Circulatory Response to Tilting Following Methotrimeprazine and Morphine in Man

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The effects of methotrimeprazine, a nonaddicting analgesic phenothiazine, on circulatory compensation following head-up tilt were compared with morphine in normal volunteers. Fainting occurred in 20 per cent with morphine and in approximately 70 per cent after methotrimeprazine. Results suggested that some factor other than the level of arterial blood pressure, contributed to the incidence of syncope. There is evidence to suggest that circulatory response to tilt, with drugs causing decompensation, may be employed to estimate the time of onset and duration of action of such drugs. The circulatory effects of methotrimeprazine would mitigate against its use for preanesthetic medication. The analgesia provided in the absence of addiction liability or apparent respiratory depression suggests further study in nonambulatory patients with pain problems.

THE SEARCH for a potent, non-narcotic analgesic continues. The goal is a compound which will provide adequate pain relief in the absence of the chief disadvantages of most of the currently available potent narcotics--respiratory depression, circulatory depression, and addiction liability. Methotrimeprazine (2-methoxy-10-(2-methyl-3-dimethyl-aminopropyl)-phenothiazine), a drug closely related to chlorpromazine, was demonstrated to have marked analgesic properties with minimal respiratory effect,[1] and no opiate-like addictiveness.[2]

Reports on this compound, from France, have been uniformly enthusiastic.[3-6] Subsequent studies in this country have resulted in conflicting opinion. For example, the incidence of drowsiness or sleepiness was found to be high,[2] moderate,[1] or low,[7] compared to morphine. Severe orthostatic hypotension has been reported in some patients,[2] yet other investigators have indicated the absence of any circulatory depression.[8] Its analgesic effect has been compared with morphine on an equivalent basis in one study[1] while another investigator reported morphine to be three times as potent as methotrimeprazine.[7]

In view of the structural similarity to chlorpromazine (figure 1), and reports of orthostatic hypotension in ambulatory patients receiving this compound, it was considered advisable to study its effect on circulatory compensation to head-up tilt in normal volunteers prior to its use as preoperative medication in surgical patients.

Method

The subjects were 10 volunteer normal medical students, 9 men and 1 woman, ranging in age from 22 to 29 years. Each received the test drug on one occasion and the standard drug on another. Since individual variation is quite wide in response to head-up tilt and to the various hypotension-producing agents, each individual served as his own control and the order of drug administration was randomized. Those who failed to compensate after the full dose of the test drug were studied again with a half dose of the compound. Subjects weighing less than 175 pounds received 10 mg. of methotrimeprazine or the same dose of morphine; those weighing more than 175 pounds received 15 mg. of either drug. Weights ranged from 125 to 205 pounds.

Studies were carried out in an air-conditioned laboratory where narrow limits of ambient temperature and humidity were maintained. An effort was made to provide quiet, with a minimum of extraneous noise. Measurements were made in the post-prandial state at approximately the same time of day, by the same investigating team. Arterial blood pres-

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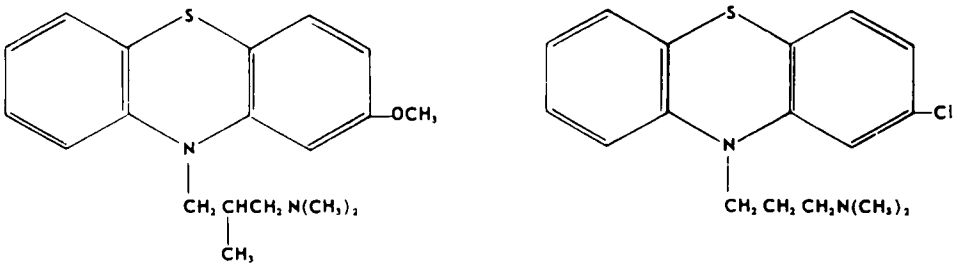

FIG. 1. Structured formula for methotrimeprazine (left) and chlorpromazine (right).

sure and pulse rate were monitored by means of an intra-arterial needle, strain gauge and recording oscillograph. Lead 2 of the electrocardiogram was recorded continuously. An interval of approximately one week elapsed between studies.

