PROMETHAZINE AND THE CIRCULATORY RESPONSE TO TILTING*

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PROMETHAZINE HYDROCHLORIDE (Phenergan), introduced into anaesthetic practice by Laborit (1) and employed as an integral part of the "lytic cocktail" (2), was shown by experiment on animals to possess many of the properties characteristic of the amine derivatives of phenothiazine:

Actions of Promethazine

Anti-histaminic	Quinidine-like, on cardiac muscle
Anti-emetic	Antagonistic to adrenaline and acetylcholine
Sedative and hypnotic	Protective, against shock
Potentiation of anaesthetics, analgesics, hypnotics, muscle relaxants	Anti-convulsant
	Spasmolytic
Local anaesthetic	Hypothermic

In man, however, the pharmacological actions of promethazine have been frequently obscured by simultaneous administration of other phenothiazine derivatives. Studies dealing with the use of promethazine in clinical anaesthesia (5, 6), and in obstetrics (7), and with its circulatory effects in a small number of patients undergoing cardio-angiography (8), have been complicated by prior administration of analgesics or barbiturates.

While it appears from clinical evidence that the central depressant and potentiating actions of promethazine are the ones most sought after and utilized by the anaesthetist, further investigation is required to clarify and define this use. The suggestion that the drug is valuable as a sedative and anti-emetic drug during spinal analgesia (5) indicates that further studies should also be undertaken on the circulatory actions of intravenous promethazine in order to establish whether it shares, in part, the postural hypotensive properties so characteristic of chlorpromazine (9).

In this investigation an attempt has been made to assess the action of intravenous promethazine on blood pressure, by continuous intra-arterial recording, and to observe the response to the circulatory stress of maintaining a 60-degree head-up tilt for fifteen minutes before and after administration of the drug. Some inferences have also been drawn in regard to the use of intravenous promethazine in clinical anaesthesia.

METHOD

Eighteen studies were carried out on seventeen unpremedicated male subjects between the ages of 17 and 60 years, who had undergone or were awaiting a wide variety of surgical procedures. The only criteria involved in selection of individual subjects were their ability to lie comfortably in the supine position, and their availability.

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At the start of each study a slow intravenous saline infusion was established in a forearm vein. A fine plastic catheter was then inserted through a No. 20 needle into the brachial artery at the elbow (of the other arm) and a continuous record of arterial pressure obtained by means of a Lilly capacitance manometer (10, 11) with a Sanborn single channel recorder. Very frequent checks of zero point and of the calibration of the manometer were carried out.

After control records had been obtained with the subject resting in the horizontal position, the table was tilted (not abruptly) into a 60-degree head-up tilt. This position was maintained for fifteen minutes (unless fainting occurred earlier), the subject then being returned to the horizontal. After a few minutes resting, promethazine hydrochloride 50–100 mg. was injected intravenously through the infusion tubing over a period of up to five minutes, as unobtrusively as possible. Fifteen minutes after completing the injection the table was again tilted to the 60-degree head-up position which was maintained for a further fifteen minutes unless fainting necessitated an earlier return to the horizontal.

Results

The subjective effects of intravenous promethazine appeared pleasant. A feeling of warmth and well-being rapidly developed and for about the first ten minutes after injection a state of sleepy relaxation was characteristic. Slurred speech was always an early feature. The skin appeared warm and dry.

