

Experimental evaluation of effects of a pyrimidine derivative 4CPTP on cardiovascular system

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Abstract

Aim: To study the effects of pyrimidine derivative 4CPTP on cardiovascular system.

Material and methods: Inotropic and chronotropic effects of 4CPTP were studied using rabbit heart and frog's heart 'in situ' preparation. Dog's blood pressure preparation was used to assess the effects of 4CPTP on blood pressure.

Results: The test compound, like phenobarbitone produced dose dependent decrease in heart rate and amplitude of contractions of rabbit and frog heart and decrease in blood pressure in dogs.

Conclusions: 4 CPTP possesses negative inotropic and negative chronotropic action along with hypotensive action in animal models.

Keywords: 'In situ' preparation, inotropic effect, chronotropic effect, phenobarbitone, pyrimidines.

1. Introduction

At present, there are several techniques of new drug development- high throughput screening of potential agents, modification of the structure of existing compounds, enhancing delivery of the currently existing drugs to their site of action, serendipitous discovery and discovery of a new drug as a result of scientific enquiry into the mechanisms underlying the pathology and pathogenesis of the disease. Among these, structural modification of the existing compound is the main line of approach to new drug development. It holds forth the hope that suitable structural variation may increase the usefulness of a given type of a compound by widening the differences between desirable actions and toxicity syndromes.

Pyrimidine is a six member cyclic compound containing four carbon and two nitrogen atoms at position 1 and 3.[1] It is pharmacologically inactive but its synthetic derivatives play an important role in modern medicine. These derivatives have been seen to possess a wide array of activities like antifungal (flucytosine), anti-tumor, anti-cancer (5 fluorouracil, floxuridine and cytarabine), anti-HIV (lamivudine, zidovudine), anti viral (idoxuridine), hypnotic (thiopentone), anti-thyroid (thiouracil), antibacterial (trimethoprim), anti-malarial (pyrimethamine), anti convulsant activity (phenobarbitone) etc.[2] All these wide range of activities have been possible due to slight modifications in the chemical structure of pyrimidine nucleus.

The test compound of this study is 4CPTP [1(4-carboxy phenyl)-4,4,6-trimethyl-1H,4H pyrimidine- 2 thiol]. It also belongs to thiopyrimidine series. Due to its structural resemblance to phenobarbitone (an anti epileptic drug), this compound has been tested for its central nervous activity in an earlier study where it showed dose dependent anti convulsant action like phenobarbitone. On the contrary, this drug also produced analgesic action which was contrary to hyperalgesic action produced by phenobarbitone.[3] In this study, we have tried to investigate and compare the effects of 4CPTP and phenobarbitone on cardio vascular system.

2. Materials and Methods

2.1 Animals

The study was approved by the institutional review board and was done as a thesis work. It was done few years back when the dog and frog experiments were not yet banned.

To study the inotropic and chronotropic effect of 4CPTP on perfused heart, 6 adult rabbits (*Oryctolagus cuniculus* species) and 6 adult frogs (*Rana tigrina* species) of either sex were used. Effect of 4CPTP on blood pressure was studied by using adult mongrel dogs of either sex, weighing between 10-12 kg. The protocol of the study was approved by the institutional review board and complied with the Guide for the Care and Use of Laboratory Animals

2.2 Drugs

The test compound 4CPTP was used in graded doses of 0.5- 4 mg for frog's heart and rabbit's heart in situ preparations. For the same experiments, phenobarbitone (graded doses of 0.5-4 mg) was used as the standard comparator. The sensitivity of the heart was assessed using 2 µg of adrenaline in both these experiments. For assessing the effect on dog's blood pressure, 4CPTP and phenobarbitone in graded doses of 2.5- 20 mg/kg body weight were used as test drug and standard comparator respectively. Adrenaline and acetyl choline (1 µg/kg body weight each) were used to observe their standard effect on dog's blood pressure.

