EFFECT OF REPEATED ADMINISTRATION OF RESERPINE AND CHLORPROMAZINE ON BLOOD COAGULATION

By

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We have earlier reported (11) that even a single dose of any one of several tranquilisers can produce significant changes in bleeding time, coagulation time and prothrombin time in rabbits. There are occasional clinical reports of haemorrhagic complications during therapy with reserpine or chlorpromazine (5, 8, 14 and 16). Since clinically chlorpromazine and reserpine are usually given for longer periods, it was decided to study the influence of repeated administration of these drugs on bleeding and clotting.

MATERIALS AND METHODS

Indian albino rabbits of either sex weighing between 1—1.5 *kg* were employed in these experiments. Bleeding time was determined by the method of Duke (3), coagulation time by the capillary tube method of Wright and Colebrook (17) and prothrombin time by the micro-method of Motingel (13) employing Thrombokinase tablets (Geigy). All the values were recorded to 0.1 sec. The details of procedures are described elsewhere (12). Control determinations were carried out at least thrice in each animal before beginning drug administration. Chlorpromazine 2 *mg/kg* or reserpine 0.25 *mg/kg* was administered once daily intramuscularly for 16 days to groups of 10 rabbits each. Another group of 5 rabbits received corresponding volume of normal saline only and was tested similarly to act as a further control. All the tests were repeated every 4 days during and after the drug administration till normal values were obtained.

The significance of any alterations from the mean control bleeding time, coagulation time and prothrombin time was judged by Students' 't' test at 95% ($P < 0.05$) and 99% ($P < 0.01$) levels of probability.

RESULTS

The data on bleeding time, coagulation time and prothrombin time in normal, saline treated, chlorpromazine treated and reserpine treated rabbits is summarised in Table I. The mean values obtained in the saline treated rabbits do not differ significantly from the values obtained in normal rabbits. Chlorpromazine produced a significant increase in bleeding time and prothrombin time on the 12th day. This increase was maintained during the period of drug administration. The values returned to normal on 8th day after stopping the drug.

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TABLE I

Effect of chlorpromazine and reserpine on bleeding time, coagulation time and prothrombin time in rabbits. All values are mean group values in sec. ±s.e. The drugs were administered daily for the first 16 days

Treatment	*Test*	*Control*	*DAY* 4	8	12	16	20	24	28
I Chlorpromazine	Bleeding Time	95±0.08	96±1.0	99±1.7	99±1.5*	101±1.0**	100±1.8*	96±1.7	
	Coagulation Time	110±3.0	113±1.4	113±1.0	111±2.3	109±1.3	114±2.3	113±0.5	
	Prothrombin Time	7.8±0.15	7.9±0.2	8.1±0.1	8.5±0.2*	8.4±0.15*	8.3±0.1*	7.9±0.2	
II Reserpine	Bleeding Time	98±1.5	98±1.6	98±1.0	98±0.51	00±1.5	98±1.0	99±2.0	102±1.7
	Coagulation Time	104±4.0	104±3.1	109±1.4	108±1.4	105±2.0	104±2.5	103±1.4	108±1.5
	Prothrombin Time	7.8±0.1	7.5±0.05*	7.1±0.07**	7.1±0.05**	7.0±0.05**	7.0±0.0**	7.1±0.5**	7.6±0.05
Saline	Bleeding Time	97±1.0	98±1.2	97±1.3	94±3.0	98±1.4	99±1.2	97±1.6	96±2.0
	Coagulation Time	102±2.8	103±2.2	106±2.4	102±1.0	104±2.6	104±1.8	103±2.4	106±3.8
	Prothrombin Time	7.8±0.1	7.6±0.2	7.7±0.0	7.7±0.1	7.8±0.05	7.8±0.05	7.8±0.05	7.7±0.2

* P= <0.05 **P= <0.01

Chlorpromazine did not affect coagulation time. Reserpine produced a significant decrease in the prothrombin time on the 4th day ($P = <0.05$) and prothrombin time continued todecrease as long as reserpine administration was continued. Recovery started on withdrawl of the drug and the values returned to normal after 12 days of withdrawl. Reserpine had no effect on coagulation time and bleeding time.

DISCUSSION

The normal values of bleeding time, coagulation time and prothrombin time reported in this paper are lower than those reported from other countries (2, 9 and 15). As pointed out in a previous paper (12) normal values for Indian rabbits may be low.

Martin *et al* (10) reported a lowering of serum calcium level on chronic administration of chlorpromazine in rats. This could account for the increase in prothrombin time with chlorpromazine observed in the present study. It is also possible that the increase in prothrombin time with chlorpromazine may be related to distrubances in liver function known to be produced by the drug. The results obtained in the present investigation provide a possible explanation for the clinical reports of haemorrhages from multiple sites during chlorpromazine therapy (5, 14). Thrombosis reported during treatment of endogenous psychosis with reserpine (7) could similarly be explained on the basis of decrease in the prothrombin time observed in the present investigation. No explanation for the reported haemorrhagic complication of reserpine therapy (1, 4) is available on the basis of the present results. A significant fact, however, is that all reports of haemorrhagic distrubances during reserpine therapy relate to bleeding from the gastro-intestinal tract (1, 4, 6, 8, 16). It is quite likely that these complications arise from local effects of the drug on the gastro-intestinal tract, rather than from any effect on coagulation time or bleeding time.

SUMMARY

1. Chlorpromazine (2 *mg/kg*) and reserpine (0.25 *mg/kg*) were administered intravenously daily to rabbits for 16 days and effects on bleeding time, coagulation time and prothrombin time were noted.

2. Chlorpromazine produced a significant ($P = <0.05$) increase in bleeding time and prothrombin time (12th day). The bleeding time and prothrombin time returned to normal 8 days after stopping the drug.

3. Reserpine decreased prothrombin time significantly on the 4th day after its administration. Prothrombin time returned to normal 12 days after stopping the drug administration.

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