Although all the subjects were drowsy, sleep did not occur, and before long fidgety body movements would accompany a state of obvious mental disorientation. There was some irritability and confusion, with an apparent inability to co-operate or keep still on command. One subject stated subsequently, "I

TABLE I

Circulatory Effects of Intravenous Promethazine

Subject	Age (years)	Dose (mg)	Arterial blood pressure and heart rate					
			Control		4–5 min after start of injection		14–15 min after completing injection	
J G	37	50	155/86	86	163/91	82	168/100	78
M C.	35	50	114/88	66	131/101	68	132/103	72
McC	36	50	130/85	66	129/89	62	133/98	93
G L	23	50	108/79	72	108/80	75	122/97	100
K H	23	100	119/80	72	119/82	69	123/90	87
J McL	23	50	127/80	63	142/94	63	171/109	81
N G	17	50	146/85	99	142/91	96	133/80	84
C H	18	50	110/52	56	109/57	60	119/66	60
J McL	23	50	119/78	64	120/79	69	135/96	114
A T	54	50	100/50	60	130/70	60	121/60	66
N B	60	50	182/110	84	191/113	72	180/110	76
P L	59	50	149/86	58	149/92	64	125/73	62
H J	48	50	141/93	72	150/91	69	146/93	88
		50	142/90	90	146/93	88	158/105	72
T G	42	100	124/77	72	146/90	78	154/106	112
J L	43	50	143/87	69	148/99	78	144/98	75
A C.	47	50	127/84	78	124/84	96	138/92	98
L M	40	50	193/101	76	197/119	76	1821101	76
A A	33	100	142/93	81	141/100	72	139/101	99

understood what you meant but could not do it"; another remarked, "I understood what was said, I knew the necessary reply, but could not say it." Disorientation was accompanied by moderate or severe restlessness in fifteen subjects (83.3 per cent); in all three subjects who received 100 mg. of promethazine restlessness was particularly troublesome, and necessitated termination of the head-up tilt after promethazine injection.

Apart from the transient faintness associated with severe hypotension during tilting, malaise and nausea were not encountered.

Blood pressure and heart rate 4–5 minutes and 14–15 minutes after injection of 50–100 mg. of promethazine hydrochloride are shown in Table I. Heart rate was little changed by 4–5 minutes, but had increased by an average of 12.6 beats at 14–15 minutes, this increase is significant ($P < 0.05$). When promethazine 50 mg. is rapidly injected intravenously, immediate tachycardia and transient hypotension may result (Fig. 1).

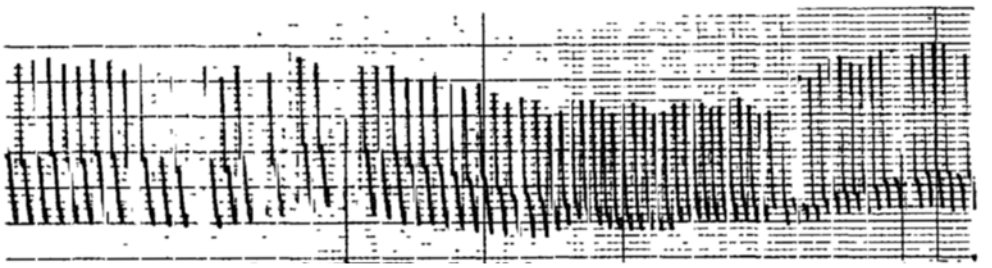

FIGURE 1 Tachycardia and transient hypotension following intravenous injection of promethazine 50 mg.

Increases in systolic and diastolic pressure frequently followed the intravenous injection of promethazine. When restlessness occurred there was usually an obvious association between movement and transient blood pressure increases. The data pertaining to blood pressure and heart rate during tilting is shown in Tables II, III, and IV. Eight subjects maintained the 60-degree head-up position

TABLE II

SUBJECTS TOLERATING BOTH TILTS

Subject	Tilt	Arterial blood pressure and heart rate					
		Before		Within 1st minute		After 15 minutes	
P L	Control	160/89	62	148/88	68	144/82	78
	Promethazine	125/73	62	125/65	82	133/60	72
H J	Control	159/95	80	155/95	72	140/95	87
	Promethazine	168/110	76	162/116	93	155/105	86
J L	Control	147/95	69	141/97	76	136/93	82
	Promethazine	144/98	75	147/99	78	143/104	78
L M	Control	196/118	80	189/128	78	186/109	93
	Promethazine	182/101	76	164/100	78	154/94	96
J G	Control	163/87	86	160/90	102	146/92	108
	Promethazine	147/88	75	156/94	102	153/95	93
J McC	Control	116/78	70	118/86	84	136/100	80
	Promethazine	133/98	93	134/110	104	137/115	102
J McL	Control	122/77	70	114/71	75	109/78	96
	Promethazine	171/109	81	154/110	92	147/102	82
J McL	Control	113/70	76	114/80	88	117/93	111
	Promethazine	135/96	114	133/100	114	127/95	98

