CIRCULATORY RESPONSE TO TILT WITH NARCOTIC ANALGESICS IN NORMAL HEALTHY MALE SUBJECTS

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WHENEVER a new narcotic is introduced, the reason that is usually offered, is that in the therapeutic dose the new drug provides the same degree of analgesia as morphine or meperidine, but with less undesirable 'side' effects.

Respiratory depression of some degree has been demonstrated by various techniques or observed clinically with all of the narcotics that were studied in this report. The effect of a therapeutic dose of these drugs administered subcutaneously on pulmonary ventilation is usually quite small in the normal subject breathing room air, but the depressant effect becomes obvious when an attempt is made to stimulate breathing with carbon dioxide inhalation, or when anesthesia is administered with any of the potent anesthetic agents immediately after these drugs are injected, or if they are given during the course of anesthesia.[1-6]

Many studies have been made to determine whether or not circulatory depression is a common occurrence with narcotics, especially when they are administered intravenously in therapeutic doses. Most clinicians have observed that when narcotics are administered to ill patients, a decrease in blood pressure is infrequent. Nevertheless, alarming hypotension may occur occasionally and should be expected.[7, 8, 9]

A reliable way to study the effect of narcotics on the circulation is by a standardized tilt table test in order to apply a stress to the circulatory system which might reveal an otherwise hidden effect.[10] In this report, the circulatory response to tilt was observed after injections of morphine, 15 mg., meperidine (Demerol) 100 mg., levorphanol (Levo-Dromoran) 2 mg., alphaprodine (Nisentil) 60 mg., anileridine (Leritine) 50 mg., dipipanone (Pipadone) 25 mg., and oxymorphone (Numorphan) 1.5 mg.

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METHOD

Serial tests were done at intervals of one to three days on eight healthy male subjects who were all between 20 and 30 years of age (mean, 24 years), and weighed between 140 and 196 pounds (mean, 172 pounds). The test dose selected by the authors for each drug was in approximate relation to its therapeutic analgesic potency compared with morphine and meperidine as recommended in the literature provided by pharmaceutical suppliers and as noted by others.[3-9] During the tests each drug was diluted to 5 ml. with physiological saline and injected slowly through a vein in the forearm in approximately 60 seconds. Each subject received the same dose of a particular drug as noted above.

The technique employed to compare these drugs was as follows: A blood pressure cuff was applied to the arm with a stethoscope secured over the brachial artery and the subjects were allowed to rest in the supine horizontal position for 10 minutes. The blood pressure was then recorded by the standard auscultatory method and the pulse rate was counted at the wrist at regular intervals. Each subject remained in the supine horizontal position for 15 minutes after the rest period and then was tilted over a period of one minute to 60-degree head-up position. This position was held for 15 minutes. The supine horizontal position was then resumed, and the test drug was injected. Blood pressure and pulse rate were recorded immediately after the injection and at 5 minute intervals for 15 minutes. Then the subjects were again tilted to the 60-degree head-up position over a period of 1 minute and the same procedure was followed. In each experiment, the arm used

TABLE 1

MEAN BLOOD PRESSURE AND PULSE RATE IN SUPINE AND 60-DEGREE HEAD-UP TILT BEFORE AND AFTER INJECTION OF NARCOTIC ANALGESICS

