ALTERATIONS IN RESPONSE TO SOMATIC PAIN ASSOCIATED WITH ANAESTHESIA

XIX: STUDIES WITH THE DRUGS USED IN NEUROLEPTANAESTHESIA

BY

J. D. MORRISON

SUMMARY

The effects of some intravenously administered drugs on sensitivity to tibial pressure-induced somatic pain were investigated in a controlled, double-blind trial. The drugs included those commonly employed in neuroleptanaesthesia (fentanyl, phenoperidine and droperidol), standard opiates (morphine, diamorphine), and a standard tranquillizer (diazepam). The analgesics were given in what are commonly regarded as clinically equipotent dosages. Fentanyl and phenoperidine decreased the subjects' sensitivity to somatic pain, whilst saline, morphine, diamorphine and diazepam did not have any effect. Droperidol caused an increase in sensitivity, and the addition of droperidol to either phenoperidine or fentanyl was associated with a simple summation of effect. It was concluded that there is a difference in the mode of action of fentanyl and phenoperidine in comparison to morphine, the former having a relatively greater effect on the perceptual mechanisms of pain and the latter a relatively greater effect on the affective experience of pain.

The usefulness of experimental pain threshold studies in the assessment of analgesic drugs in man is at best the subject of considerable controversy. Indeed Beecher (1957) considers such studies quite useless in the clinical evaluation of these drugs, because no method of experimental induction of pain is able to reproduce the same quality of psychic reaction as does pain arising from trauma or disease process. In experimental studies the pain represents a minor and usually fleeting discomfort for the subject and is of little consequence to him, whilst in clinical circumstances the significance of the pain may be of serious portent and may be a threat to the patient's very life, and in these circumstances the reaction to it becomes of supreme importance. It is quite possible, therefore, that (even if an ideal method of algsemetry were available) a drug which was of proven analgesic usefulness in a clinical situation, but which owed its efficacy to a purely central action on the reaction component, would not cause any significant alteration in experimental pain threshold or tolerance. On the other hand, one would expect that if another analgesic drug was to exert its action at least partially by an effect on the apparatus of perception of pain, then one would find a threshold-raising effect from such a drug.

Thus, it would seem that if a reasonable method of algsemetry was available, and if it could be used in such a way as to minimize or standardize the reaction component induced by the circumstances of the experiment, then such a method would be useful in the comparison of analgesic drugs which act on the apparatus of perception of pain and would be a useful tool in investigating the mode of action of analgesic drugs. This is likely to be an especially interesting study when analgesic drugs normally used as supplements to general anaesthesia are under consideration, for in these circumstances it is unlikely that a reaction component can exist and so the true worth of the drug would depend mainly on its action on the perceptual mechanisms of pain. It is likely that this quality would be reflected in a pain-threshold-raising action and it was to test this hypothesis that the presently described experiments were undertaken.

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METHOD

The method of algesimetry used in these studies was basically that described by Clutton-Brock (1957) and further evaluated by Dundee and Moore (1960). It consists of application of gradually increasing pressure to the skin overlying the anterior surface of the tibia by means of a small metal disc attached to a spring balance, the balance allowing a quantitative estimate of the pressure applied. The subject is asked to say "now" when the sensation of pressure first gives way to pain, and "stop" when the sensation of pain becomes unbearable. These are termed "threshold" and "response". It should be noted that the readings are not given in any absolute units, each 1-lb. division on the scale of the balance simply being designated as one pain unit. An identical pattern of algesimeter was used throughout the study and the precise method of use was that described by Dundee and Moore (1960).

All observations were carried out on fit female patients, in one ward unit, awaiting minor gynaecological surgery. Each patient was prepared for theatre, and her bed screened off from the rest of the ward. She was told that she would be given her premedication intravenously rather than by the more usual intramuscular route and the use of the algesimeter was explained. The patients were not told to expect any specific effect from the injection. At this stage two readings were taken (i.e. two sets of threshold and response readings) and if these differed individually by one unit or less the average was taken as the control for that particular patient. The patients were not able to see the algesimeter scale. If the first two readings differed by more than one unit then a third reading was taken and if any two of the three agreed to within one unit, then the average of these two was taken as the control. If no two of the three readings agreed within these limits, then the patient was excluded from the study, as was any patient who found the discomfort of algesimetry in any way distressing.

