A Pharmacological Study on the Maintenance of Postural Equilibrium

by

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Introductory

In proportion as strides have been made in aviatational medicine or space medicine, the concept of the vestibular apparatus is beginning to take on additional importance and its applications are in the form of various anti-train sick drugs commercially available on the market.

In view of ever increasing progress in the air transportation, the study into this direction is considered to be very necessary for the welfare of both pilots and passengers.

Hitherto researches in vertigo and nausea have been more or less confined to the fields of physiology and otorhinology and an attempt from the pharmacological point of view is rather scanty. The present paper deals with a series of tests undertaken on the ordinary commercial drugs which are believed to work favorably for the inhibition of vertigo as well as on these which are concerned with the maintenance of postural equilibrium. It is needless to point out that the occurrence of vertigo at a place of low altitude may be prevented by squatting down but at a high altitude a fall because of vertigo may result in a severe injury. Therefore, efforts were directed to this point with reference to the artificial hibernating agents, chlorpromazine and prometazine (commonly known as anti-shock drugs),* on their effects on animals that were made to fall from a place of high altitude.

Materials and Method

Experiment I. Pharmacological Effects on the Postural Maintenance of Concussive Mice.

A glass vessel of 300 cc content and 70 mm in diameter was placed on a shaking machine which rotates 240 times per minute over the turntable of 305 mm in diameter. Male mice of mongrel breed, weighing around 15 g, were placed in the glass vessel following an administration of drugs and were shaken in the horizontal manner for 20 minutes. This shaking process of 20 minutes was thought adequate to generate complete vertigo on the part of experimental mice and having been subjected to the vertigo generation, animal were placed on a glass rod 10 mm in diameter set horizon-

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* Effect of these drugs upon non-anesthetized resection of upper and lower jaws and tongue were previously reported by the present authors.

tally. The assumptions were that if the pre-medication of anti-vertigo drugs was favorable animals would be able to stay on the rod but otherwise they would sustain a fall. It was brought to light in the process of these tests that there is a stage, before the final postural maintenance on the glass rod, where animals fall when they are made to grasp the rod from the under side. It must be kept in mind with the tests of this kind that animals once on the rod cannot change their position, that is, if they are on the upper side of the rod they remain there, and this is true of those which are made to grasp the rod from the under side.

Table 1 below gives the numbers of fall under five different lengths of shaking time (5, 10, 15, 20 and 30 minutes), each repeated ten times so as to calculate the mean values. It is clear that the number of falls sustained by animals increase in proportion to the length of shaking procedure and the figures on Table 1 are graphically represented by Fig. 1.

TABLE 1

No.			1	2	3	4	5	6	7	8	9	10	Mean values	
Lengths of Shaking Time	5'	Upper side	0	0	30''	0	0	0	0	0	0	0	3''	9''
		Lower side	0	0	1'30''	0	0	30''	0	0	30''	0	15''	
	10'	Upper side	1'	1'	30''	1'	30''	30''	30''	1'30''	1'30''	1'30''	54''	1'06''
		Lower side	1'	1'30''	30''	40''	30''	1'40''	1'30''	1'	30''	4'20''	1'19''	
	15'	Upper side	1'	1'10''	30''	45''	1'45''	45''	0	0	30''	30''	41''	46''
		Lower side	1'10''	1'10''	45''	30''	1'45''	1'45''	20''	0	30''	45''	52''	
	20'	Upper side	1'	5'	6'	3'	1'	0	1'	0	2'	7'	2'36''	3'01''
		Lower side	3'	6'	2'	6'	1'	0	2'	0	10'30''	4'	3'27''	
	30'	Upper side	3'	3'	1'30''	2'40''	8'	40''	1'15''	—	4'	—	3'	3'33''
		Lower side	5'	5'	4'	2'10''	11'30''	40''	1'15''	—	3'30''	—	4'	

Fig. 1

TABLE 2

	Constituents	Dosage mg/kg	Method	Human dosage as unit
Dramamine	β -Dimethyl-aminoethylbenzhydrylether, 8-chlorotheophyllinate 50 mg	3.3	Oral	4 times
Bonamine	1-p-Chlorobenzhydryl-4-m-methylbenzyl Piperazine HCl 25 mg	3.3	Oral	7 times
Dentomin	Chlorpromazine 6.25 mg Promethazine HCl 3.125 mg Aspirine 12.5 mg Coffeine 7.5 mg Phenacetin 25 mg Phenobarbital 7.5 mg	3.3	Oral	same amount
Meylon	Sodium Bicarbonate 7 %	467.0	Cordal vein	3 times
Crystalline Dihydrostrepto- mycin (C. D. S.)	Crystalline Dihydrostreptomycin (C. D. S.) 1 %	67.0	Dorsal injection	2 times

Five anti-train sick drugs were selectively employed for these tests (Table 2) and they were pre-medicatively administered half an hour prior to the shaking but, of them only crystalline dihydrostreptomycin was administered for 20 consecutive days before the shaking, the last day of which falling on the start of the test.

