Downloaded from http://asa2.silverchair.com/anesthesiology/article-pdf/27/4/497/284740/0000542-196607000-00016.pdf by guest on 09 April 2024

The Earlobe Algesimeter. 2. The Effect on Pain Threshold of Certain Phenothiazine Derivatives Alone or Combined with Meperidine

E. S. Siker, M.D., Bernard Wolfson, M.D., William D. Stewart, M.D., Paul J. Schaner, M.D.*

After the introduction of chlorpromazine by Courvoisier and her colleagues [1] in 1951, Laborit [2] reported that narcotic induced analgesia was potentiated by phenothiazine derivatives. The combined administration of narcotics and phenothiazine derivatives was soon widely applied clinically and many publications attesting to the potentiation of analgesic effects appeared. The principal areas in which these combinations were studied including preanesthetic medication and pain relief during the first stage of labor. Few of these studies were controlled and in still fewer was the double blind technique used. In 1961, Keats and his associates,[3] in one of the first contradictory reports were unable to show any potentiation of meperidine induced analgesia by promethazine in patients with postoperative pain.

In 1960, Clutton-Brock,[4] using a method of algesimetry based upon the application of graded pressure to the anterior tibial surface, demonstrated that barbiturates could reduce the degree of analgesia otherwise afforded by a dose of meperidine. He coined the word "antanalgesia" to describe this pharmacological effect. In 1961, using a modification of Clutton-Brock's method of algesimetry, Dundee and Moore [5] published the first of an exhaustive series of investigations concerning the effects of various phenothiazine derivatives on pain threshold. They found that promethazine alone consistently increased the patient's sensitivity to pain and that the combination of 100 mg. of meperidine and 50 mg. of promethazine, while producing no consistent pattern, generally produced less analgesic effect than meperidine alone. In subsequent investigations Dundee classified a large number of phenothiazine derivatives as either markedly or slightly antanalgesic or as having some analgesic activity.[6] Unlike the results with promethazine these classifications were based solely on estimations made after the intramuscular injection of the phenothiazine prior to surgery. In a later publication [7] the same group of investigators pointed out that all the phenothiazines exhibited a biphasic response of antanalgesia followed by analgesia and that the timing of the change in response varied from drug to drug. A number of investigators [6, 7, 8] reported that restlessness frequently followed the administration of phenothiazine derivatives. The occurrence of excitatory phenomena during methohexital anesthesia following premedication with the "antanalgesic" group of phenothiazines has also been reported.[8]

Keats [9] took exception to the term "antanalgesia" on the grounds that it did not sufficiently delineate algesimetric experiments using artificial pain sources from clinical situations where patients had pain of organic origin. He suggested that the term "hyperalgesia" would better describe an increased appreciation for painful stimuli. In rebuttal, Clutton-Brock [10] pointed out that the term had been coined specifically to describe the effects of one drug in reducing the analgesic effect of another and not to describe increased sensitivity to pain following a single drug. Indeed, he was unable to demonstrate any lowering of pain threshold following barbiturate alone in his original work.

Impetus for the present study came in part from the availability of the recently described modification of the earlobe algesimeter [11] and in part from the report by Robson and his associates [12] of opposite results with tibial pressure and radiant heat algesimetry following the injection of sodium thiopental.

* Department of Anesthesiology, Mercy Hospital, Pittsburgh, Pennsylvania.

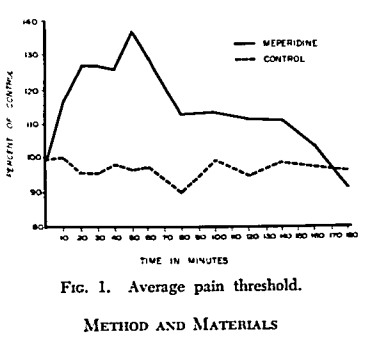

FIG. 1. Average pain threshold.

METHOD AND MATERIALS

The same 8 male and 8 female volunteers who served as the subjects for the recent assessment of the modified earlobe algesimeter [11] were the subjects for the present study. The earlobe algesimeter was used to determine pain threshold and the same pretest procedure was followed. After predrug control determinations were obtained, each subject received 0.3 mg./kg. of promethazine, promazine or propiomazine, alone, or in combinations with 1.0 mg./kg. meperidine. The drug or drugs were administered intravenously in a total volume of 5.0 ml. over a two-minute period. Six tests were therefore performed on each subject at approximately 4 to 6 week intervals. During the first half of the study, four instances of thrombophlebitis were seen. The volume of the diluent (distilled water) was then increased to 10 ml. and the intravenous injection restricted to a vein in the antecubital fossa. The end of the injection was taken as "zero" time and pain threshold, recorded in volts, was measured at 10-minute intervals for the first hour and 20 minute intervals for the next two hours. The test operator also noted whether or not the subject was sedated and recorded any spontaneous subjective complaints. Neither the subject nor the test operator knew the nature of the medications injected. Each subject served as his own control and the pretest pain threshold was noted as 100 per cent with the remainder of the values changed to per cent of control.