The drug to be used in any particular patient was selected by a medical colleague who prepared the appropriate amount, according to the patient's weight, into a syringe, the contents of which were then diluted to a standard volume (5 ml). In this way the observer was unaware of the identity of the drug he was using, although if necessary this information could have been rapidly obtained as the colleague who had prepared the injection remained in the same ward unit until the study had been completed, at which time the name of the drug and the dosage was written on the patient's chart.

After the control readings had been established, the unknown drug was given by slow intravenous injection, timed over 5 minutes. Algesimeter readings were repeated at 5, 10, 15, 20, 25 and 30 minutes from the completion of the injection. In these instances only one reading of threshold and response values was taken because of the limitation of the number of observations which could be carried out on any one leg.

The drugs included in the trial are shown in Table I, together with the dosages, which were related to the mean weight of the ward population from which the subjects were drawn, which in a sample of 2,000 patients was approximately 60 kg.

<table>
<thead>
<tr>
<th>Number of subjects</th>
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<tbody>
<tr>
<td>Drugs and dosage</td>
</tr>
<tr>
<td>Saline</td>
</tr>
<tr>
<td>Morphine 10 mg/60 kg</td>
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<tr>
<td>Diamorphine 5 mg/60 kg</td>
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<tr>
<td>Fentanyl 0.2 mg/60 kg</td>
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<tr>
<td>Phenoperidine 2 mg/60 kg</td>
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<tr>
<td>Droperidol 5 mg/60 kg</td>
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<tr>
<td>Diazepam 10 mg/60 kg</td>
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<tr>
<td>Fentanyl 0.2 mg/60 kg plus droperidol 5 mg/60 kg</td>
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<tr>
<td>Phenoperidine 2 mg/60 kg plus droperidol 5 mg/60 kg</td>
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RESULTS

The findings in each individual subject are presented graphically in figures 1–9 as changes in the mean of threshold and response readings, the mean of threshold and response being indicative of the patient's sensitivity to somatic pain, although inspection of the detailed results (data not presented here) shows that the same qualitative relationships would have obtained had the response and threshold levels been treated separately.

(i) Saline (fig. 1). The changes from control showed a small degree of scatter around zero, only 11 of the total 60 readings being outside the
suggested normal scatter of ±1 pain unit. The mean change in the entire group of 10 subjects (fig. 10) showed an overall insignificant effect from the placebo.

(ii) Morphine (fig. 2). There was a wide variation in the response of individual subjects, 6 patients escaping from the “control lines”, 4 showing a significant increase in change from pretreatment readings whilst 2 showed significant decrease. Grouping all these patients together (fig. 10) the predominant change was an increase in algesimeter readings, maximal at 10 minutes after injection and which thereafter declined steadily to have practically returned to control levels at 35 minutes.

(iii) Diamorphine (fig. 3). Of the 5 patients studied, the changes in 3 showed a tendency to rise while in 2 they remained generally unaltered from control levels. The overall mean result showed an increase over pretreatment readings, reaching a maximum at 15 minutes after injection and not showing any marked tendency to fall off rapidly (fig. 10).

(iv) Fentanyl (fig. 4). Eight of the 10 subjects escaped at one point or another from the upper “significance” boundary. The overall means showed the predominant effect to be a rise in both end-points: this rise was apparent at the first observation 10 minutes after injection and reached its maximum 20 minutes after injection, thereafter falling away rapidly (fig. 10).

(v) Phenoperidine (fig. 5). The results showed a marked and consistent increase in changes from pretreatment levels, only 1 of the subjects showing an “insignificant” degree of change. Amalgamating the results (fig. 10), the maximum effect was not seen until 25 minutes after injection and was followed by a slight fall off, although at the end of the observation period the level was still well above the upper “significance boundary”.

(vi) Droperidol (fig. 6). The overall tendency was for the readings to fall; in only 2 subjects was there any maintained increase in algesimeter readings and in only 1 of these did the increase reach the designated “significance” level. The remainder of the subjects showed a fall in readings, a fall which was maintained throughout the observation period. The mean effect (fig. 10) was a progressive fall during the first 20 minutes following injection, followed by a more or less stable plateau for the remainder of the observation period.
Fig. 2
Morphine 10 mg/60 kg.
Changes in mean of threshold and response readings in 10 subjects.

Fig. 3
Diamorphine 5 mg/60 kg.
Changes in mean of threshold and response readings in 5 subjects.
Fig. 4
Fentanyl 0.2 mg/60 kg. Changes in mean of threshold and response readings in 10 subjects.