for fifteen minutes without circulatory stress, before and after intravenous injection of promethazine (Table II).

By the end of fifteen minutes two subjects showed marked hypotension, during the control tilt only; after promethazine both withstood tilting without adverse effects (Table III). Four other subjects showed signs of an impending faint during both tilts and were returned to the horizontal. The average time of onset of hypotension in this group was 7.3 minutes during the control tilt and 7.8 minutes during the promethazine tilt (Table III).

TABLE III

SUBJECTS SHOWING HYPOTENSION DURING CONTROL TILT ONLY, AND DURING BOTH TILTS

		Arterial blood pressure and heart rate							
Subject	Tilt	Before		Within 1st minute		Termination		Duration of tilt (minutes)	Terminal effect
C.H.	Control	155/58	68	108/60	70	42/22	84	15	Hypotension
	Promethazine	119/66	60	110/70	78	107/66	82	15	—
A T.	Control	113/66	66	98/63	70	88/52	82	15	Hypotension
	Promethazine	121/60	66	96/57	82	115/68	82	15	—
G L	Control	102/77	72	114/96	102	55/48	108	4	Hypotension
	Promethazine	130/101	90	129/109	123	63/53	90	10	Hypotension
N G	Control	128/77	116	115/68	114	49/28	105	7	Hypotension
	Promethazine	133/80	84	131/86	96	60/40	78	6	Hypotension
A C	Control	127/84	87	127/89	90	84/55	72	11	Hypotension
	Promethazine	138/92	98	131/95	104	77/51	87	6	Hypotension
M C	Control	124/92	78	117/95	81	49/37	48	7	Hypotension
	Promethazine	132/103	72	102/106	93	65/49	66	9	Hypotension

Only one subject developed marked hypotension during the promethazine tilt alone, at 9 minutes (Table IV). Part of this record is illustrated in Figure 2. Three of our other subjects were so restless and generally uncontrollable during the tilt following injection of 100 mg. promethazine that termination of the study was clearly necessitated (Table IV). Wide swings of blood pressure, probably induced by irregular respiratory patterns, frequently accompanied restlessness especially when the subjects were in the head-up position (Fig. 3).

TABLE IV

SUBJECTS SHOWING HYPOTENSION OR RESTLESSNESS DURING PROMETHAZINE TILT ONLY

		Arterial blood pressure and heart rate							
Subject	Tilt	Before		Within 1st minute		Termination		Duration of tilt (minutes)	Terminal effect
N B	Control	176/106	78	151/99	80	162/113	96	15	—
	Promethazine	180/110	76	143/100	90	80/62	70	9	Hypotension
K H	Control	110/77	63	115/84	92	116/93	93	15	—
	Promethazine	123/90	87	135/110	94	142/103	112	9	Restlessness
A A	Control	114/78	72	106/78	76	141/98	84	15	—
	Promethazine	139/101	99	130/94	105	113/64	120	2	Restlessness
T G	Control	125/86	80	125/83	92	120/83	92	15	—
	Promethazine	146/105	110	128/91	114	115/78	116	9	Restlessness

