INFLUENCE OF SEX HORMONES ON THIOPENTONE SODIUM-INDUCED GENERAL ANAESTHESIA IN RABBITS

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Summary: Effects of testosterone, progesterone, oestrogen and progesterone combination were studied on thiopentone sodium-induced general anaesthesia in nonpregnant female and male rabbits. Three days' treatment either with testosterone 1 *mg/kg* or progesterone 1.5 *mg/kg* or oestrogen 0.03 *mg* in combination with progesterone 0.5 *mg/kg* delayed the onset and shortened the duration of general anaesthesia.

Key words: general anaesthesia, progesterone, oestrogen, testosterone

INTRODUCTION

There are no references in the literature on the influence of pregnancy and early puerperium on the dose of thiopentone sodium required for general anaesthesia. It was repeatedly observed by us in the laboratory that if the rabbits are pregnant or in early puerperium the dose of thiopentone sodium required to induce general anaesthesia is approximately 4–5 times more than what is required otherwise. Andreasen *et al.* studied the influence of age and sex on pharmacokinetics of thiopentone and observed that the plasma concentration of thiopentone was significantly less in elderly women compared to young women (1). It was thought worth while to investigate the influence of exogenously administered sex hormone on thiopentone sodium-induced general anaesthesia in rabbits.

MATERIAL AND METHODS

Sixteen non-pregnant female and twelve male adult albino rabbits weighing from 0.5 to 1.4 *kg* were used for the study. By preliminary experiments it was found that 16 *mg/kg* of thiopentone sodium given into the ear vein induces general anaesthesia in all the rabbits studied. This dose was always administered slowly and at the same rate

to each rabbit and the time taken for onset and duration of action was determined. The onset of general anaesthesia was taken from the moment the injection was given to the loss of corneal reflex. The duration for anaesthesia was determined from the time of loss of corneal reflex to the reappearance of the rightning reflex.

In 6 rabbits of each sex thiopentone sodium was repeated every 10th day to assess the degree of development of tolerance or otherwise. In the remaining ten female and six male rabbits, the time needed for the onset and duration of general anaesthesia was determined before and after pretreatment for three days with one of the following drugs (German Remedies Ltd., Bombay).

I testosterone propionate 1 *mg/kg* (Testoviron)

II hydroprogesterone caproate 1.5 *mg/kg* (Proluton Depot)

III progesterone 0.5 *mg* and estradial benzoate 0.3 *mg/kg* (Cumorit–forte).

After a washout period of 7 days the next regimen was given and the process was repeated in the same rabbits. The observations before and after treatment in the same rabbits were compared after each regimen. The results were analysed by using 't' test.

RESULTS

Significant shortening of the period of onset and lengthening of the duration of general anaesthesia was observed on repeated administration of thiopentione sodium to six male and six female untreated rabbits at an interval of 10 days (Table I).

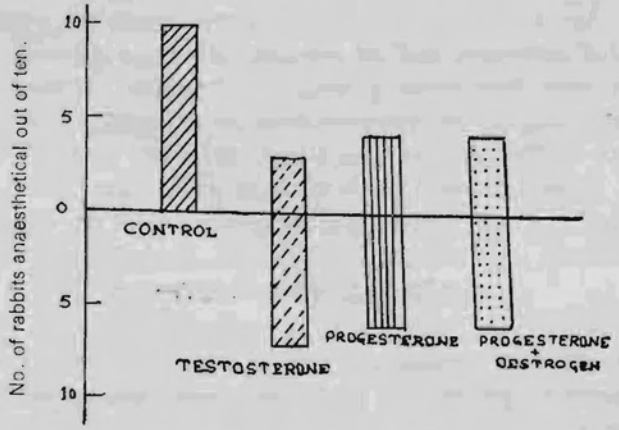

Fig. 1: Anaesthetic response to thiopentone sodium 16 *mg/kg/iv.*

TABLE I : Effect on the onset and duration of general anaesthesia in control rabbits repeatedly anaesthetized with thiopentone sodium (16 *mg/kg, iv*). of an interval of 10 days.

Number of days	*Sex*	*Mean time (sec. S.E.)*	
		Onset of anaesthesia	*Duration of anaesthesia*
0	Female (6)	6.2±0.8	495.00±7.6
	Male (6)	6.6±0.2	488.4 ±14.2
10	Female (6)	5.8±0.24*	608 ±13.2*
	Male (6)	5.6±0.8*	540 ±14.16*
20	Female (6)	5.6±0.4*	632 ±14.0*
	Male (6)	5.4±0.4*	632 ±40.2*

Value significantly differs from the control

* $P<0.01$ (0 day)

Figures in parentheses indicate the number of animals used.