Fig. 5
Phenoperidine 2 mg/60 kg. Changes in mean of threshold and response readings in 10 subjects.
Droperidol 5 mg/60 kg. Changes in mean of threshold and response readings in 10 subjects.

Diazepam 10 mg/60 kg. Changes in mean of threshold and response readings in 5 subjects.
Fig. 8
Fentanyl 0.2 mg/60 kg plus droperidol 5 mg/60 kg. Changes in mean of threshold and response readings in 10 subjects.

Fig. 9
Phenoperidine 2 mg/60 kg plus droperidol 5 mg/60 kg. Changes in mean of threshold and response readings in 10 subjects.
(vii) **Diazepam** (fig. 7). The predominant effect was a downward trend, similar in pattern, although not quite in magnitude, to that with droperidol.

(viii) **Fentanyl plus droperidol** (fig. 8). There was a wide variation in individual subjects, half the patients showing a varying degree of elevation outside the “significance” range, the other half not escaping from this range. The overall effect (fig. 11) was to increase the mean of threshold and response, an increase detectable after 10 minutes and remaining more or less constant for the following 25 minutes.

(ix) **Phenoperidine plus droperidol** (fig. 9). The overall effect was an upward change, 7 patients showing a degree of change sufficient to escape from the upper “significance” limits. No subject showed a significant downward trend. Amalgamating the results from the whole group (fig. 11) the maximum elevation was seen after 15 minutes, remained more or less constant for the next 10, thereafter tending to fall away, although pre-treatment levels were not regained by the end of the observation period.

**DISCUSSION**

There is considerable difficulty in handling the data obtained from studies of pain thresholds in any meaningful way, and Miller (1948) has shown how errors in interpretation of such data may be attributed to differences in mathematical manipulation. For this reason, no effort has been made to present a formal analysis of the data: the presentation has been limited to a qualitative rather than a quantitative survey and follows that which was used by Dundee and Moore (1960) in their original description of the method.

Although it has been suggested that threshold
to pain and tolerance to pain are quite separate phenomena not necessarily related (Gelfand, 1964) inspection of the tabulated results in the present study indicated that changes in threshold and response readings were more or less parallel. Thus, the comparison made, between groups of subjects, of means of threshold and response readings would not be materially different from that made of changes in threshold alone or changes in response alone.

The various drugs investigated can readily be divided into three groups:

1. Those which reduced the subject's sensitivity to tibial pressure pain, i.e. those in which the mean of all the changes recorded at any one time in the post-injection period was greater than the arbitrary "significance" level of +1 unit. This group consisted of:
   - phenoperidine 2 mg/60 kg;
   - phenoperidine 2 mg/60 kg plus droperidol 5 mg/60 kg;
   - fentanyl 0.2 mg/60 kg plus droperidol 5 mg/60 kg.

2. Those in which the mean change fell within the range ±1 unit. This group is considered to be without significant effect on sensitivity to tibial pressure pain and consisted of:
   - saline;
   - morphine 10 mg/60 kg;
   - diamorphine 5 mg/60 kg;
   - diazepam 10 mg/60 kg.

3. Those drugs in which the mean downward change was of greater magnitude than −1 unit, i.e. those which are associated with an increase in subject's sensitivity to tibial pressure pain. Only one treatment fell into this group, namely droperidol 5 mg/60 kg.

The ability of this method of algesimetry to detect drug-induced changes in the subject's sensitivity to somatic pain has been established by Dundee and Moore (1960), and the results in the present trial tend to confirm their findings in that the dummy treatment consistently failed to
produce an elevation of threshold while a drug such as phenoperidine produced a consistent rise in threshold.