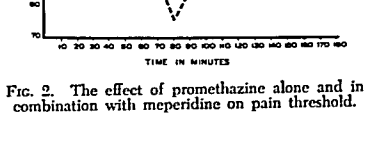

FIG. 2. The effect of promethazine alone and in combination with meperidine on pain threshold.

RESULTS

Analgesia. Figure 1 represents the average pain thresholds of the 16 subjects following the administration of 1.0 mg./kg. meperidine alone and normal saline alone. The average pain thresholds following the administration of promethazine with and without meperidine are shown in figure 2. The pain thresholds shown by these curves do not differ significantly from those of the saline control. The average pain thresholds following the administration of promazine with and without meperidine are shown in figure 3. The pain thresholds following the administration of promazine alone do not differ significantly from the saline control, and those following its combined administration with meperidine do not differ significantly from those following the administration of meperidine alone. As with promethazine, the average pain thresholds following the administration of propiomazine alone or with meperidine do not differ significantly from the saline controls (fig. 4).

Sedation. Sedation appeared within the first 10 minutes with all three phenothiazine derivates when administered in combination with meperidine. In the absence of meperidine, sedation appeared within 10 minutes following the administration of promazine alone. However, with promethazine alone, marked restlessness was seen in 5 and moderate restlessness in 3 of the 16 subjects. After an interval of 30 to 45 minutes, the restlessness disappeared and the subjects manifested sedation that was not distinguishable from that which occurred when meperidine was also administered. The administration of propiomazine alone was followed by marked restlessness in 4 and moderate restlessness in 3 of the 16 subjects. Those

Downloaded from http://asa2.silverchair.com/anesthesiology/article-pdf/27/4/497/284740/0000542-196607000-00016.pdf by guest on 09 April 2024

who did not become restless did not appear to be particularly sedated, until 30 to 45 minutes after the injection when this entire group also manifested marked sedation. Of the restless subjects in the propiomazine group, 4 complained of inability to find a comfortable position, found it difficult to remain still, and stated that either their arms or legs felt cramped.

Thrombophlebitis. Thrombophlebitis was observed twice with promazine and once each with propiomazine and promethazine when these drugs were combined with meperidine and injected in a volume of 5.0 ml. The fifth episode of thrombophlebitis occurred after the volume had been increased to 10 ml., following the administration of propiomazine alone into a vein on the dorsum of the hand. This occurred in a female subject who had previously developed thrombophlebitis after the injection of a promazine-meperidine combination into a vein in the anticubital fossa.

Miscellaneous Effects. Two instances of nausea were seen, both when meperidine alone was administered. There was a significantly greater number of complaints of dryness of the mouth following the administration of meperidine-promethazine than following any other drug.[5] There was no significant difference in the incidence of dizziness following the administration of the various drugs or combination of drugs, and indeed, two instances of dizziness followed the administration of normal saline.

Discussion

In the present investigation neither promethazine, promazine nor propiomazine when given alone had a significant effect upon pain thresholds determined by means of the earlobe algesimeter. This is in contrast to the reports of Dundee[7] who demonstrated a biphasic response with these drugs and classified the main effects as being mildly analgesic for promazine and propiomazine and markedly antanalgesic for promethazine. However, when the results of the combined administrations of the phenothiazines with meperidine are considered it can be seen that the results in both investigations are to some extent similar. Thus in both series promethazine is shown to be markedly antanalgesic. The preliminary antanalgesic phase demonstrated by Dundee[7] for propiomazine is shown here in a more marked form and would appear to be equal to that produced by promethazine. The subsequent analgesic phase is not demonstrated in the present study. Neither the antanalgesic nor the analgesic response described by Dundee[7] for promazine is demonstrated here either by its solitary or combined administration with meperidine. The differences between the present observations and those of Dundee and his associates can at least in part be explained by the differences in technique, *i.e.*, volunteers as opposed to patients, intravenous as opposed to intramuscular injection, and finally, the use of a different type of algesimeter. The incidence of moderate to severe restlessness was high when promethazine or propiomazine was used alone. However, with both agents this disappeared spontaneously within 30–45 minutes and was followed by sedation in all of the subjects.

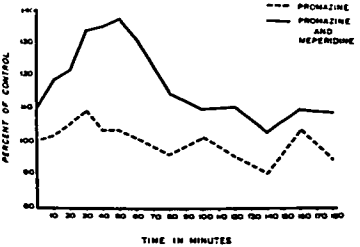

FIG. 3. The effect of promazine alone and in combination with meperidine on pain threshold.

Although this study was unable to corroborate the antanalgesic-analgesic sequence reported by Dundee[7] following the administra-

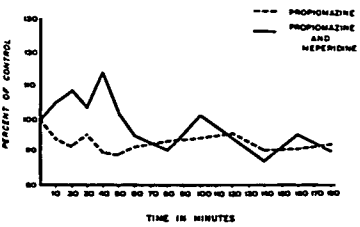

FIG. 4. The effect of propiomazine alone and in combination with meperidine on pain threshold.