Drugs and Dose (mg.)			Before Drug		After Drug		Change Supine (*A to B*)	Change Tilt (*A to B*)
			Supine (*A*)	Tilt (*A*)	Supine (*B*)	Tilt (*B*)		
Morphine	15	BP	127/69 ± 18/12	130/81 ± 20/12	122/69 ± 17/12	125/81 ± 16/11	−5/0	−5/0
		P	75 ± 7	75 ± 6	75 ± 7	75 ± 8	0	0
Meperidine	100	BP	125/72 ± 12/8	134/83 ± 13/8	125/72 ± 13/9	135/84 ± 16/11	0/0	1/1
		P	72 ± 5	75 ± 8	75 ± 9	72 ± 6	+3	−3
Levorphanol	2	BP	128/71 ± 15/10	135/89 ± 14/11	117/67 ± 14/12	132/89 ± 14/12	−11/−4	−3/0
		P	72 ± 11	76 ± 12	72 ± 12	75 ± 11	0	1
Alphaprodine	60	BP	128/75 ± 18/11	136/84 ± 19/10	127/74 ± 25/14	135/84 ± 28/12	−1/−1	−1/0
		P	76 ± 12	78 ± 14	78 ± 11	75 ± 7	+2	−3
Anileridine	50	BP	127/72 ± 15/10	128/79 ± 15/8	123/72 ± 15/11	135/82 ± 20/14*	−4/0	+7/+3
		P	75 ± 9	75 ± 9	73 ± 11	72 ± 9	−2	−3
Dipipanone	25	BP	124/69 ± 9/5	129/80 ± 11/9	122/68 ± 16/8	130/76 ± 17/8*	−2/−1	+1/−4
		P	74 ± 10	75 ± 8	73 ± 9	72 ± 11	−1	−3
Oxymorphone	1.5	BP	124/68 ± 13/9	130/80 ± 19/8	112/68 ± 12/9	120/79 ± 15/9	−12/0	−10/−1
		P	70 ± 9	75 ± 9	70 ± 7	69 ± 7	0	−6

BP = Blood pressure.
P = Pulse.
* 2 subjects not tilted.

for blood pressure and pulse rate estimations was held at the level of the heart throughout the test. The subjects were instructed not to move on the cart or to talk during the test but were not restrained beyond having a foot rest. Any side effects that were observed were annotated during and after each test, and each subject was requested to report on any discomfort during the 24 hours after a test. None of the subjects were in a 'basal state' when the tests were done, but they were carried out in sequence—four were done in the morning after their usual breakfast and the other four were done beginning in the early afternoon. With a few exceptions, the tests were done at approximately the same time for each individual subject.

RESULTS

The mean and standard deviation of the blood pressure and pulse rate at each time interval during each drug test was computed for the eight subjects and is shown in the figures (1 to 7). Table 1 shows the mean blood pressure and pulse rate during the supine position and during 60-degree head-up tilt before and after each drug test for the eight subjects.

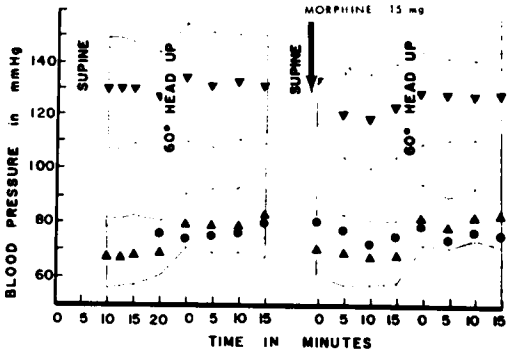

FIG. 1. Blood pressure (systolic ▼, diastolic ▲), and pulse rate • during test with morphine 15 mg. One standard deviation for systolic and diastolic blood pressure is represented by solid lines.

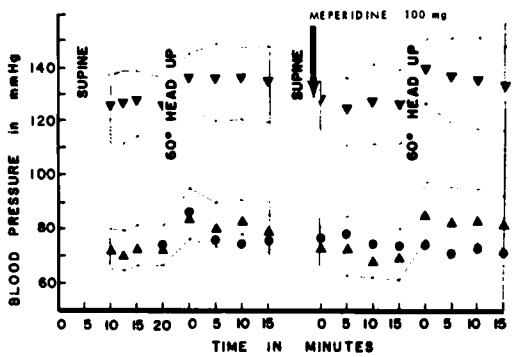

FIG. 2. Blood pressure (systolic ▼, diastolic ▲), and pulse rate • during test with meperidine 100 mg. One standard deviation for systolic and diastolic blood pressure is represented by solid lines.

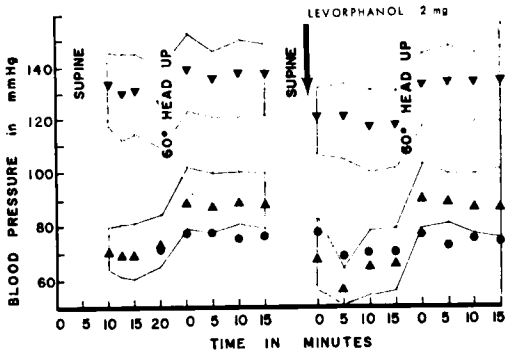

FIG. 3. Blood pressure (systolic ▼, diastolic ▲), and pulse rate • during test with levorphanol 2 mg. One standard deviation for systolic and diastolic blood pressure is represented by solid lines.