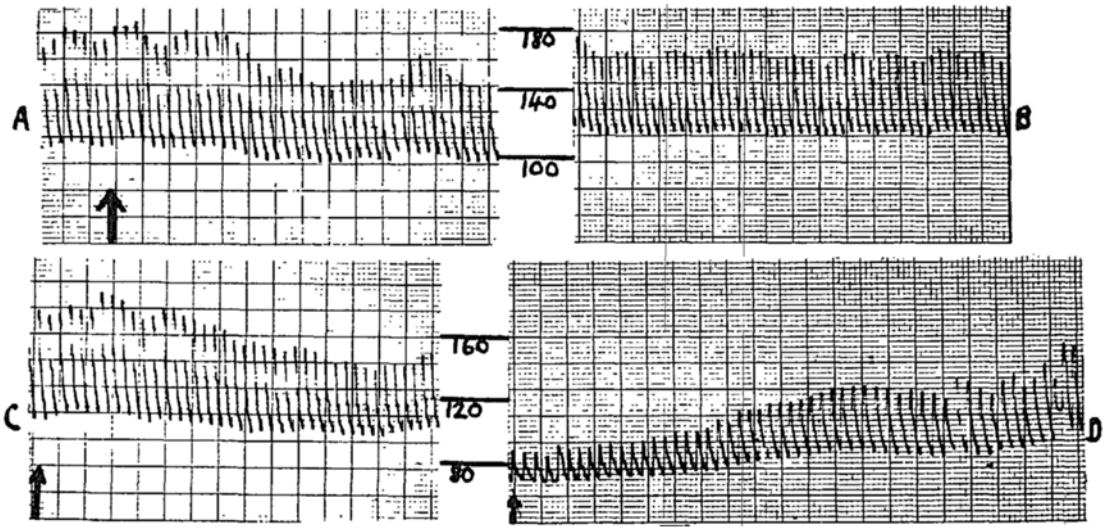

FIGURE 2. Record obtained from one subject showing hypotension during tilt following promethazine injection: A, control tilt; B, after 15 min. in 60-degree head-up position; C, tilt 20 min. after promethazine 50 mg. intravenously; D, severe hypotension after 9 min. in head-up position.

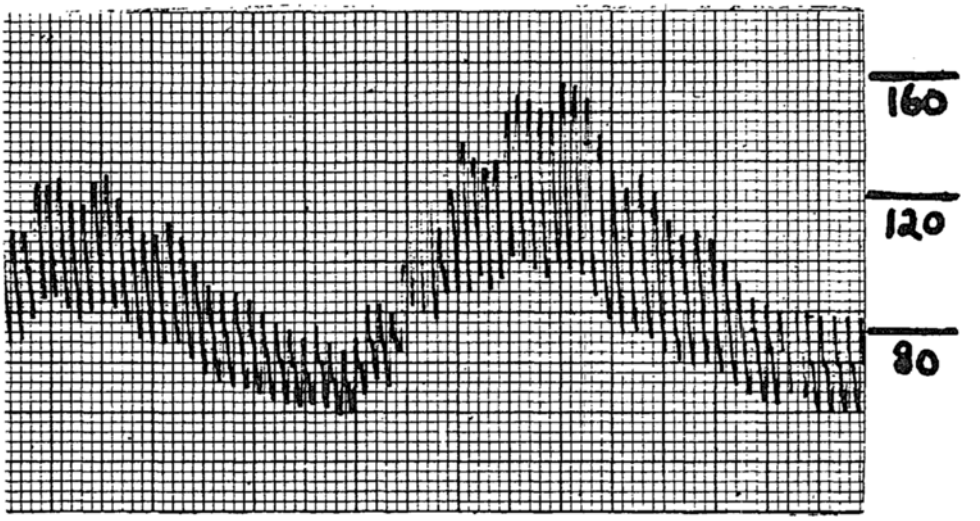

FIGURE 3. Wide swings of blood pressure in tilted position following promethazine injection.

In summary, a total of six subjects (33.3 per cent) developed hypotension during the control tilt, while only five subjects (27.8 per cent) showed signs of impending circulatory collapse during the tilt which followed intravenous injection of promethazine.

