

## Short report

# The effect of anticonvulsant drugs on the development of male rats and their fertility

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**SUMMARY** Albino male rats were injected with diphenylhydantoin, carbamazepine, valproic acid or clonazepam for three months immediately after weaning. Following the treatment the fertility of the rats was tested by caging them with proestrus females and recording impregnations. The males were decapitated and their sex organs weighed. Epididymal sperm content and motility rate were recorded. A decrease in the prostate weight was found in the valproic acid and the carbamazepine treated rats. Epididymal weights were found decreased only in the valproic acid treated rats. These rats had diminished sperm content and sperm motility and their fertility was decreased. Carbamazepine treated rats had a lowered epididymal sperm content which did not affect their fertility.

A large battery of anticonvulsant drugs is available for the treatment of epilepsy. Since this condition involves long term use of drugs and since epilepsy tends to start in childhood, it is essential to study the effect of such drugs on the development of the reproductive tract and on sexual maturation. The purpose of this study was to follow the growth curves of rats who were treated immediately after weaning for three months with commonly used anticonvulsant drugs such as diphenylhydantoin, carbamazepine, valproic acid and clonazepam and to record the activity of the reproductive system.

### Material and methods

Albino male rats of original Wistar stock were used. Following weaning, three weeks postpartum, they were given the dose by daily subcutaneous injection. Doses were diphenylhydantoin, eleven rats, 2 mg/100 g body weight; clonazepam, eleven rats, 0.18 mg/100 g body weight; valproic acid, ten rats, 3.0 mg/100 g body weight. The doses selected were high clinical ones multiplied by the factor of metabolic rate. Control groups of ten rats were injected

with 0.1 saline subcutaneously. Nine rats were injected with carbamazepine, 2 mg/100 g body weight, dissolved in propylene glycol. Body weights were recorded weekly. Following three months of treatment the rats were tested for fertility as described previously.<sup>1</sup> The last drug injection was administered two days prior to necropsy; methods are given elsewhere.<sup>1,2</sup> The values are reported as means  $\pm$  SE. Significance of differences were calculated using Student's *t* test. Differences in fertility rates were compared using the Fisher exact probability test.

### Results

The effect of treatment on the growth curves are given in the figure. It was found that rats in all treated groups gained weight and developed normally. The table summarises the effect of the various drugs on the body weight, on the day of necropsy and on the weights of male sex accessory glands, that is seminal vesicles, coagulating gland and prostate as well as the function of the epididymis and rat fertility. A decrease in the prostate weight was found in the valproic acid and in the carbamazepine treated rats. All other glands were not affected. The drugs did not change the weight of the testes. Epididymis weights were decreased only in the valproic acid treated rats, which was also manifested in decreased sperm quality. Sperm content was decreased by 69% ( $p < 0.0005$ ) and sperm motility by 46% ( $p < 0.005$ ). The fertility rate was also diminished

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Table Effect of the various treatments on the weights of the testis, epididymis, male accessory sex glands, the quality of the sperm in the epididymis and the fertility rate. Numbers are mean  $\pm$  SEM. Body weights are given in the figure

Group	N	Glandular weights mg/100 g body weight				Epididymis			Fertility rate pregnant rats (%)
		Testis weight mg/100 g body weight	Seminal vesicle	Coagulating gland	Prostate	Weights mg/100 g body weight	Sperm cont mill	Motility	
Control (saline)	10	934 $\pm$ 44	242 $\pm$ 60	60 $\pm$ 6	256 $\pm$ 28	319 $\pm$ 15	134 $\pm$ 14	80 $\pm$ 5	% = 50%
Diphenylhydantoin	11	958 $\pm$ 46	206 $\pm$ 38	65 $\pm$ 6	231 $\pm$ 17	305 $\pm$ 32	169 $\pm$ 14	72 $\pm$ 6	% = 64%
Clonazepam	11	908 $\pm$ 103	170 $\pm$ 15	61 $\pm$ 6	232 $\pm$ 20	317 $\pm$ 34	72 $\pm$ 10†	78 $\pm$ 2	% = 73%
Valproic acid	10	981 $\pm$ 28	260 $\pm$ 36	48 $\pm$ 4*	194 $\pm$ 11*	282 $\pm$ 10*	42 $\pm$ 10‡	43 $\pm$ 8†	% = 20%§
Control Prop gly	6	944 $\pm$ 46	271 $\pm$ 56	46 $\pm$ 4	266 $\pm$ 9	286 $\pm$ 8	58 $\pm$ 23	60 $\pm$ 5	% = 67%
Carbamazepine	9	1031 $\pm$ 63	186 $\pm$ 38	52 $\pm$ 6	178 $\pm$ 12‡	288 $\pm$ 17	35 $\pm$ 4	63 $\pm$ 5	% = 67%