Subjects were tilted rapidly (5 to 10 seconds) into the 60 degree head-up position on a standard operating table employing a footboard and a belt above the knees. This position was maintained for 15 minutes unless fainting or profound hypotension occurred. Following the control tilt, the subject was returned to the supine position and the test drug injected intramuscularly. Test tilts were then done at 30, 60, 90, and 180 minutes as indicated. An intravenous infusion of 5 per cent dextrose in water was supplied at a slow constant rate throughout the study.

Results

Of the 10 individuals receiving morphine, there were 2 who fainted at some time during the head-up period, an incidence of 20 per cent. Of the 16 studies done with methotrimeprazine, 11 individuals fainted, an incidence of approximately 70 per cent. These differences are significant at the 5 per cent level.* Of the 9 subjects receiving the full dose of methotrimeprazine, there were 5 fainters, an incidence of 56 per cent. Among the 7 receiving the half dose of methotrimeprazine there were 6 fainters, or 85 per cent.

The time elapsing before fainting in those individuals who fainted during the test head-up tilt was related to drug and dosage. With morphine there were 6 faints which occurred from 7 to 12 minutes after the head-up posi-

* Chi square = 4.1 (employing Yates correction), $P < 0.05$.

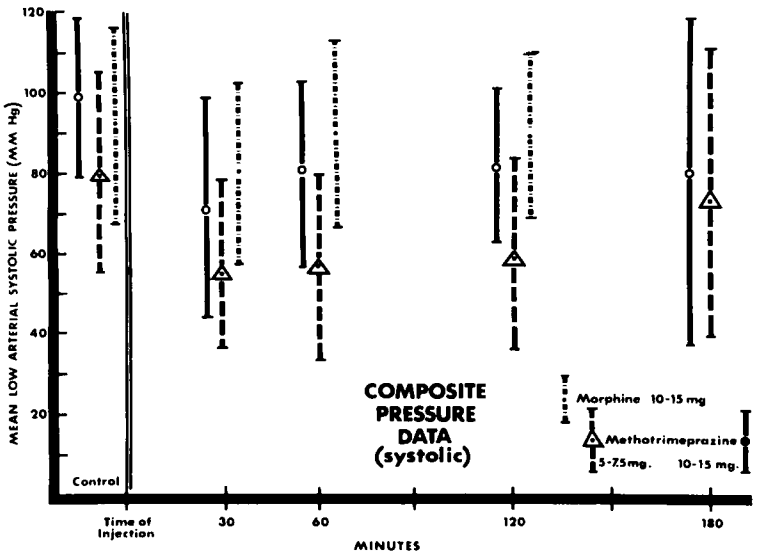

FIG. 2. Mean low arterial systolic pressure (plus or minus 1 standard deviation) following head-up tilt.

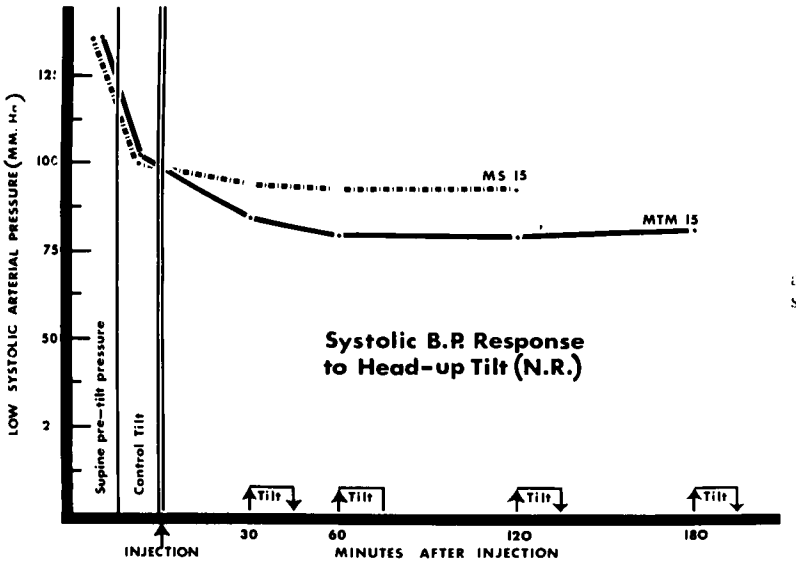

FIG. 3. Low systolic arterial pressures observed after head-up tilt.