2.3 Assessment of ionotropic and chronotropic activity

2.3.1 Rabbit's heart preparation

A healthy adult rabbit was taken, stunned and bled through carotid arteries. The heart along with an inch of ascending aorta was taken and put up on Langendorff's assembly and connected to modified starling's heart lever. The heart was perfused with oxygenated ringer locke solution at 37° C. The sensitivity of the heart was assessed using 2 µg of adrenaline. The effect of the test compound and the comparator was studied by injecting it through the canula. Initially effect of phenobarbitone and later that of 4 CPTP was observed. Next dose of the drug was given when a complete recovery in heart rate and amplitude was observed by washing it with ringer locke solution. 6 such experiments were set up and their mean values were calculated and analysed statistically.

2.3.2 Frog's heart preparation

An adult frog was pithed and fixed on frog's board. The heart was exposed and connected to modified starling lever. The right truncus arteriosus was tied off. A venous canula was introduced and tied in the inferior venacava which was connected to reservoir bulb with murphy's drip through rubber tubing. Frog's ringer solution was used as perfusion

fluid at the rate of 45 drops per minute. The sensitivity of the heart was assessed using 2 µg of adrenaline. The drugs were administered through rubber tubing. Initially effect of phenobarbitone and later that of 4 CPTP was observed. 6 such experiments were set up and their mean values were calculated and analysed statistically.

2.3.3 Dog's blood pressure preparation

An adult dog was anaesthetised with pentobarbitone sodium in dose of 35 mg/kg body weight and supplemented with intravenous pentobarbitone sodium as and when required. The anaesthetised dog was tied on brodie's operation table. An intravenous cannula was inserted in right femoral vein for administration of drugs and normal saline. Tracheal cannula was put in trachea and connected to artificial respiration pump. An arterial cannula was inserted into left common carotid artery. It was in turn connected to mercury manometer and the blood pressure recordings were taken on a smoked drum.^[4] Adrenaline and acetyl choline (1 µg/kg each) were used to observe their standard effect on dog's blood pressure. Initially effect of phenobarbitone and later that of 4 CPTP was observed. 6 such experiments were set up and their mean values were calculated and analysed statistically.

3. Results

The effect of graded dose of phenobarbitone and 4CPTP on heart rate (per minute) and amplitude (in mm) on rabbit's heart 'in situ' preparation has been described in table 1, figure 1 and figure 2. Table 2, figure 3 and figure 4 show the effect of graded doses of phenobarbitone and 4CPTP on heart rate (per minute) and amplitude (in mm) on frog's heart 'in situ' preparation. Effect of phenobarbitone and 4CPTP on anaesthetised dog's blood pressure has been depicted in table 3 and figure 5.

Table 1: Table showing mean effect of graded doses of phenobarbitone and 4CPTP on heart rate (per minute) and amplitude (in mm) on rabbit's heart 'in situ' preparation

Drug	Dose (mg)	Heart rate (mean effect ± S.E.)		Amplitude in mm (mean effect ± S.E.)	
		Before drug	After drug	Before drug	After drug
Phenobarbitone	0.5	74.66± 7.86	73.00±7.92	34.66±4.01	29.50±3.89
	1	66.33±7.25	64.33±7.97	29.50±4.85	22.50±3.81
	2	69.66±6.66	67.33±7.01	19.16±4.84	11.16±3.20
	4	75.33±7.27	72.33±6.99	25.50±3.33	13.50±3.52
4CPTP	0.5	74.33± 7.05	73.33±7.96	26.66±4.37	26.10±4.31
	1	71.66±7.07	69.66±6.48	23.33±3.16	22.83±3.22
	2	66.33±7.31	63.33±6.96	30.83±4.70	30.16±5.12
	4	68.33±7.05	64.66±5.74	18.00±4.51	17.50±4.38

Figure 1: Diagram showing mean percentage decrease in heart rate with phenobarbitone and 4CPTP on isolated perfused rabbit's heart