It is noteworthy that amongst the opiates included in this study only the two synthetic derivatives of pethidine effectively decreased the subject's sensitivity to tibial pressure pain, whereas morphine and diamorphine in equipotent doses with the former as judged by ability to relieve pathological pain (Loan and Morrison, unpublished data) were much inferior in this respect. There have been conflicting reports in the literature concerning whether or not morphine can be demonstrated to reliably increase the threshold of experimentally induced pain. Macht, Herman and Levy (1916) were unable to demonstrate any effect from morphine 5 mg and Seevers and Pfeiffer (1936) could find little threshold-raising effect from morphine compared to other narcotic analgesics. On the other hand, Hardy, Wolff and Goodell (1940) and Jones and Chapman (1944) claimed that they could demonstrate a consistent threshold-raising effect from morphine. The present study failed to demonstrate any consistent effect on sensitivity to tibial pressure pain. It had been felt initially that, because of the relatively short duration of the period of observation in these experiments, an opiate-induced elevation of threshold might be missed due to a prolonged period of onset of action before the maximum effect had been reached. In the case of morphine, however, there was no evidence to support this hypothesis as the threshold effect was waning rather than rising towards the end of the observation period. Further evidence to suggest that this observation period was probably long enough was seen in the case of diamorphine which was included because of its reputedly more rapid onset of action than morphine. Here again, however, there was no demonstrable significant effect on sensitivity to tibial pressure pain. This is in agreement with the findings of Javert and Hardy (1951) who, using a radiant heat method, were unable to detect any effect on threshold from diamorphine 5 mg and of Jackson (1952) who also was unable to detect any effect on experimental pain thresholds from either morphine or diamorphine.

It could be inferred from these results that there may be a difference in the mode of action of phenoperidine and fentanyl in comparison with morphine and diamorphine, in that the analgesic properties of phenoperidine and fentanyl are probably dependent, at least partially, on an influence on the perception of pain. Morphine and diamorphine, on the other hand, possibly depend more on the production of an alteration in the affective component of the total pain experience than on a significant effect on perception of the pain-producing stimulus.

The two tranquillizers included in these experiments, diazepam and droperidol, both tended to increase the subject's sensitivity to tibial pressure, although diazepam just failed to reach "significant" antanalgesic status. There are no reported investigations on the effects of these drugs on experimentally induced pain in human subjects with which to compare the results of the present study, but results with tranquillizers of the phenothiazine series (Moore and Dundee, 1961) showed that the various members of this series could be classified, with respect to tibial pressure pain, into three groups, namely slight analgesics, slight antanalgesics and marked antanalgesics. Droperidol would be comparable in its effects to members of the last group, which included promethazine and pethidine.

It is interesting to speculate whether the threshold-lowering effect of droperidol is due to any direct effect on the perception of the stimulus or to an effect on the reaction component secondary to the lack of sedation, or even to the presence of frank dysphoria which frequently attends the use of this drug given by itself (Morrison et al., 1970).

The addition of droperidol to fentanyl and phenoperidine produced a straightforward summation of effect in that the mixture, in both cases, was associated with a lesser threshold-raising effect than that of the opiates given alone. It is interesting to note that the antanalgesic effect of droperidol was apparently of longer duration than the observation period itself, in contrast to the analgesic effect of fentanyl and phenoperidine which were both waning towards the end of the observation period. This would tend to confirm views concerning the relative duration of action of these three drugs, namely that fentanyl is the shorter-acting of the two opiates and that droperidol exerts its action for a longer period than either fentanyl or phenoperidine.
ACKNOWLEDGEMENTS

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REACTIONS A LA DOULEUR SOMATIQUE ASSOCIEE A L'ANESTHESIE

XIX: ETUDES DE MEDICAMENTS UTILISES EN NEUROLEPTANALGESIE

SOMMAIRE

Les effets de certains médicaments administrés par voie intraveineuse, sur la sensibilité à la douleur somatique causée par pression sur le tibia, ont été étudiés au cours d'un essai contrôlé à double-insu. Parmi les médicaments figuraient ceux employés d'habitude en neuroleptanalgesie (fentanyl, phenoperidine et droperidol), des opiaces standard (morphine, diamorphine) et un tranquillisant standard (diazepam). Les analgésiques ont été administrés en doses communément considérées cliniquement équivalentes. Fentanyl et phenoperidine réduisirent la sensibilité des sujets à la douleur somatique, tandis que la solution saline, morphine, diamorphine et diazepam n'eurent aucun effet. Droperidol causa une augmentation de la sensibilité et l'addition de droperidol, soit à la phenoperidine, soit au fentanyl, ne causa qu'une simple sommation de l'effet. On en conclue qu'il existe une différence entre le mode d'action de fentanyl et phenoperidine et celui de morphine; pour les deux premiers, il s'agit d'un effet relativement plus prononcé sur le mécanisme de perception de la douleur, tandis que la morphine agit relativement plus sur l'expérience affective de la douleur.

ÄNDERUNGEN DER SCHMERZBEANTWORTUNG WAHREND ANAESTHESIE

XIX: UNTERSUCHUNGEN MIT NEUROLEPTANALGETICS

ZUSAMMENFASSUNG