Respiratory Arrest Caused By Demerol

By R. R. Grayson, M. D.

(Editor's Note—In April, 1956 the Perry County Memorial Hospital celebrated its fifth anniversary. The occasion was celebrated as their Hospital Day, which we were privileged to attend. We took this opportunity to devote a portion of the issue of our April Journal to the recognition of our neighbors, Perryville. While their hospital celebration is not an annual affair, we have again chosen this month of April as the month in which we wish to salute Perryville again, and to show recognition to them by publishing contributions from some of its physicians. The article by Dr. R. R. Grayson, "Respiratory Arrest Caused by Demerol," appears in this issue. While it is our wish that we may get contributions for our Journal for publication from our collegues at Perryville throughout the year, we are particularly interested in having this one for our April issue.)

Meperidine (Demerol) ordinarily is looked upon as a safe drug to use for all instances in which pain is to be relieved. One of the impressions in many physicians' minds, which carries over from the early days of the drug, is that Demerol has little potentiality for causing serious respiratory depression.

As will be seen by the following case report and the review of some of the available literature on the subject, Demerol is a dangerous drug in some instances and is to be used with great caution because of its potentiality for severe respiratory depression.

Case Report

Mrs. E. D., age 81, was seen on an emergency house call at 11:00 P.M., August 30, 1956, because of severe chest pain.

The patient previously had been seen on several occasions with severe chest pain due to coronary insufficiency and had been treated with 75 to 100 milligrams of Demerol intramuscularly, and on one other occasion with 1/6 grain of morphine sulphate, I.M., without difficulty.

On this particular occasion the patient was pale, vomiting and sweating, and complaining of excruciating, crushing, chest pain. It was decided, on the basis of the clinical picture, that the patient was probably suffering from acute coronary thrombosis. In view of this and also in view of recent advice in the medical literature in regard to the use of intravenous morphine and Demerol in cases of this sort, the patient was administered 100 milligrams Demerol intravenously over a period of two minutes.

Following this, the patient rapidly became comatose and her respirations decreased in depth and frequency until, within a period of 8 minutes, her respirations had all but ceased.

The situation was of extreme urgency and it was thought by all present in the room that the patient had expired. However, artificial respiration was administered and one ampule of Nalline (N-allyl-normorphine hydrochloride), 10 milligrams, was administered intravenously. This was without apparent effect and accordingly Coramine (Nikethamide), 5 cc., was administered intravenously with immediate benefit. The patient recovered from her apnea and became somewhat alert following this.

Thereafter, the patient required 5 cc. of intravenous Coramine every 10 to 15 minutes for the next 3 hours to maintain a semi-conscious state. One more ampule of Nalline was administered 30 minutes later when the patient arrived in the hospital, but this again failed to reverse the effect of the Demerol.

Fortunately, the patient survived this therapeutic misadventure. Serial electrocardiograms and other appropriate studies indicated that a coronary occlusion had not occurred on the night of the misadventure but that the patient in actuality had suffered from acute myocardial insufficiency. Subsequently, the patient was relieved of her attacks of nocturnal myocardial insufficiency by digitalization.

Discussion

In retrospect, it is apparent that this patient should have been administered a smaller dose of Demerol than 100 milligrams. For a person her age, half of the dose, probably, would have been adequate and would have been without danger of severe respiratory depression.

It will be noted, however, in the following review of the literature that the danger of respiratory depression due to Demerol is not generally recognized. The author, in addition, has failed to find in the literature available to him any episodes of actual respiratory arrest such as the one reported here due to the administration of Demerol by either the intravenous or the intramuscular route.

However, there have been unreported instances of respiratory depression due to Demerol by the intramuscular route, in the Perry County Memorial Hospital. One such case was a 76-year-old man who was given 50 milligrams of Demerol I.M. on the orders of another physician and who developed severe respiratory depression with a respiratory rate of approximately 6 per minute. This occurred several years ago and the patient, fortunately, survived after appropriate therapy.

Review of the Toxicity of Demerol

According to Orkin[1] the status of Meperidine as a respiratory depressant is becoming more apparent. He states that many authors have claimed that Meperidine does not depress respiration. This opinion was based upon the finding that the respiratory rate was not depressed and was often elevated 30 to 60 minutes following subcutaneous administration. He quotes Loeschcke et al,: "They found that 150 milligrams of Meperidine depressed both rate and depth of respiration. With 100 milligrams of Meperidine, all the subjects in the investigation had increased respiratory rates. The reduction in the minute and effective minute volumes was thereafter entirely an expression of the decreased depth of respiration."

Van Dyke[2] stated that Meperidine differs from morphine in causing less respiratory depression, less sedation, less euphoria, no suppression of coughing, no interference with gastro-intestinal motility, and less dizziness or nausea.