Occurrence of hypotension or restlessness during tilting in 18 subjects

Tolerating both tilts for 15 minutes without hypotension	8
Hypotension during control tilt only	2
Hypotension during both tilts	4
Hypotension during promethazine tilt only	1
Severe restlessness requiring termination of promethazine tilt	3

In an attempt to induce further circulatory stress in several subjects while in the 60-degree head-up tilt, they were asked to inspire deeply and hold their breath while tightening their abdominal muscles—a modified Valsalva manœuvre. An example is illustrated in Figure 4. The secondary increase in blood pressure

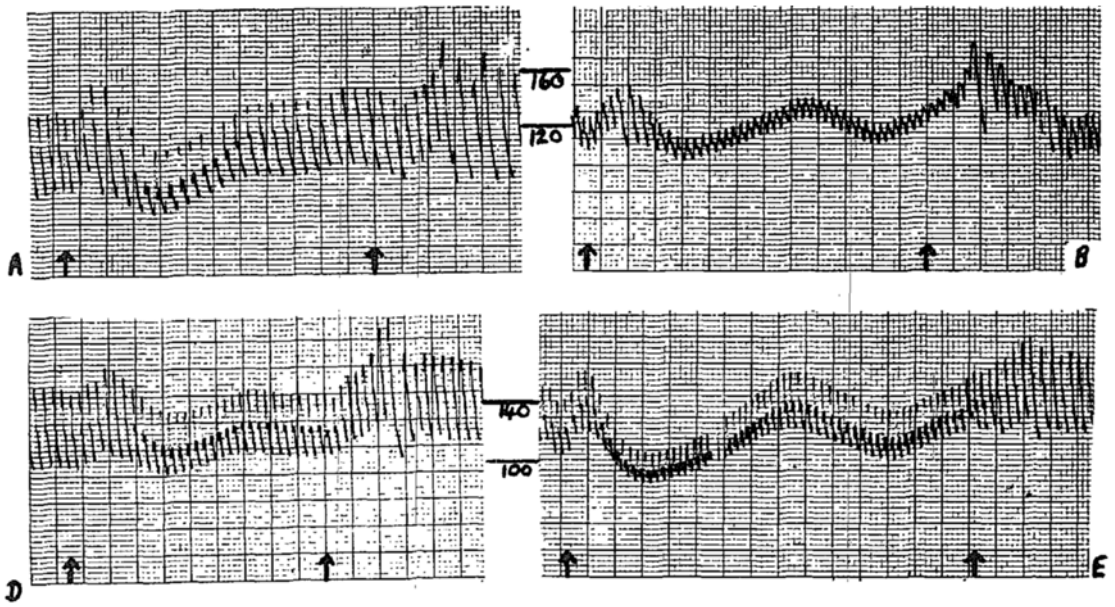

FIGURE 4. Breath-holding in one subject: A, in supine positior before promethazine injection; B, during control tilt; D, in supine position after 50 mg. promethazine intravenously; E, during tilt 20 min. after promethazine injection.

followed by the "overshoot" when airway pressure is released are both present in all four tracings, although in the tilted position, both before (B) and after (E) promethazine injection, the secondary increase in arterial pressure is not maintained as a plateau; this may result from the more prolonged period of breath-holding which reaches 30 seconds in the promethazine tilt (E). With the exception of an increased heart rate, the circulatory pattern following promethazine compares very favourably with that observed before drug administration. In no study was it possible to induce circulatory changes outlasting the well-recognized effects of the Valsalva manœuvre.

DISCUSSION

The circulatory response to head-up tilting may be conveniently utilized in an assessment of premedicant drugs in man. Studies similar to the one employed here have been carried out with morphine (12), Demerol (13) and other synthetic analgesics (14). An increased incidence of hypotension in the head-up position may be expected after injection of these agents.