Downloaded from http://asa2.silverchair.com/anesthesiology/article-pdf/27/4/497/284740/0000542-196607000-00016.pdf by guest on 09 April 2024

tion of all phenothiazine drugs, it did demonstrate a restlessness-sedation sequence following both promethazine and propiomazine. When meperidine was administered with the phenothiazine no restlessness was seen and marked sedation was observed with all three drugs. These findings are in keeping with those of other investigators [13, 14] who found that opiates prevented promethazine-induced restlessness and are highly suggestive of a relation between restlessness and antanalgesic properties. Since peak blood levels must occur soon after intravenous administration, the findings suggest that with the dosage used, higher blood levels of both promethazine and propiomazine are associated with antanalgesia while lower levels cause sedation. Dundee *et al.*[15] have also reported greater restlessness with high than with low doses of promethazine. Possible explanation for the more marked antanalgesia found with propiomazine in this study is that higher plasma concentrations may result from 20 mg. administered intravenously than from 40 mg. intramuscularly (Dundee).

Some of the limitations that must be placed on the interpretation of algesimetric findings have been stressed previously.[11] The results of the present study suggest that still further limitations must be added before extrapolating to clinical situations. The presence of such side effects as sedation or restlessness may well affect the subject's ability to interpret the painful end point. Further, the tense and apprehensive preoperative patient may react differently to the pharmacological effects of the phenothiazine compounds than does the experienced conscious volunteer.

The present findings suggest that with reference to analgesia, neither promethazine nor propiomazine should be used alone or in combination with narcotics. However, many studies attest to the advantages of such combinations in both the pre- and postoperative periods. These advantages must stem mainly from the increased sedation afforded by the mixture over the narcotic alone. From an investigative point of view, algesimetry may be of value in the study of this group of drugs provided it is recognized that the results are indicative of only one facet of their pharmacology. Clinical evaluation in any given situation must necessarily be based on a much wider range of information.

References

1. Courvoisier, S., Fournel, J., Ducrot, R., Kolsky, M., and Koetschet, P.: Proprietes pharmacodynamiques du chlorhydrate de chloro-3-(dimethylamino-3'-propyl)-10-phenothiazine (4560 R.P.); etude experimentale d'un nouveau crops utilise l'anesthesie potentialisee et dans l'hibernation artificielle, Arch. Int. Pharmacodyn. 92: 305, 1953.
2. Laborit, H., Jaulmes, C., and Benitte, A. C.: Quelques aspects experimentaux de l'hibernation artificelle, Anésth. Analg. (Paris) 9: 232, 1952.
3. Keats, A. S., Telford, J., and Kuroso, Y.: Potentiation of meperidine by promethazine, Anesthesiology 22: 34, 1961.
4. Clutton-Brock, J.: Some pain threshold studies with particular reference to thiopentone, Anaesthesia 15: 71, 1960.
5. Moore, J., and Dundee, J. W.: Alterations in response to somatic pain associated with anaesthesia. V. The effect of promethazine, Brit. J. Anaesth. 33: 3, 1961.
6. Moore, J., and Dundee, J. W.: Alternations in response to somatic pain associated with anaesthesia. VII. The effects of nine phenothiazine derivatives, Brit. J. Anaesth. 33: 422, 1961.
7. Dundee, J. W., Love, W. J., and Moore, J.: Alterations in response to somatic pain associated with anaesthesia. XV. Further studies with phenothiazine derivatives and similar drugs, Brit. J. Anaesth. 35: 597, 1963.
8. Dundee, J. W., and Moore, J.: The effects of premedication with phenothiazine derivatives on the course of methohexitone anaesthesia, Brit. J. Anaesth. 33: 382, 1961.
9. Keats, A. S.: Pain, analgesia, and anti-analgesia (Editorial), Anesthesiology 26: 1, 1965.
10. Clutton-Brock, J.: Anti-analgesia (Letter to the Editor), Anesthesiology 26: 697, 1965.
11. Siker, E. S., Wolfson, B., and Stewart, W. D.: Further experience with the earlobe algesimeter, Anesthesiology 27: 88, 1966.
12. Robson, J. B., Davenport, H. T., and Sugiyama, R.: Differentiation of two types of pain by anesthetics, Anesthesiology 26: 31, 1965.
13. Eckenhoff, J. E., Helrich, M., and Rolphw W. D.: Effects of promethazine upon respiration and circulation of man, Anesthesiology 18: 703, 1957.
14. Miller, R. A.: Promethazine and circulatory response to tilting, Canad. Anaesth. Soc. J. 4: 346, 1957.
15. Dundee, J. W., Moore, J., Love, W. J., Nicholl, R. M., and Clarke, R. S. J.: Studies of drugs given before anaesthesia. VI. The phenothiazine derivatives, Brit. J. Anaesth. 37: 332, 1965.

Downloaded from http://asa2.silverchair.com/anesthesiology/article-pdf/27/4/497/284740/0000542-196607000-00016.pdf by guest on 09 April 2024