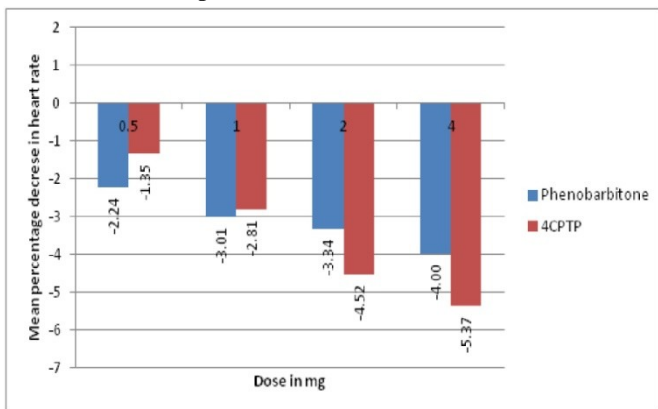


Figure 2- Diagram showing mean percentage decrease in amplitude with phenobarbitone and 4CPTP on isolated perfused rabbit's heart

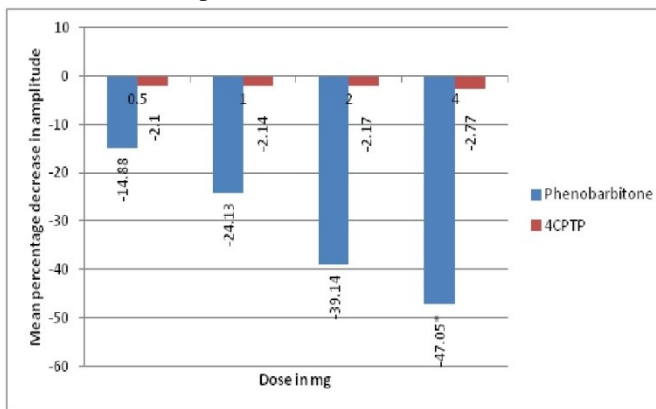


Table 2- Table showing mean effect of graded doses of phenobarbitone and 4CPTP on heart rate (per minute) and amplitude (in mm) on frog's heart 'in situ' preparation

Drug	Dose (mg)	Heart rate (mean effect ± S.E.)		Amplitude in mm (mean effect ± S.E.)	
		Before drug	After drug	Before drug	After drug
Phenobarbitone	0.5	14.83±1.35	14.66±1.66	9.50±0.42	8.00±0.63
	1	19.33±2.41	19.00±2.33	7.83±0.74	6.00±0.68
	2	15.83±2.08	15.33±1.64	7.66±0.71	3.50±0.99
	4	19.50±2.95	18.00±2.93	7.33±0.80	2.50±0.88
4CPTP	0.5	19.50±3.06	17.50±3.03	9.50±0.80	9.00±0.57
	1	19.00±2.73	16.83±2.88	7.66±0.71	7.13±0.84
	2	15.66±2.01	12.50±1.92	7.66±1.45	8.83±1.16
	4	16.00±1.94	13.00±2.25	9.16±1.35	8.16±1.19

Figure 3- Diagram showing mean percentage decrease in heart rate with phenobarbitone and 4CPTP on frog's heart 'in situ'

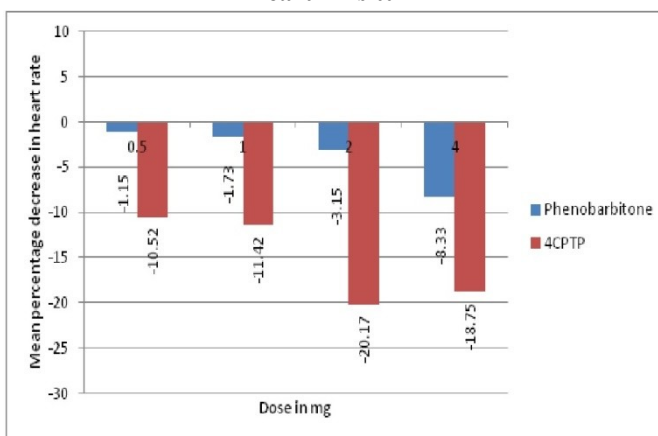


Figure 4- Diagram showing mean percentage decrease in amplitude with phenobarbitone and 4CPTP on frog's heart 'in situ'