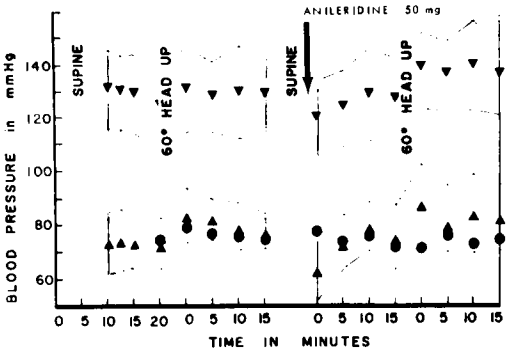

FIG. 5. Blood pressure (systolic ▼, diastolic ▲), and pulse rate • during test with anileridine 50 mg. One standard deviation for systolic and diastolic blood pressure is represented by solid lines.

Morphine sulphate (15 mg.), levorphanol tartrate (2 mg.) and oxymorphone hydrochloride (1.5 mg.) caused only a slight decrease in the blood pressure in the supine position which was not appreciably augmented by the head up tilt. Virtually no consistent change in the blood pressure occurred after the administration of meperidine hydrochloride (100 mg.), alphaprodine hydrochloride (60 mg.) anileridine hydrochloride (50 mg.) or dipipanone hydrochloride (25 mg.) although each tended to systolic hypotension. This trend was not augmented appreciably by the head up tilt. None of the drugs appeared to cause any consistent change in the pulse rate.

Even though no striking effects were observed on the pulse rate and blood pressure after the administration of these narcotic analgesics, other important changes were observed. These occurred during the test, shortly afterward, or later on, and generally were considered unpleasant side effects (table 2).

Morphine initially caused a warm, pleasant and relaxed feeling, but later the subjects complained of dizziness, drowsiness and nausea. Levorphanol appeared to cause less of the pleasant warm feeling, and less drowsiness, but more subjects felt dizzy and 2 complained of marked nausea. Meperidine caused drowsiness in 5 and nausea in 1. Alphaprodine caused dizziness in 7, nausea in 1 and nausea and vomiting in 1. Oxymorphone appeared to provide a pleasant, warm relaxing

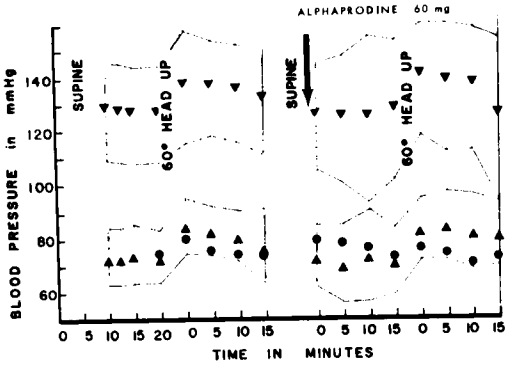

FIG. 4. Blood pressure (systolic ▼, diastolic ▲), and pulse rate • during test with alphaprodine 60 mg. One standard deviation for systolic and diastolic blood pressure is represented by solid lines.

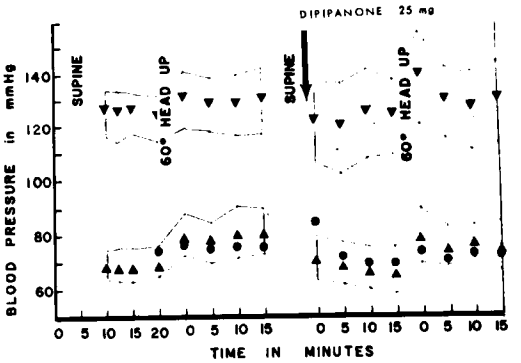

FIG. 6. Blood pressure (systolic ▼, diastolic ▲), and pulse rate • during test with dipipanone 25 mg. One standard deviation for systolic and diastolic blood pressure is represented by solid lines.

effect, somewhat similar to that of morphine, but 1 subject was nauseated, 3 were slightly drowsy and 1 was somewhat euphoric after the test.