Another example of the type of information which has led to the impression that Demerol does not depress respiration is the information given in the Textbook of Pharmacology by Salter in 1952[3]: "The lethal dose (LD_{50}) of Demerol in laboratory animals ranges from 20 to 150 milligrams per kilo when given parenterally and has about twice this range when administered orally. In moderate dosage it depresses both

blood pressure and respiration in the anesthetized dog; but the respiratory depression is less than with codeine or methadon and considerably less than with morphine at equal levels of sedation. Meperidine in doses of about 200 milligrams in human individuals, especially when repeated within four hours, causes symptoms and signs resembling atropine poisoning."

EVIDENCE REGARDING POTENTIALITY FOR RESPIRATORY DEPRESSION

Loeschcke and his co-workers, in 1953[4], measured the effect of morphine and meperidine upon the respiratory response of normal men to low concentrations of inspired carbon dioxide. They discovered that meperidine was considerably more depressant than morphine, as manifested in the respiratory rate, depth and minute volume at a given alveolar $_{p}CO_2$. and in the increase in the minute volume for each increment in the $_{p}CO_2$. They concluded that in equivalent analgesic dosage, meperidine is at least as depressant as morphine to the normal human respiratory center.

Van Dyke[2] stated that pharmacological experiments readily demonstrate that meperidine depresses respiration apparently by a central action. Such an effect has rarely been observed after clinical use except in patients with intracranial lesions.

The analgesic potency of 100 mg. of meperidine parenterally approaches that of 10 mg. of morphine administered subcutaneously. Meperidine does not cause constipation and it does not lessen cough. Peculiar toxic effects were observed in a high proportion (35 per cent) of 20 patients in Van Dyke's series who had intracranial lesions. The most serious sign was a depression of respiration manifested by a respiratory rate of 12 or less per minute. Meperidine is not a suitable analgesic for such patients.

The toxic effects of therapeutic doses of meperidine may be annoying and sometimes are frequent, especially in ambulatory patients. They rarely are serious and only infrequently require discontinuance of the drug. They are dizziness, lightheadedness, nausea or vomiting or both, flushing, perspiration, dryness of the mouth, syncope, euphoria, delirium, cyoclonic contractions, cerebral irritation with nervousness, disorientation, tremors, and jerking movements.

Brotman and Cullen[5], in an article on supplementation with Demerol during nitrous oxide anesthesia, noted that almost all of the respiratory complications that occurred during their series of 317 patients receiving anesthetics consisted of respiratory depression or apnea and that these occurred during the early part of the series before experience concerning the proper dosage and timing of injections of Demerol had been acquired. In other words, it is apparent that these authors experienced episodes of severe respiratory depression during anesthesia much like the case in question[5].

McDermott and Papper, in commenting on respiratory complications associated with Demerol[6], stated that the concept that Demerol is not depressant to respiration and has no adverse effects upon breathing patterns cannot be accepted in all circumstances of its use. Experiments in anesthetized animals can be cited to demonstrate its depressant action which appears benign only in contrast with the more important effects of morphine. The clinical experience of an insignificant alteration of res-

piratory function in unanesthetized man cannot be applied to the circumstances of clinical anesthesia with Pentothal and nitrous oxide without modification. It appears probable that the combined circumstances of general anesthesia and the intravenous injection of Demerol can account for much of the respiratory depression.

PHARMACOLOGY OF CORAMINE

Inasmuch as Coramine apparently was the life-saving antidote in the case reported in this paper, the following information regarding the drug will be of some interest.

Coramine[7] stimulates the respiratory and vasomotor centers, and in higher doses produces delirium and muscular twitching, eventually leading to clonic convulsions. It has been used with some success in stimulating the medullary centers. It has no direct effect, however, upon the circulation other than through the vasoconstrictor center.

Probably its most effective site of action is the chemoreceptors of the carotid and aortic bodies which it stimulates rather specifically. Coramine influences the respiratory center by stimulating the chemoreceptors of the carotid body.

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SUMMARY

1. A case of respiratory arrest due to the administration of 100 milligrams of Demerol intravenously in an 81-year-old woman suffering from acute myocardial insufficiency is reported.

2. The patient recovered after the intravenous administration of large doses of Coramine. Two 10 milligram doses of intravenous Nalline appeared to be ineffective in reversing the respiratory depression.

3. The available literature on the respiratory depression caused by Demerol is reviewed. It is apparent that the potentialities for respiratory depression by Demerol have been underestimated in the past.

4. It is concluded that Demerol can cause dangerous respiratory depression in certain individuals. The present experience would indicate that the aged patient should be administered Demerol in cautious amounts.

5. Intravenous Coramine in frequent doses appears to be an effective antidote for the respiratory depression caused by large doses of Demerol.

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