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EFFECTS OF SOME CENTRALLY ACTING DRUGS ON BLOOD COAGULATION

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Many drugs acting on the central nervous system, like, tranquillizers, and barbiturates are amongst the agents used in thromboembolic discorders and before, during or after surgery. In these patients an alteration in the coagulability of blood has a considerable significance. Very little is known, however, regarding the effect of most of these drugs on coagulation, except for occasional clinical reports (1, 2) of haemorrhagic or thrombotic complications in course of therapy. A study of the effect of these drugs on coagulation has, therefore, been under-taken and the results obtained with 25 drugs are being reported here. A preliminary report of part of this work has been published (3).

METHODS

The experiments were performed in adult Indian albino rabbits of either sex. The animals, maintained on a standard diet, were used once a week and fasted overnight before use. The drug effects were studied on bleeding time, coagulation time and prothrombin time. The details have been described earlier (4). The bleeding time was measured by the method of Duke (5), coagulation time by the capillary tube method of Wright and Colebrook (6) and the prothrombin time by the micro-method of Motingel (7). All values were obtained correct upto 1/10 second. At least 2 control measurements were made in each animal.

Each drug (or each dose of a drug) was tested in at least one batch of 5 rabbits. The values of bleeding, coagulation and prothrombin time were measured immediately before drug administration, at the time of its anticipated peak effect and thereafter at regular intervals till normal values returned. The drug were administered intramuscularly or intravenously (see Tables 1 and 2). Aqueous solutions of drugs were used except in cases of isocarboxazid, meprobamate and nialamid which were dissolved in propylene glycol and mephenesin which was dissolved in a mixture of ethyl alcohol, propylene glycol and water. Propylene glycol itself had no effect on bleeding, coagulation or prothrombin time.

The results of each batch were pooled and mean values (±s.e.) calculated. The significance of drug induced alterations from the mean control values was judged by Students' 't' test at 95% and 99% levels of significance ($P=0.05$ and 0.01).

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RESULTS

The normal values of bleeding, coagulation and prothrombin were calculated from the results of 290 determinations in 93 rabbits and were found to be 95±0.6, 103±0.8 and 7.3±0.1 seconds respectively.

Central Nervous System Stimulants

Two hallucinogens-lysergic acid diethylamide (LSD-25) and mescaline sulfate; 4 monoamine oxidase (MAO) inhibitors-iproniazid phosphate, isocarboxazid, nialamid and tranylcypromine sulfate; and 4 other anti-depressants viz. amitryptiline hydrochloride, imipramine hydrochloride, metamphetamine hydrochloride and methylphenidate hydrochloride were tested. The results have been summarised in Table 1. Mescaline, isocarboxazid, nialamide, metamphetamine and methylphenidate were ineffective in all the tests. LSD-25 produced a transient though significant ($P=<0.05$) decrease in bleed-

TABLE 1. Effect of CNS stimulant drugs on bleeding time, coagulation time and prothrombin time.

Drugs were given intravenously except wherein otherwise indicated. All values are mean values of at least one group of 5 rabbits along with the standard error (s.e.).

Drug	Dose mg/kg	Time in hours after drug administration	Bleeding time in sec±s.e.	Coagulation time in sec±s.e.	Prothrombin time in sec±s.e.
Hallucinogens					
Lysergic acid diethylamide	0.05	Control	92±1.2	104± 5.0	7.5±0.09
		1	88±1.3*	96± 3.2	8.6±0.05**
		4	93±1.5	106± 3.0	8.1±0.05**
		24	91±1.4	104± 2.0	7.8±0.2
Mescaline sulphate	25.0	Control	92±1.2	104± 5.0	7.6±1.0
		1	94±2.4	98± 3.0	7.8±0.1
		4	94±1.3	98± 2.6	7.5±0.1
		24	95±1.4	98± 3.0	7.5±0.05
Antidepressants					
Iproniazid phosphate	50.0	Control	105±2.1	99± 7.9	6.8±0.1
		12	98±2.3*	111± 6.0	7.5±0.1*
		24	95±1.3**	100±11.5	10.0±0.6**
		40	95±2.2*	96±11.4	8.1±0.2**
		48	102±2.4	98± 4.0	7.5±0.1**
		72	104±2.8	102± 4.6	7.3±0.1*
		96	106±2.6	100± 4.5	6.8±0.1
Isocarboxazid (intramuscular)	40.0	Control	93±0.6	95± 2.1	7.4±0.1
		4	93±0.7	97± 1.4	7.4±0.1
		12	93±0.6	96± 1.5	7.5±0.1
		24	93±0.8	97± 1.9	7.5±0.1
Nialamid (intramuscular)	20.0	Control	99±3.2	103± 3.6	7.6±0.1
		4	99±2.2	110± 3.5	7.6±0.1
		12	103±3.4	106± 3.8	7.6±0.2
		24	101±3.9	102± 3.2	7.5±0.2