Effects of these drugs pre-medicatively used were measured and correlated with the numbers of falls in each group of different shaking lengths (Tables 3, 4 and Figs. 3, 4). In terms of the average human dosage of which anywhere from 4 to 7 times were used here crystalline dihydrostreptomycin and meylon possess the shortest time before recovery with dramamine coming next, and bonamine and dentomin taking longer time. However, any of the drugs had pronounced effects in inhibiting vertigo when used pre-medicatively. It is an interesting findings that although crystalline dihydrostreptomycin is generally believed to have less equilibrating effects with stronger adverse effect on the auditory organ, we have found the picture reverse and it possesses beneficial effects toward the maintenance of posture. With reference to Dramamine which is commercially marketed as an anti-vertigo agent, effects vary from dosage to dosage and in the present experiment a dosage of 3.3 mg/kg (which is nearly one thousand times as much as that of humans) was found to have the highest degree of effects, effects becoming less on either side from this dosage.

It must be warned here that in the series of present tests most of the drugs used were administered anywhere from four to ten times the average human dosage while others administered on the basis of human dosage and therefore, it is not possible to compare effects of some drugs with those of others in the same light. It is believed, however, that a new method of examination developed by these tests will serve a useful purpose of exactly determining assumed effects of anti-train sick drugs.

Experiment II. Effects of Chlorpromazine on the Posture Maintenance of Falling Animals and Shocks

A mouse of 17 g, and a rat and a Guinea pig of 200 g each were artificially

TABLE 3

	Dentomin			Meylon			Bonamine	
	Upper side	Lower side		Upper side	Lower side		Upper side	Lower side
1	1'25"	1'07"	1	54"	34"	1	52"	50"
2	41"	1'01"	2	1'12"	26"	2	46"	1'05"
3	1'08"	1'53"	3	46"	42"	3	51"	1'07"
4	1'12"	2'27"	4	28"	38"	4	39"	1'26"
5	54"	1'09"	5	1'03"	50"	5	1'23"	43"
6	1'01"	54"	6	37"	39"	6	1'06"	1'17"
7	47"	1'11"	7	53"	37"	7	53"	2'23"
8	1'00"	1'30"	8	50"	41"	8	41"	1'49"
9	53"	47"	9	49"	38"	9	1'12"	57"
10	41"	1'21"	10	51"	35"	10	59"	1'03"
Means	58"	1'20"	Means	50"	38"	Means	56"	1'16"

	C. D. S.			Dramamine	
	Upper side	Lower side		Upper side	Lower side
1	1'01"	20"	1	23"	1'16"
2	1'11"	9"	2	32"	11"
3	49"	0"	3	36"	52"
4	58"	38"	4	44"	48"
5	1'23"	21"	5	51"	1'33"
6	1'07"	24"	6	26"	1'08"
7	1'05"	13"	7	15"	1'20"
8	1'14"	31"	8	1'01"	1'00"
9	1'02"	41"	9	53"	35"
10	1'10"	23"	10	45"	1'57"
Means	1'06"	22"	Means	38"	1'04"

induced to fall from places of varying heights on a windless day and immediately after their fall, 30 mg/kg of chlorpromazine was intramuscularly injected. This post-medical group was compared with a group which were injected with the same drug half an hour prior to the fall, the results being correlated. In addition, tails which play

TABLE 4
Dramamine

80 mg/kg			40 mg/kg			20 mg/kg			7 mg/kg		
	Upper side	Lower side		Upper side	Lower side		Upper side	Lower side		Upper side	Lower side
1	2' 0"	4'10"	1	2'23"	2'25"	1	56"	2'38"	1	2'28"	2'18"
2	1'36"	3'17"	2	1'59"	1'25"	2	1'15"	1'20"	2	1'37"	2'03"
3	1'58"	57"	3	1'52"	3'12"	3	1'25"	1'12"	3	15"	1'23"
4	3'15"	6'18"	4	3'05"	2'51"	4	40"	2'07"	4	1'42"	1'46"
5	2'05"	3'32"	5	1'46"	2'51"	5	1'44"	56"	5	1'34"	30"
6	2'16"	1'55"	6	1'27"	3'06"	6	2'00"	3'23"	6	31"	1'25"
7	3'07"	1'23"	7	2'28"	3'12"	7	2'26"	1'46"	7	1'20"	1'17"
8	2'31"	5'36"	8	2'46"	1'58"	8	1'40"	2'16"	8	1'24"	1'31"
9	2'52"	1'45"	9	2'40"	4'31"	9	14"	30"	9	1'16"	45"
10	3'20"	5'12"	10	2'08"	1'58"	10	1'00"	1'23"	10	1'24"	1'02"
Means	2'30"	3'14"	Means	2'18"	2'46"	Means	1'20"	1'46"	Means	1'29"	1'24"