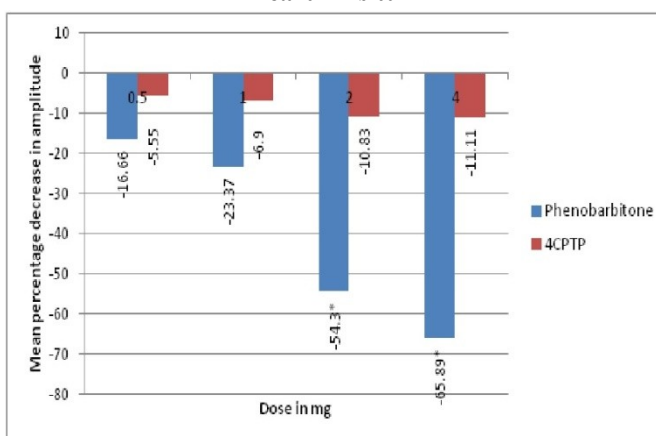
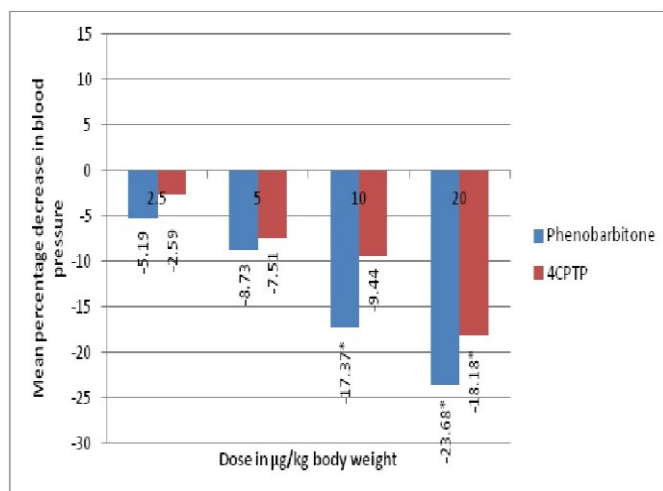


Table 3- Table showing mean effect of graded doses of phenobarbitone and 4CPTP on anaesthetised dog's blood pressure (mm of Hg)

Dose (mg/kg body weight)	Phenobarbitone (mean effect ± S.E.)		4CPTP (mean effect ± S.E.)	
	Before drug	After drug	Before drug	After drug
2.5	102.66±4.66	97.33±3.81	103.00±4.55	100.00±4.21
5.0	103.00±4.56	94.00±3.38	102.33±4.08	94.66±3.74
10.0	103.66±4.23	85.66±3.70	102.33±4.60	92.66±4.69
20.0	101.33±4.49	77.33±3.48	99.66±4.45	81.66±4.44

Figure 5- Diagram showing mean percentage decrease in dog's blood pressure with phenobarbitone and 4CPTP



4. Discussion

In the present study, 4CPTP and phenobarbitone both were seen to produce dose dependent negative inotropic and negative chronotropic action in rabbit's heart and frog's heart 'in situ' preparation as is evident by decrease in heart rate and amplitude of the contractions. However, 4CPTP showed more negative inotropic action and less negative chronotropic action as compared to phenobarbitone in both the preparations. Negative inotropic action of 4CPTP was more evident in frog's heart preparation as compared to rabbit's heart preparation. The mean percentage decrease in blood pressure was dose related effect with phenobarbitone as well as 4CPTP but it was more with phenobarbitone as compared to 4 CPTP when used in similar doses.

Thus it may be predicted from the study that the test compound 4CPTP possesses cardio depressant and hypotensive actions. These properties of the test compound suggest that it may be used clinically for decreasing heart rate as in arrhythmias or for decreasing cardiac work as in angina where its hypotensive action would provide additional advantage. It can be used for the treatment of hypertension also. To the best of our knowledge, no other similar study could be found which assesses the effects of 4CPTP on cardiovascular system in experimental animals. Hence more number of animal studies and clinical studies are required to confirm these findings.

5. Conclusions

The test compound 4CPTP possesses negative inotropic and negative chronotropic action along with hypotensive action in animal models.

References

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