	100.0	Control	95±1.2	104± 2.6	7.3±0.1
		4	97±2.4	106± 2.4	7.3±0.1
		12	98±3.6	101± 2.4	7.4±0.1
		24	98±3.6	101± 1.0	7.4±0.1
Tranylcypromine sulphate	50.0	Control	92±3.5	94± 5.2	7.7±0.1
		4	93±3.0	100± 3.8	7.6±0.2
		12	95±2.7	103± 5.4	8.3±0.1**
		24	91±2.1	98± 3.7	8.4±0.1**
		48	93±1.3	95± 8.8	7.5±0.2
Amitryptiline hydrochloride	10.0	Control	91±1.2	103± 2.3	7.7±0.1
		2	93±0.9	108± 2.0	7.3±0.3**
		4	93±0.8	108± 2.0	7.5±0.05
		24	93±0.7	107± 1.6	7.6±0.62
Imipramine hydrochloride	5.0	Control	103±5.9	110± 5.0	7.8±0.15
		1	91±3.0	97± 8.4	7.2±0.1**
		4	99±3.9	109± 1.4	7.2±0.1**
		24	101±3.7	100± 3.3	7.8±0.2
Metamphetamine hydrochloride (intramuscular)	2.0	Control	105±2.1	99± 7.9	6.8±0.1
		1	105±1.0	109± 6.7	7.0±0.2
		4	104±2.5	113± 5.8	7.0±0.1
		24	105±2.2	110± 8.0	6.9±0.1
	5.0	Control	104±8.0	95±11.5	6.9±0.1
		1	108±7.1	95±10.0	6.7±0.1
		4	108±6.2	101± 8.7	6.6±0.1
		24	101±9.0	99± 6.7	6.7±0.1
Methylphenidate hydrochloride	10.0	Control	93±1.6	99± 1.8	7.3±0.1
		1	96±0.7	104± 2.8	7.4±0.1
		4	93±0.6	105± 2.6	7.3±0.1
		24	94±2.2	102± 2.0	7.4±0.1

N.B. : * and ** indicate that the value differs significantly from the control measurement at $P=<0.05$ or $P=<0.01$ respectively.

ing time. A more marked ($P<=0.01$) and persistent (40 hours) decrease was produced by iproniazid. Changes in prothrombin time were observed with five of these agents. Amitryptiline and imipramine decreased it, the later having a more persistant effect (4 hours). A marked increase in prothrombin time was produced by iproniazid, the normal values returning only after 96 hours (see Table 1). Prothrombin time was also increased by LSD-25 (4 hours) and tranylcypromine (24 hours).

Tranquillizers

The results are shown in Table 2. Azacyclonol, carphenazine, hydroxyzine, meprobamate and tetrabenazine had no effect. Chlorprothixene in 5 mg/kg dose increased only the bleeding time while the dose of 10 mg/kg increased the coagulation and prothrombin time as well. A delayd (18 hours) decrease in coagulation time was seen with a large dose (1 mg/kg) of reserpine. Three drugs caused alterations in prothrombin time. Chlor-

TABLE 2. Effect of CNS depressant drugs on bleeding time, coagulation time and prothrombin time in rabbits.

Drugs have been administered intramuscularly unless mentioned otherwise. The control measurements were obtained just before drug administration. Other details are similar to Table 1.