tion was assumed and averaged 10.2 minutes. With the full dose of methotrimeprazine there were 15 faints within 1.5 to 11 minutes, averaging 4.8 minutes, and with the half dose of methotrimeprazine there were 17 faints ranging from 1.5 to 14.5 minutes, averaging 7.1. Thus, when a subject lost consciousness during tilt, he did so more rapidly with methotrimeprazine at either dosage than with morphine and more rapidly with the full dose of methotrimeprazine than with the half dose. The difference between morphine and the full dose of methotrimeprazine was statistically significant. That between the half dose of methotrimeprazine and either morphine or the full dose was not.

Pulse rate varied considerably from subject to subject and in the same individual with different tilts and different drugs. There was no correlation between pulse rate and the ability to compensate, and no change in pulse rate that would predict failure to compensate. The electrocardiogram remained unchanged following the injection of drug and head-up tilt in all of the studies.

Figure 2 summarizes the blood pressure re-

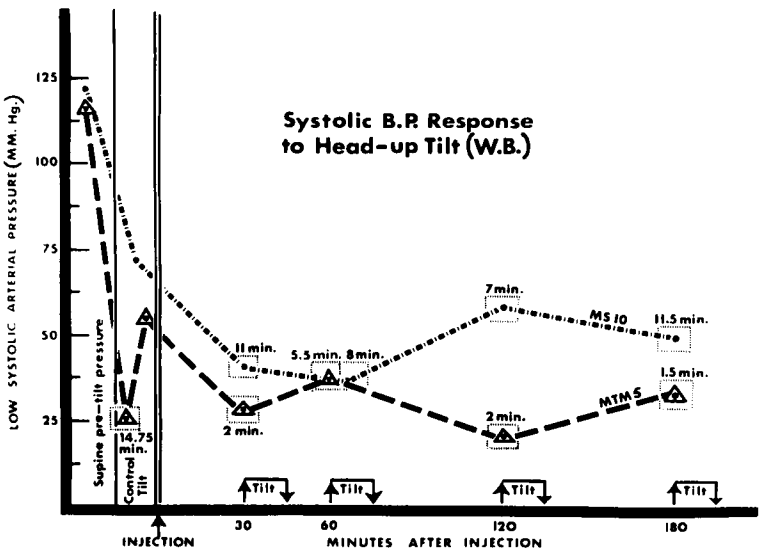

FIG. 4. Low systolic arterial pressures observed after head-up tilt. Square surrounding point indicates faint. Numbers above square are times that syncope occurred after assumption of head-up position.

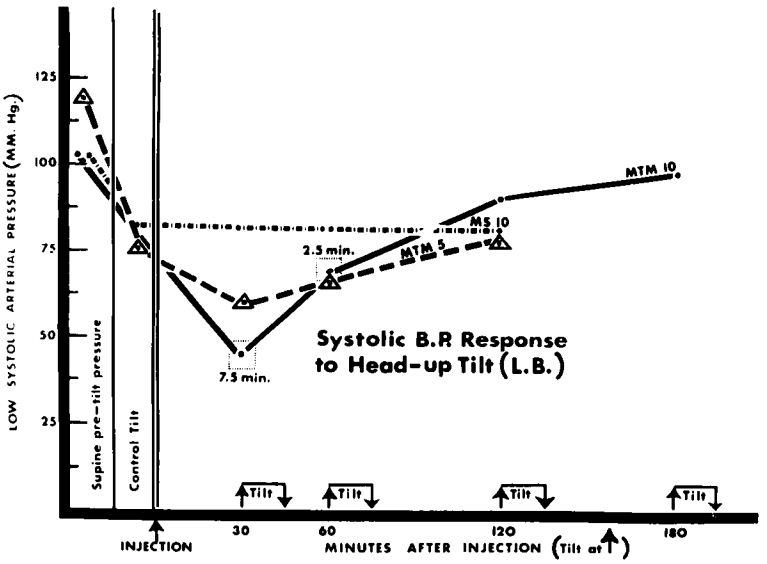

FIG. 5. Low systolic arterial pressures observed after head-up tilt. Square surrounding point indicates a faint. Numbers above square are times that syncope occurred after assumption of head-up position.