The effect of pretreatment with sex hormones on onset and duration of general anaesthesia is shown in Table II. Seven out of ten testosterone–treated female rabbits were not at all anaesthetized with the standard dose of thiopentone sodium. In three remaining female rabbits the onset was delayed and duration of general anaesthesia was shor-

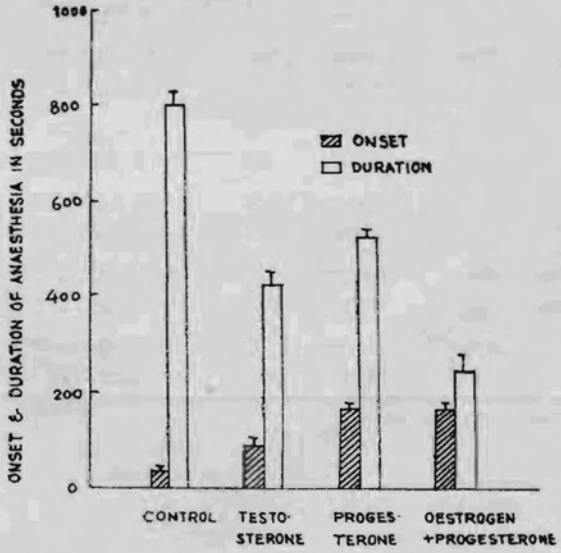

Fig. 2: The onset and duration of general anaesthesia in rabbits after thiopentone sodium 16 *mgm/kgm/iv*.

tened. Progesterone and progesterone–oestrogen combination produced similar effects, but progesterone alone was less active while the combination was more active in this respect (Fig. 1, Table II).

In the male rabbits six out of six animals were anaesthetized with the standard dose of thiopentone sodium. This is in contrast to female rabbits where seven of the ten and six of the ten were just not anaesthetized after pretreatment with testosterone and progesterone respectively with the standard dose of thiopentone sodium. All the same, there was a significant delay in the onset and shortening in the duration of general anaesthesia in male rabbits pretreated with testosterone and progesterone. However, on increasing the dose of progesterone to 5 *mg/kg* and testosterone to 4 *mg/kg* no further change was observed in the duration and onset of general anaesthesia in male rabbits. In progesterone–oestrogen combination treated male rabbits 4 animals could not be anaesthetized with the standard dose of thiopentone sodium while in remaining two rabbits the onset was lengthened and the duration was shortened (Fig. 2, Table II).

TABLE II : Effects of testosterone progesterone and oestrogen in combination with progesterone on thiopentone sodium–induced general anaesthesia in male and non-pregnant female rabbits.[1]

Treatment		*Sex*		*Mean time (sec. ± S.E.)*	
				Onset of general anassthesia	*Duration of general anaesthesia*
Testosterone 1 *mg/kg* (im) for 3 days.	Before	Female	(10)	7.5±0.8	595.00±7.6
		Male	(6)	6.8±0.2	463.3 ±15.4
	After	Female	(10)	75.0±3.00**	393.50±28.3**
		Male	(6)	20.2±0.9*	393.00±23.4*
Progesterone 105 *mg/kg* (im) for 3 days.	Before	Female	(10)	7.8±0.8	595.00±7.6
		Male	(6)	6.8±0.2	463.3 ±15.4
	After	Female	(10)	120.6±18.1**	358.00±34.7**
		Male	(6)	34.4±9.8*	252.20±29.2**
Progesterone 0.5 *mg*+Oestrogen 0.03 *mg* (im) for 3 days	Before	Female	(10)	7.8±0.8	595.00±7.6
		Male	(6)	6.8±0.2	463.3 ±15.4
	After	Female	(10)	165±18.1**	242.4±7.5**
		Male	(6)	20±1.1*	280.4±1.1**

Value significantly differs from the control.

* $P<0.01$

** $P<0.001$

1 See Methods for experimental design.

Figures in parentheses indicate the number of animals used.

DISCUSSION

Anaesthesia after thiopentone sodium, like other intravenously given ultrashort acting barbiturates, is known to be related to its high lipid solubility and quick large delivery to the brain. The termination of action is thought to be due to dissipation from brain and redistribution to fatty depots elsewhere. The observed effects may be due to changes in the pharmacokinetics or sensitivity of brain to the drug. Christensen *et al.* (2) observed greater sensitivity to thiopentone in young women as compared to young men but this difference disappeared when the sensitivity was observed in terms of body weight. Andreasen *et al.* (1) observed higher clearance value in edlderly women compared to young women. In the present study the rabbits were practically of the same age and the effect was studied in both sexes.

In view of these observations it would seem reasonable that changes in sensitivity rather than changes in pharmacokenetics may account for the observed significantly delayed onset and reduced duration of general anaesthesia in both sexes. It has been reported that removal of testes increases the pain threshold and testosterone treatment restores it in castrated male rats (3). The sensitivity of brain cells may be related to the presence of sex hormones, lack of it raises the threshold of pain by decreasing their sensitivity to painful stimuli. The antagonism of sex hormones to the depressant action of thiopentone sodium might be due to altered responsiveness.

REFERENCES

1. Andreasen, F., J.H., Chiristensen and J.A. Jansen. The influence of age and sex on the pharmacokinetics of thiopentone. *Brit. J. Pharmac.* **73** : 175–176, 1981.
2. Christensen J.H., F. Andreasen and J.A. Jansen Pharmacokinetics of thiopentone in a group of young women and a group of young men. *Brit. J. Anaesth.*, **52** : 913–917, 1980.
3. Rao, S.S. and A.Q. Saifi. Effect of testosterone on threshold of pain. *Ind. J. Physiol. Pharmac.*, **25** : 387–388, 1981.