Anileridine and dipipanone caused the greatest subjective discomfort both during the test and afterward.

Two subjects became unconscious or fainted within ten minutes after the injection of anileridine while supine, and were not tilted. In both subjects there was only a slight fall in blood pressure: Subject 7—130/60 to 118/58, and subject 8—126/70 to 120/68. One of these (subject 7) was given 5 mg. nalorphine hydrochloride (Nalline) intravenously because he had very slow breathing (4–8/minute) and cyanosis. After injection of nalorphine, the blood pressure rose promptly to 132/80. The cyanosis disappeared while subject 7 was given direct artificial respiration with air from a self-inflating bag and mask, and shortly thereafter he was conscious. At later questioning, the subject 7 was unaware of the period of unconsciousness, and said he thought he was asleep for a few minutes.

Both of the above subjects vomited several times after the test was completed, and only one subject failed to have undesirable effects after anileridine.

Three subjects fainted after dipipanone. Two fainted within ten minutes after the injection and while in the supine position (7 and 8) and one of these (7) was given 5 mg. nalorphine hydrochloride intravenously. These two subjects were not tilted, even though there was little variation observed in their blood pressures (decreased in subject 7: 130/82 to 120/80; increased in subject

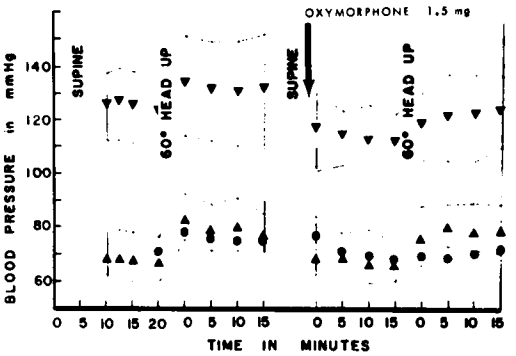

FIG. 7. Blood pressure (systolic ▼, diastolic ▲), and pulse rate ● during test with oxymorphone 1.5 mg. One standard deviation for systolic and diastolic blood pressure is represented by solid lines.

8: 110/60 to 128/78). A third subject (3) fainted within five minutes after being tilted (or approximately 18 minutes after receiving the drug), and it was observed that his blood pressure rose from 116/70 to 134/78 within the few minutes before the tilt and after fainting. The supine position was resumed immediately, and he was also given 5 mg. nalorphine hydrochloride because he became cyanotic and breathing rate was very slow (6/minute). The cyanosis disappeared promptly while the subject was given direct artificial respiration with air, and he regained wakefulness within a few minutes of the injection of nalorphine hydrochloride. During the following fifteen minutes his blood pressures at 5-minute intervals were 126/74, 120/84 and 124/84.

These three subjects that fainted after injection of dipipanone hydrochloride were nauseated for several hours after the test and

TABLE 2

PREDOMINANT SIDE EFFECTS OF NARCOTIC ANALGESICS ON EIGHT HEALTHY MALE SUBJECTS (Ambulatory Volunteers)

Subject	Morphine	Meperidine	Levorphanol	Alphaprodine	Anileridine	Dipipanone	Oxymorphone
1	dizzy; blurred vision	sl. drowsy	dizzy	dizzy	drowsy; dizzy	dizzy; drowsy	euphoric
2	drowsy	drowsy	none	none	drowsy	dizzy; nausea	drowsy
3	nausea; dizzy	dizzy; tired	nausea; dizzy; tired	dizzy	nausea; dizzy	fainted (Nalline); nausea	none
4	drowsy; nausea	dizzy; nausea	nausea	dizzy; nausea	dizzy; nausea	dizzy; nausea	none
5	tired; nausea	none	dizzy	dizzy	none	nausea	nausea
6	drowsy; itchy	drowsy	none	nausea and vomit; dizzy	drowsy; nausea	nausea	none
7	dizzy	drowsy	dizzy	dizzy	fainted (Nalline); vomit	fainted (Nalline); vomit	drowsy
8	drowsy	drowsy	dizzy	dizzy	dizzy; vomit; fainted	fainted; vomit	drowsy

two of them (subjects 7 and 8) vomited repeatedly.