sponse to tilting. Mean lowest systolic pressures, plus or minus 1 standard deviation, are plotted for morphine and the two dosage levels of methotrimeprazine at each time interval. In general, compensation following methotrimeprazine was less effective. The large standard deviations are a consequence of having to use either fainting or hypotension as an endpoint and immediately return the subject to the supine position. Blood pressure and pulse were analyzed in terms of deviation from control values and produced the same wide standard deviations, presumably for the same reason.

The type of response, however, was not consistent and may be best reported by considering specific individuals. In the subject depicted in figure 3 there was a moderate fall in blood pressure with the head-up tilt as compared to the control in the supine position. However, there was no specific response to the test drugs that differed in any way from the control response. This individual apparently possesses an extremely stable circulatory sys-

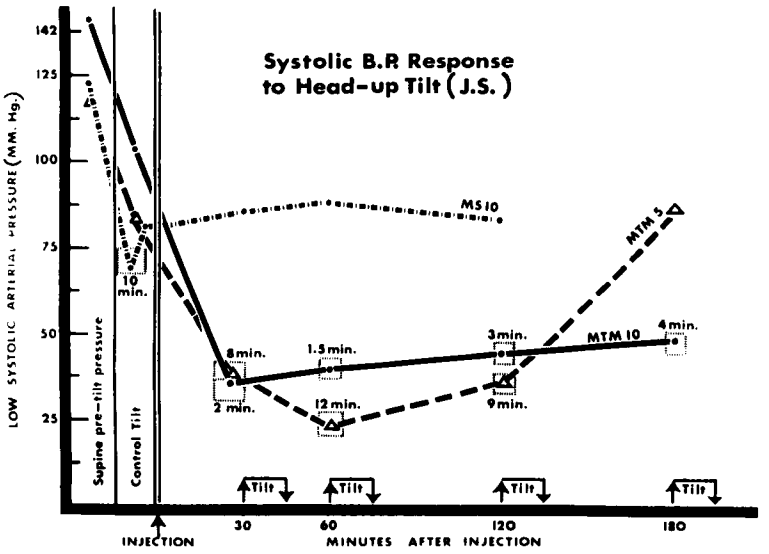

FIG. 6. Low systolic arterial pressures observed after head-up tilt. Square surrounding point indicates faint. Numbers above square are times that syncope occurred after assumption of head-up position.

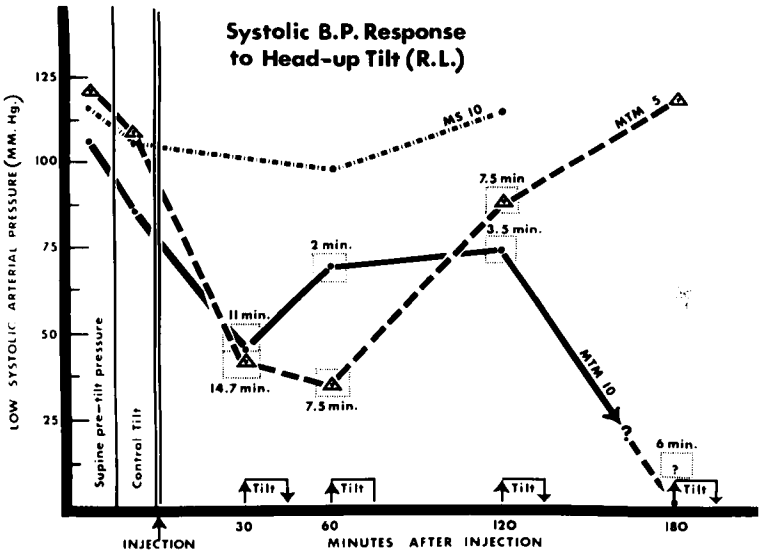

FIG. 7. Low systolic arterial pressures observed after head-up tilt. Square surrounding point indicates faint. Numbers above square are times that syncope occurred after assumption of head-up position.

tem as measured by this test. The counterpart is presented in figure 4. This subject fainted in response to the head-up tilt in the presence of both of the drugs. The sole method for differentiation of the drug effects was afforded by the difference in time required for the break in compensation.