\*Significantly different from the control group by *t* test  $p < 0.05$ .  
 † $p < 0.005$ .  
 ‡ $p < 0.0005$ .  
 §Significantly lower from the control group by Fisher exact probability test.  
 N = Number of rats.

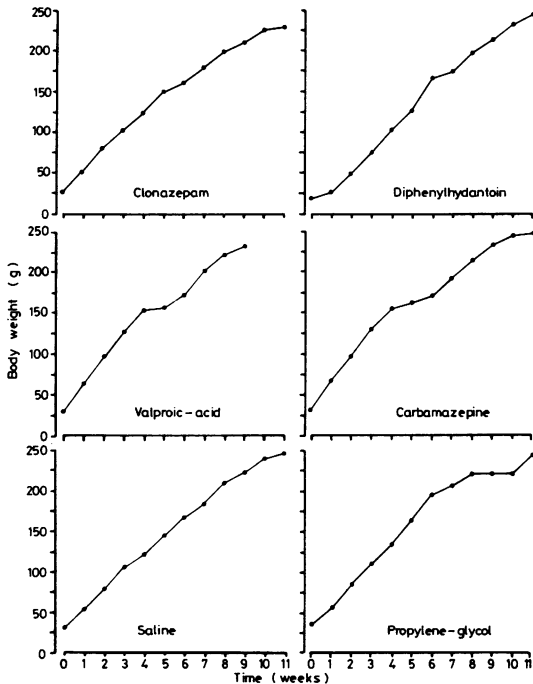


Figure Growth curves of treated rats starting at first week after weaning. Points are means of the rats weights. Number of rats are given in the table.

by 60% ( $p < 0.0001$ ). A decrease in epididymal content was also found in the clonazepam treated rats (47%,  $p < 0.005$ ). This, however did not affect the fertility of the rats.

### Discussion

Fertility abnormalities were recently observed in epileptic males receiving long term anticonvulsive treatment.<sup>3</sup> We have studied 136 epileptic men treated with diphenylhydantoin, carbamazepine and phenobarbitone, in varying combinations for many years. Semen analysis and male hormone balance studied in 22 of our patients did not show significant differences when compared with a control group (unpublished data). In another study we tested the diphenylhydantoinate effect on the reproductive function of the male rat and we concluded that in treated adult rats the fertility abnormalities observed were most probably on a behavioural basis, namely loss of libido.<sup>1</sup> However, since seizures commonly begin in childhood we decided to test in the present study the effect of some anticonvulsive drugs on the development of the rats and their male sex organs, when treatment was initiated prior to sexual maturation. We have found that development and weight gain of all treated animals was normal. Striking effects were noticed in the clonazepam treated rats on the epididymal function, reflected in decreased sperm content and motility. Two drugs, valproic acid and carbamazepine caused decreased prostatic weights, while valproic acid also affected the coagulating gland development. The findings of the effect of valproic acid on the epididymis are interesting. Sperm content and motility were decreased and the fertility rate diminished. It is important to remember that valproic acid has been found in the semen of treated rabbits and men and that chronic toxicity studies in animals showed that testicular damage, including degeneration of the interstitial cells, may occur.<sup>4</sup>

The clinical implications of this preliminary study are possibly important; therefore further studies are indicated before final conclusions are drawn.

#### References

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