine would thus be equivalent to that of 2.25 mg/kg of pethidine. In fact, the analgesic potency of this dose of dihydrocodeine as measured by its effectiveness as a supplement to thiopentone-nitrous oxide-oxygen anaesthesia is considerably less than that of 1.0 mg/kg pethidine. It is interesting to note in the present work that the analgesia obtained with the smaller doses of dihydrocodeine was not inferior to that found with 1.5 mg/kg doses. This observation is in agreement with the report of Keats and his colleagues (1957) that on subcutaneous administration 30 mg dihydrocodeine is only 9 per cent less effective than 60 mg and no greater analgesia can be obtained by increasing the dose to 90 mg. It is possible that in larger doses the central nervous system stimulating action of dihydrocodeine antagonizes its analgesic effect, thus preventing an increased analgesic response.

Because of its undesirable circulatory effects, its histamine-releasing and central nervous system stimulating properties, and its relatively weak analgesic potency, dihydrocodeine bitartrate was not found to be a satisfactory supplement to thiopentone-nitrous oxide-oxygen anaesthesia. This does not necessarily imply that dihydrocodeine has no place in the management of pain in con-
muscular administration in smaller but analgesic doses, it causes relatively little respiratory depression and no marked circulatory changes have been reported following its subcutaneous or intramuscular administration in smaller but analgesic doses, its use does not seem to be contra-indicated in relatively fit individuals. Indeed, there is evidence (Dundee, 1957) that it may be an agent of some value in chronic pain. However, further studies will be necessary to determine whether it can be safely used in patients with disorders of the cardiovascular system and in allergic individuals.

SUMMARY
The circulatory and respiratory effects of 1.5 mg/kg dihydrocodeine administered intravenously were investigated in 19 lightly anaesthetized subjects.

There was a significant decrease in the respiratory rate and increase in the tidal volume; these changes reached their maximum 15 minutes after administration of the drug. Because of the compensatory nature of these changes, the effect on minute volume was relatively small.

There was a marked increase in pulse rate and a precipitous drop in both systolic and diastolic blood pressure. These changes were maximal 3 minutes after injection of the drug and later readings showed a trend to return towards control levels.

In the majority of patients the intravenous injection of dihydrocodeine was followed by various signs and symptoms of histamine release and of central nervous system stimulation.

In 7 of the patients who received 1.5 mg/kg and in 35 patients who received smaller doses of dihydrocodeine the efficacy of this analgesic as a supplement to thiopentone-nitrous oxide-oxygen was observed.

As measured by the ability of lightly anaesthetized patients to tolerate skin incision and surgery the intensity of analgesia obtained by intravenously administered doses of dihydrocodeine was less than that of comparable doses of pethidine or alphaprodine.

The results of this investigation indicate that when administered in large intravenous doses to anaesthetized patients dihydrocodeine causes unwanted side effects. It was also found that dihydrocodeine is not a satisfactory supplement to thiopentone-nitrous oxide-oxygen anaesthesia.

ACKNOWLEDGMENT
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REFERENCES