Drug	Dose (mg/kg)	Time in hours after drug administration	Bleeding time in sec ± s.e.	Coagulation time in sec ± s.e.	Prothrombin time in sec ± s.e.
Tranquillizers					
Azacyclonol hydrochloride	5.0	Control	102± 9.5	90± 8.6	6.5±0.1
		2	80±11.0	83± 9.6	6.7±0.2
		4	91± 9.0	90±10.4	6.6±0.1
		24	85± 2.9	97±12.3	6.6±0.1
Carphenazine hydrochloride	1.0	Control	94± 1.4	105± 2.4	7.5±0.0
		1	94± 1.5	104± 2.0	7.5±0.1
		4	96± 1.3	108± 2.1	7.5±0.0
		24	94± 1.0	105± 1.3	7.5±0.1
Chlordiazepoxide hydrochloride	15.0	Control	95± 1.4	100± 2.9	7.6±0.16
		2	94± 0.9	103± 1.5	7.4±0.2
		4	95± 1.1	101± 1.4	7.0±0.1**
		24	95± 1.5	100± 1.4	6.5±0.16**
		48	94± 0.5	100± 2.0	7.5±0.2
Chlorpromazine hydrochloride	5.0	Control	95± 1.2	94± 1.0	7.0±0.1
		1	95± 0.7	96± 1.0	7.3±0.05*
		2	96± 2.7	104± 4.5	7.4±0.1*
		4	95± 1.5	95± 2.1	7.0±0.1
		24	99± 3.7	94± 2.2	7.0±0.1
Chlorprothixene hydrochloride (intravenous)	5.0	Control	97± 1.1	106± 2.2	7.5±0.0
		1	123± 2.1**	105± 3.0	7.5±0.1
		4	114± 1.6**	108± 0.7	7.7±0.1
		24	100± 1.2	102± 2.5	7.5±0.1
	10.0	Control	95± 0.8	100± 2.3	7.6±0.1
		1	122± 3.5**	110± 1.6*	7.8±0.1
		4	120± 0.3**	105± 2.1	8.1±0.1**
		24	97± 1.5	94± 2.4	7.6±0.1
Hydroxyzine hydrochloride (intravenous)	10.0	Control	92± 0.5	96± 2.0	7.8±0.1
		1	94± 0.9	98± 2.8	7.6±0.1
		4	92± 0.6	101± 0.8	7.6±0.1
		24	92± 1.3	100± 2.0	7.8±0.1
	20.0	Control	94± 1.3	99± 1.6	7.9±0.2
		1	93± 0.8	99± 2.2	8.6±0.1
		4	93± 0.9	100± 2.9	8.3±0.1
		24	94± 0.4	102± 4.2	8.3±0.2
Meprobamate	25.0	Control	96± 1.5	104± 2.2	7.4±0.1
		2	93± 1.6	104± 5.4	7.5±0.1
		4	94± 1.5	99± 3.2	7.5±0.1
		24	95± 1.5	102± 2.8	7.4±0.1