It appears from this study that promethazine does not depress circulatory compensation to tilting to any marked extent. The tendency revealed by intravenous injection of 50–100 mg. is rather in the direction of an hypertensive response although it seems very likely that this is largely attributable to the marked restlessness which occurred in the majority of subjects studied. The

possibility exists, however, that promethazine, when administered in the "lytic cocktail," does not potentiate the postural hypotensive action of chlorpromazine and may even antagonize it to some extent.

The circulatory responses to the Valsalva manœuvre have been extensively studied (see 15) and may be broadly similar to the circulatory mechanisms acting during head-up tilting (16). Failure to cause circulatory collapse in any subject by induction of a modified Valsalva manœuvre following intravenous promethazine, whether in the supine or tilted position, further implies that this drug has a minimum of adverse circulatory effects, at least in the reasonably healthy subjects studied in this investigation.

Intravenous injection of promethazine in doses greater than 50 mg. is probably rarely indicated in clinical practice and cannot be recommended on the basis of this study. A prolonged sedative and hypnotic effect may be obtainable with doses of 50–100 mg. intravenously, but the drug appears to induce marked restlessness when any form of discomfort is present or when enforced inactivity is required.

The impression derived from observations is that promethazine may change a co-operative subject, who is prepared to tolerate some relatively minor discomforts (e.g., the degree of immobility of the arms necessitated by the presence of an intravenous infusion or an intra-arterial catheter), to one who is restless, confused and disorientated and unable to understand or respond to command.

For these reasons it is recommended that promethazine, at least when administered intravenously, should be given only in conjunction with an analgesic drug. The usefulness of small intravenous doses of promethazine has not been assessed from this study, but owing to variations in individual patients it would appear safer to adhere to the principle of simultaneous administration of an analgesic agent even when small doses of promethazine are injected intravenously.

Summary

Continuous intra-arterial blood pressure recording during eighteen studies has shown that promethazine, when injected intravenously in doses of 50–100 mg., does not induce circulatory depression, although tachycardia may occur especially with rapid injection. A tendency for blood pressure to increase appears to be at least partly attributable to the moderate or severe restlessness which frequently occurs.

Induction of a 60-degree head-up tilt before and after intravenous injection of promethazine revealed a somewhat lower incidence of severe hypotension after injection than before. It appears that intravenous promethazine has little depressant action on the circulatory response to head-up tilting and does not share the postural hypotensive properties of chlorpromazine.

It is concluded that, if restlessness is to be avoided, intravenous promethazine should be administered to conscious patients only in conjunction with an analgesic drug. Severe and uncontrollable restlessness may occur following intravenous injection of 50–100 mg. in patients who are required to remain immobile or who are experiencing even minor degrees of discomfort.

RÉSUMÉ

Nous pouvons affirmer, après avoir étudié l'enregistrement continuel de la pression artérielle chez 18 malades, que la prométhazine, injectée dans les veines à la dose de 50 à 100 mgm., ne produit pas de dépression circulatoire bien qu'une tachycardie soit observée occasionnellement surtout quand l'injection a été rapide. Le fait que la pression sanguine a une tendance à monter semble être attribuable en partie du moins à l'état d'agitation plus au moins prononcé que nous observons fréquemment.

La position de Fowler de 60 degrés avant et après l'injection de prométhazine nous a permis de constater une plus faible incidence d'hypotension grave après l'injection qu'avant l'injection. Il semble que l'injection intraveineuse de prométhazine a peu d'effet dépresseur sur la réponse circulatoire à la position de Fowler et qu'elle ne partage pas les propriétés de la chlorpromazine sur l'hypotension posturale.

Nous en venons à la conclusion que, si nous voulons éviter l'agitation, il est préférable d'injecter la prométhazine aux malades conscients seulement et associer une médication analgésique. A la suite d'injections intraveineuses de 50 à 100 mgm. de prométhazine il arrive d'observer une agitation considérable et ingouvernable chez des malades dont on exige l'immobilité ou qui ne ressentent que de légers malaises.

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