Discussion

In the resting healthy male adult subject, it appears unlikely that acute circulatory depression will occur when a narcotic analgesic is administered in a therapeutic dose by the intravenous route while he is lying in the supine horizontal position. There is also little circulatory change when the 60-degree head-up position is assumed *gradually*. In our subjects the prominent initial change was respiratory depression. This effect might account for some of the so-called side effects, such as dizziness and nausea.

The occurrence of acute hypotension and vasodepressor syncope may be more likely if the 75-degree head-up position is assumed abruptly, with or without narcotics. This response becomes prominent approximately 10 minutes after the intravenous administration of a narcotic and remains a likely response for a few hours.[10, 11, 12] Drew, Dripps and Comroe have shown that this circulatory response and vasodepressor syncope can be reduced or averted by the application of elastic bandages to the legs to prevent peripheral pooling of the blood.[10] This study showed that it can also be reduced by tilting the subject gradually to 60-degrees, rather than abruptly to the steeper incline.

In those five instances in which the subjects became unconscious, it is probable that this state was similar to that seen during a stage of light general anesthesia, and any trend to hypotension may have been reduced by a vasopressor response to depressed pulmonary ventilation (which undoubtedly occurred). Vasodepressor syncope or "fainting" as seen after sudden change of posture with or without the administration of drugs that cause a marked reduction in peripheral resistance, acute lowering of the arterial blood pressure, hyperventilation, and reduction of cardiac output presents quite a different picture both clinically and physiologically from the observations in the present report. Vasodepressor syncope can always be shown in man by tilting to a 60-degree head-up position 10 to 15 minutes after the oral administration of sodium nitrite or by the method described above.[10, 13] Weissler and his colleagues have demonstrated that this reaction is characterized by a sudden fall in total peripheral resistance with failure in compensation by the cardiac output, which forms the striking feature of the 'fainting' reaction. They believe that this reaction is due to neurogenic myocardial inhibition or to a sudden markedly limited volume of blood available to the heart. This reaction can be averted with inflation of an antigravity suit, negative pressure breathing or albumin infusions, but not by the injection of atropine.[13]

Even though the subjects that took part in this study did not show any outward signs of apprehension, they may have had sufficient nervous upset at the time of the injections to have caused a masking of any greater trend to hypotension. Data are not yet available which could also rule out a sympatho-adrenal response to the injection of some or all of these narcotics, that might also have a stabilizing effect on the arterial blood pressure and pulse rate, as is seen with some general anesthetics.[14]

Although the narcotic analgesics undoubtedly cause an alteration in peripheral blood flow, the normal healthy non-ambulant adult appears to be able to compensate for this effect, so that no alarming change in the blood pressure or pulse rate is seen as long as sudden alterations in posture are not made. This stability in blood pressure and pulse rate is probably less likely in the elderly patient with a diseased cardiovascular system, or in the patient under anesthesia in whom reflex compensatory mechanisms cannot operate effectively. In the latter circumstances, these drugs should be administered with greater trepidation, particularly in view of their potent depressant effects on respiration and their potential effect on the peripheral circulation.[15, 16]

Summary and Conclusions

The circulatory response to tilt was studied in eight healthy subjects after the intravenous injection of morphine, 15 mg., meperidine, 100 mg., levorphanol, 2 mg., alphaprodine, 60 mg., anileridine, 50 mg., dipipanone, 25

mg., and oxymorphone, 1.5 mg. No appreciable alteration in the pulse rate or blood pressure was seen after these drugs were injected slowly, or after the circulatory stress of 60-degree head-up tilt was gradually applied 15 minutes after administration of the narcotic. The primary initial undesirable effect of all these drugs was respiratory depression, which may be one of the causes of other side effects. Caution should be exercised, however, when these drugs are to be given to elderly patients with diseased cardiovascular systems, or during general anesthesia. Latent circulatory effects may be exaggerated under these circumstances.

The following pharmaceutical firms supplied drugs for this study: Winthrop Laboratories of Canada Ltd., Aurora, Ontario; Hoffmann LaRoche, Ltd., Montreal; Burroughs Wellcome & Co., Montreal; Endo Drugs (Canada) Ltd., and Merck, Sharp & Dohme, Montreal, Canada.

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