Reserpine phosphate	0.1	Control	98± 1.7	106± 1.7	7.4±0.1
		4	91± 3.9	105± 1.4	7.0±0.2
		24	95± 1.5	104± 3.2	7.4±0.1
	0.5	Control	100± 3.2	93± 5.3	6.1±0.1
		4	96± 2.1	81± 5.0	6.1±0.5
		24	98± 2.4	89± 5.2	6.1±0.1
	1.0	Control	95± 1.2	94± 1.0	7.0±0.1
		4	91± 2.7	90± 8.2	5.5±0.8**
		18	92± 1.1	85± 3.6*	6.5±0.4**
		24	96± 4.0	88± 4.5	7.0±0.2
Tetrabenazine sulphate	50.0	Control	94± 0.6	98± 4.2	7.9±0.2
		1	95± 0.3	102± 1.0	7.9±0.1
		4	95± 0.4	104± 1.0	7.9±0.1
		24	94± 0.6	101± 1.6	8.2±0.1
Barbiturates					
Phenobarbitone sodium	30.0	Control	98± 1.7	106± 1.7	7.4±0.1
		1	102± 1.4	108± 0.7	5.4±0.2**
		4	93± 3.4	111± 3.3	5.1±0.2**
		24	103± 2.2	105± 0.2	5.1±0.2**
		48	100± 1.9	102± 4.2	7.2±0.2
Pentobarbitone sodium	30.0	Control	100± 3.1	93± 5.3	6.1±0.1
		½	104± 4.0	86± 3.4	6.2±0.2
		4	102± 2.5	88± 2.5	6.2±0.1
Thiopentone sodium	25.0	Control	108± 4.7	91± 2.1	6.7±0.1
		¼	106± 3.1	87± 3.9	6.4±0.2
		1	10€± 2.1	89± 3.9	6.5±0.2
		4	108± 2.4	89± 1.8	6.5±0.1
Narcotic Analgesics					
Morphine sulphate	1.0	Control	96± 1.0	112± 4.0	7.7±0.2
		1	97± 1.5	115± 1.5	7.6±0.1
		4	95± 1.5	113± 4.0	7.5±0.1
		24	96± 1.5	113± 3.5	7.6±0.1
Pethidine hydrochloride	10.0	Control	102± 2.4	104± 4.3	7.8±0.1
		1	95± 1.3*	103± 2.0	7.7±0.2
		4	98± 1.2	103± 2.7	7.8±0.2
		24	99± 2.0	104± 3.0	7.8±0.1
Miscellaneous					
Mephenesin	20.0	Control	95± 1.2	94± 1.0	7.0±0.1
		1	98± 1.8	109± 3.5**	7.0±0.1
		4	101± 4.1	104± 3.4**	7.0±0.3
		24	100± 3.8	96± 2.0	7.0±0.2

N.B. : * Difference from control values significant $P = < 0.05$
** Difference from control values significant $P = < 0.01$

promazine produced a significant increase in prothrombin time. The prothrombin time was on the other hand decreased with chlordiazepoxide and reserpine, the former having a more persistent effect (see Table 2).

Other Central Nervous System Depressants

Two narcotic analgesics, morphine sulphate and pethidine hydrochloride; three barbiturates, phenobarbitone sodium, pentobarbitone sodium and pentothal sodium and one internuncial neurone blocking agent, mephenesin, were also investigated. The results have been given in Table 2. Pethidine produced a decrease in bleeding time which returned to normal after 4 hours. Phenobarbitone decreased the prothrombin time only and mephenesin increased coagulation time.

DISCUSSION

The normal values of bleeding, coagulation and prothrombin time obtained in the present investigation, even though lower than those reported from other sources (8) represent the normal value for the inbred Indian albino rabbits (9). Out of the three tests employed here for detecting any effect of drugs on coagulation, only two (coagulation time and prothrombin time) are indices of the coagulability of blood. The bleeding time has been, however, included, since clinically the haemorrhagic complications might arise due to vascular damage also.

LSD-25 produced a significant increase in prothrombin time (see Table 1). This may be due to an action of the drug on the liver where it is known to change the electrophoretic pattern of proteins (10). Iproniazid had the most marked effect among the antidepressant agents tested. It increased the prothrombin time while reducing the bleeding time. An increase in prothrombin time with iproniazid has also been reported in rats (11). This could be due to an action of the drug on the liver. Many clinical reports of hepatotoxicity of iproniazid are available (12, 13). Furthermore, it is known to potentiate the anticoagulant action of ethylbiscoumacetate and phenylindanidione (11). The decrease in bleeding time with iproniazid is unlikely to be related to MAO inhibition since other similar agents had no effect (Table 1). Tranylcypromine also produced a significant increase in prothrombin time (Table 1). There are clinical reports of intracranial haemorrhage following tranylcypromine (14–16). The hemorrhage has generally been ascribed to a sudden hypertension, supposed to be due to MAO inhibition. This appears, however, to be unlikely since haemorrhage has not been reported with other MAO inhibitors. Espir and Mitchell (1) have reported intracranial haemorrhage without hypertension following the use of tranylcypromine. It has also been reported to produce petechial haemorrhage (17, 18) and liver damage (19) and to potentiate the indirectly acting anticoagulants (11). These observations coupled with the finding of the present investigation suggest that increase in the prothrombin time may be an important factor concerned in intracranial haemorrhage with this drug. Nialamid has been reported both, to increase clotting time and prothrombin time (20) and to have no effect on prothrombin time (8). The later finding is in agreement with our results. Further, clinically also it has

been reported to have no effect on prothrombin time (21). Imipramine produced maximum effect on prothrombin time among the antidepressants which do not inhibit MAO enzyme. It has been reported to increase the platelet count in patients (22) which might account for the decrease in prothrombin time observed in the present study.