3.3 mg/kg			2 mg/kg			0.7 mg/kg		
	Upper side	Lower side		Upper side	Lower side		Upper side	Lower side
1	23"	1'16"	1	2'16"	2'52"	1	2'11"	41"
2	32"	11"	2	1'17"	1'53"	2	2'50"	33"
3	36"	52"	3	57"	54"	3	1'10"	1'02"
4	44"	48"	4	1'19"	3'11"	4	3'11"	13"
5	51"	1'33"	5	1'21"	2'04"	5	1'53"	43"
6	26"	1'08"	6	1'35"	1'09"	6	1'07"	46"
7	15"	1'20"	7	54"	2'13"	7	53"	44"
8	1'01"	1'00"	8	2'27"	3'24"	8	3'01"	1'13"
9	53"	35"	9	1'06"	1'10"	9	2'04"	52"
10	45"	1'57"	10	1'21"	2'00"	10	2'00"	24"
Means	38"	1'04"	Means	1'26"	2'04"	Means	2'02"	42"

an important role in the postural maintenance mechanism of animals were cut off either at the root or in the middle and their effects in the posture equilibrium were investigated.

Fig. 2

Fig. 3
Dramamine

Table 5 gives findings on the fall of animals. It was generally found that the cutting off of tail at the root had more adverse effects in keeping postural equilibrium than in the middle, some of animals coming to die in a few minutes after a fall. At any rate, those animals whose tails were cut off suffered a higher rate of death than others and this is to be accounted for by various factors not only by defect in keeping postural equilibrium, but also resistance against air, shock at landing etc. An animal with a sound tail is observed to fall with its limbs spreading and tail straight so that the resistance against air may be maximum. On the other hand, a tailless animal

cannot sufficiently keep his body in equilibrium by its limbs alone and usually falls in a tail-spin fashion.

TABLE 5

Heights of fall	No. of survival after 24 hours	Number of deaths		
		Within a few minutes after landing	Within 24 hours	Total
8 m	9	1	0	1
10 m	8	1	1	2
12 m	8	2	0	2
16 m	6	3	1	4
16 m (Tail half cutting)	0	9	1	10
16 m (Tail total cutting)	0	10	0	10
16 m Chlorpromazine (Pre-medication)	9	8	1	9
16 m Chlorpromazine (Post-medication)	8	2	0	2
Total	40	4	4	40

When chlorpromazine was pre-medically given, it tended to work adversely on the equilibrium mechanism because the drug contained a certain function of relaxing muscles but when used post-medically immediately following a fall, it was found to work beneficially and checked the number of deaths by half. Anatomical observations of the animals which died upon landing revealed a high degree of hemorrhage due to disruption of liver, bone fracture and hemorrhage of the basilar region of skull, pulmonary hemorrhage, hypodermal hemorrhage, disruption of other internal organs and cutting of veins among other things. Of those which came to die in twenty-four hours, the irregularities were confined to the fracture of pelvis, hemorrhage of meninges and ventral hemorrhage. If there were others, it was not possible for the naked eye to detect them. In comparison with mice, the findings relative to rats gave a higher rate of death as they could not keep their posture in equilibrium regardless of tail or otherwise, even on with a sound tail dying upon landing instantaneously. The anatomical findings were almost identical to those of mice referred to above. Lastly, Guinea pigs seem to have least resistance to this kind of fall as against mice and rats. When they were made to fall from a height of 10 meters, all the subjects died and their anatomical findings differed from others in that the large intestines and kidneys were disrupted. When they died, they took shorter time than either mice or rats.

Summary

Mice and similar subjects were used in a series of tests where they were placed in a shaking apparatus of simple mechanism and the state of being train-sick was artificially generated. They could not grasp a glass rod immediately after this state but when anti-train drugs were pre-medically administered, the time before they

recovered an ability to grasp the rod was much reduced. From this, it has been established that the use of a shaking apparatus and a glass rod proves effective in an examination of effects attributed to these anti-train sick agents which are now commercially available.

In this connection, it was also found out that effects of chlorpromazine which is accepted as anti-shock agent work adversely on the generation of vertigo in the case of a fall. It is thought that the study on this subject furnishes a useful insight in the training of personnel engaged in the air transportation where they are faced with the necessity of parachuting down from a considerable height.

It may be added that a part of the present report was read before the Tokyo meeting of 23rd Japan Pharmacological Society Congress, held in November 1961.

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