In figure 5 one notices that the fall in blood pressure produced by the two doses of methotrimeprazine at 60 minutes was the same, however, syncope occurred only with the larger dose. Figure 6 is the record of an individual who fainted during the morphine control tilt. He is obviously the type of individual who is less likely to withstand circulatory stress. It is significant that he fainted more rapidly at 30 minutes with the larger dose of methotrimeprazine even though the blood pressure recorded at the time of faint is the same. At 60 and 120 minutes he reached a lower systolic pressure with the half dose before fainting. One is able to estimate the duration of drug action in that the larger dose of methotrimeprazine produced syncope and greater hypotension at 180 minutes while compensation had returned at this time with the half dose.

This seemingly paradoxical situation is again illustrated in figure 7. At 30 minutes syncope occurred with both doses of methotrimeprazine at approximately the same systolic blood pressure level, but more rapidly with the larger dose. At 60 minutes greater fall in blood pressure was seen with the lower dose of methotrimeprazine. Presumably, fainting occurred too rapidly with the larger dose to permit the low blood pressures to be reached. At 120 minutes the blood pressure picture was reversed although the time required for fainting was similar. This subject also demonstrated the relative duration of circulatory effects.

Discussion

Despite the limitations of the tilt-table method which have been enumerated in the past,[9,10] it remains as the best simple, safe test for circulatory competence. If a concerted effort is made to control the possible variables, this technique may indeed have a wide area of usefulness and provide some insight into the degree of circulatory compensation following the administration of various pharmaceutical agents. An indication of its accuracy is given by the rather consistent results when the technique has been employed following the administration of morphine. It seems reasonable, therefore, that morphine should serve as the standard of comparison for any new drug to be so studied.

The incidence of fainting or marked hypotension with morphine in young healthy adults

approximated those results reported in the literature, about 20 per cent.[11] That with methotrimeprazine in both equivalent and half dosage was significantly greater. It would seem, on the basis of these results, that the degree of circulatory compensation following stress after methotrimeprazine is significantly less than that following morphine. The use of opiates preoperatively has been questioned on the basis of the circulatory and respiratory effects.[12] In view of the apparently greater circulatory unstability following methotrimeprazine, its preoperative use is open to question. However, the apparently high level of analgesia in the absence of addiction liability or respiratory depression would suggest that further study of this drug in nonambulatory patients with pain problems is indicated.

In the past, the response of individuals to head-up tilt following various test drugs has been described exclusively from a circulatory standpoint. The results obtained in this study seem to indicate that other factors may be involved. A large or a small dose may result in the same degree of blood pressure fall in an individual tilted to the head-up position, yet fainting occurs only with the larger dose. Syncope may occur with both doses but at a lower blood pressure with the smaller dose. Finally, syncope may be produced at the same pressure level with both doses but occur more rapidly with the larger dose. These observations suggest that some basic alteration in circulatory homeostasis occurs in response to the drug. When a reduction in blood flow following arterial hypotension is superimposed, consciousness is lost.

The data also suggest that the circulatory response to tilt may be utilized to estimate the time of onset and duration of action of drugs. If tilt is done at frequent intervals after drug injection, one may approximate the time of onset for those drugs that produce circulatory decompensation. As the drug wears off the return of compensation delineates the end point of action.

Summary

The circulatory response to head-up tilt following the injection of methotrimeprazine was compared with that of morphine in 10 volunteer subjects. Failure of circulatory compensation to head-up tilt following morphine was 20 per cent; with methotrimeprazine approximately 70 per cent. In some subjects it was apparent that a factor other than the level of arterial blood pressure, possibly some central nervous system alteration due to the drug, influenced the incidence of syncope. The circulatory response to tilt following those drugs which cause a high incidence of circulatory decompensation may be employed to estimate the time of onset and duration of action of such drugs.

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