None of the minor tranquillizers tested (azacyclonol, hydroxyzine, meprobamate) had any action on bleeding, coagulation or prothrombin time. Meprobamate has been reported clinically to produce purpura (23, 24) but in all these cases symptoms developed within a few hours of administration of small amounts of the drug and probably represent drug allergy.

Chlorpromazine produced a significant increase in the prothrombin time (see Table 2). We have earlier reported an increase in bleeding time also following chronic administration of chlorpromazine (25). Mazza and Pallotta (26) also found evidence of reduced clotting ability following chlorpromazine therapy. Chlorpromazine is well known to cause hepatic damage (27). This may, however, not be contributing much towards the increase in prothrombin time or the haemorrhagic disturbances reported clinically (28, 29) since chlorpromazine fails to modify the effect of anticoagulants like ethylbiscoumacetate or phenindione which act via liver (30). Chlorpromazine is also known to have deleterious effects on the platelet. Passonen (31) has found it to decrease platelet volume and to increase permeability of the limiting membrane. The limiting membrane is broken and the cytoplasmic material leaks out (32). The lowering of serum calcium by chlorpromazine (33) may also be a factor in increasing the prothrombin time. Carphenazine was without any effect, even though epistaxis has been reported following its use (34). Chlorprothixene, which resembles chlorpromazine pharmacologically, had more marked effects. It was the only drug in the present investigation to have produced significant increase in all the tests. It has been reported to produce jaundice (4) and other manifestations of hepatic damage (35). Toxic doses of chlorprothixene are also reported to cause vascular damage and detectable permeability disturbances (36).

Chlordiazepoxide and reserpine caused a significant reduction in prothrombin time. Unlike chlorpromazine chronic administration of reserpine did not produce a change in any other test (25). Reserpine has no effect on the packed platelet volume, permeability of the limiting membrane (31) or the ultrastructure of the platelets (32). More work is required to elucidate the possible mechanism of this reduction in prothrombin time by reserpine. It is interesting to note that tetrabenazine, which does not share the peripheral effects of reserpine, was inactive in the present tests. Clinicians have found thrombotic episodes, during therapy with reserpine and related agents (2, 37) and attribute these to immobilization. An important contributory factor in these thrombotic episodes, however, must be the decreased prothrombin time observed in the present study. It is also interesting to note that haemorrhages during reserpine therapy have been reported only from the gastro-intestinal tract (38–40) contrasted with haemorrhage from multiple sites with chlorpromazine (*vide supra*). This is probably due to well known local effects of reserpine on the stomach rather than disturbances in the coagulation mechanism.

Phenobarbitone decreased prothrombin time (Table 2). Kronberger (41) has reported increase in prothrombin time with phenobarbitone. Hrdina (30) and Lewis (42) have, however, found phenobarbitone to antagonize the hypo-prothrombinemic effects of ethylbiscoumacetate and other coumarines thus supporting the findings of the present investigation. A lowering of prothrombin time with certain other barbiturates has also been reported (43).

The results of the present investigation clearly show that drugs having similar central effects differ widely in their effects on coagulation. This is an important factor to be considered while choosing a suitable agent for therapeutic purposes. There is also a close correlation between the effect on the coagulation and reported haemorrhagic or thrombotic complications and hepatotoxicity of many of these agents.

SUMMARY

1. Twenty-five drugs acting on the central nervous system were screened for their effects on bleeding time, coagulation time and prothrombin time in albino rabbits. Thirteen of them had no effect.

2. Chlorprothixene significantly increased the bleeding time while iproniazid, LSD-25 and pethidine reduced it.

3. Coagulation time was increased by chlorprothixene and mephenesin and decreased by reserpine.

4. Prothrombin time was prolonged by chlorpromazine, chlorprothixene, iproniazid, LSD-25 and tranylcypromine and reduced by amitryptiline, chlordiazepoxide, imipramine, phenobarbitone and reserpine.

5. The possible mechanisms of action and clinical implications of these findings have been discussed.

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