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A COMPARATIVE STUDY OF CENTRALLY AND PERIPHERALLY ADMINISTERED TRIPELENNAMINE IN RABBITS

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ABSTRACT

The effects of the H_1-histamine blocker tripelennamine (Trp) on blood pressure, heart rate, ECG pattern, serum sodium, potassium and calcium levels as well as its effect on serum GOT and GPT, creatinine and urea levels were investigated, when administered intravenously (i.v.) and intraceerbroventricular (i.c.v.), in a trial to compare between these two routes. Trp (2.5 mg/kg) i.v. and i.c.v. caused a significant long lasting rise in blood pressure, no significant difference occured between i.v. and i.c.v. data at $P<0.01$ was recorded. Trp injection i.v. or i.c.v. did not alter the heart rate, but significantly affected ECG pattern. Also no significant difference between i.v. and i.c.v at $P<0.01$, except at time 10, 15 and 20 minutes on ECG pattern. Intravenous and i.c.v. injection of Trp significantly increased the respiratory rate. Intravenous and i.c.v administration of Trp did not alter serum Na^+ or Ca^{++} ions level, while it significantly elevated serum K^+ ions in rabbits. Marked significant differences between i.v. and i.c.v. findings were observed regarding K^+ level. Trp either i.v. or i.c.v. significantly raised the serum transaminases and urea levels at $P>0.01$. In conclusion the route of administration may play a role in the effect induced by Trp The ECG changes produced by Trp may be related to electrolyte imbalance caused by this drug. Trp alters the liver function in the form of increased serum transaminases and changes the renal function as shown by increased serum urea level. These findings need more human studies in order to be considered when applying such therapy on man.

INTRODUCTION

Among the H_1- antagonists, tripelennamine (vetibenzamine) was identified by the majority of subjects as a depressant. In contrast, when tested in animals, it produced signs of CNS excitations such as increased locomotor activity, stereotypic behaviour and convulsions at higher doses [1-3]. Intracerebroventricular injection of Trp significantly blocks the vasodilatation response to histamine[4], this action is not verified by the i.v. administration of the drug. The reduction in post stimulation vasodilatation produced by Trp is related to a cocaine-like action in neuronal re-uptake of noradrenaline[5].

The mechanism of central action of Trp was the aim of several studies. Sewall et al[6] reported that histamine H_1-antagonists had been shown to potentiate the stimulant effect of nicotine. Trp was able to interact with H_1 binding sites, muscarinic receptors as well as sigma sites in rat brain[7].

On the other hand it was used in laboratory discrimination of stimulant properties of many drugs. It is also used to identify histamine in tissue extract[8]. Trp is used in a combination with pentazocine or with morphine to potentiate the action of the opiate by increasing its brain uptake through increasing the permeability of blood brain barrier to it[9].

The present study was designed to compare between the effect elicited by Trp, administered intravenously and intracerebroventricularly. These effects include blood pressure, heart rate, ECG pattern, respiratory rate. The present work also throw light on possible changes in liver and kidney functions and electrolytes in order to specify their role in the cardiovascular effects induced by Trp.

EXPERIMENTAL

1- Drugs and Chemicals:

Tripelennamine (Vetibenzamine) (Ciba Geigy Co.), $CaCl_2$, NaCl, KCl, ethyl alcohol 95%, glucose 50% solution and heparin (El-Nasr Co., Egypt), gentian violet (Medex, England); hydrogen peroxide (Hopkins and Williams); dental cement (Spofa); kits for liver and kidney functions (Biomerieux- France); penicillin G sodium (Cid, Co. Egypt)

2- Animals:

24 adult rabbits of either sexes weighing 1.25-1.5 kg were used in the present work. The animals were allowed free access to food and water, they were divided into three groups, each consisting of 8 rabbits.

The first group was used as control.

The second group was given Trp i.v 2.5 mg/kg.

The third group was given Trp i.c v 2.5 mg/kg.

Each group was used to study the effect of Trp on blood pressure, heart rate, ECG pattern and respiratory rate. Blood samples were withdrawn, centrifugated and the serum was collected and kept at -20°C to investigate the electrolytes, GOT, GPT, creatinine and urea levels.

3- Methods:

i- Implantation of i.c.v. Cannula:

A small hole was made through the parietal bone of the rabbits skull with the tip of 20 gouge needle. This site was located as modification of the method of Feldberg and Sherwood[10]. A stainless steal 12 gauge cannula was inserted into the right lateral ventricle to the depth of 4.5 mm blow the outer surface. The cannula was plugged and fixed in position by dental cement. Correct placement of i.c.v. cannula was determined by aspiration of CSF and by injection of gentian violet and subsequent microscopic examination.

ii-Blood Pressure Recording:

The method described by Burden et al.[11] was adopted using oscillograph, PT 400, blood pressure transducer.

iii-Recording of ECG:

ECG changes were recorded using oscillograph (400 MD 2C-planar, Bioscience, Washington) with ECG electrodes.

iv- Determination of Serum Electrolytes:

Serum Na^+, K^+ and Ca^{++} levels were estimated using a spectrophotmetric method as described by Osman et al.[12].

v- Estimation of Serum Transaminases:

Determination of serum GOT, and GPT

They were determined spectrophotometrically following the method of Reitman and Frankel[13].

vi- Estimation of Serum Urea and Creatinine:

Colourimetric determination of serum urea was performed according to the method reprted by Fawcett and Scott [14].

Serum creatinine was estimated following the method of Husdan and Rapoport[15].

VII-Statistical Analysis:

Data obtained from this work were statistically analysed using Student's "t" test [16] according to Snedecor. P<0.01 was considered significant.

RESULTS

1- Effect on Blood Pressure:

Intravenous injection of Trp elicited a long-lasting hypertension for 60 minutes. Mean blood pressure was raised from 111.2±9.99 to 186.3±2.50 mm Hg after 5` then it decreased gradually (but was still significantly high) till 15` and reached 129.5±12.5 at 60`. Intracebroventricular injection of Trp also resulted in a significant rise of the mean arterial blood pressure. It reached 162.2±2.63 mm/Hg after 40` and remained around this value till 90 minutes. No significant difference between i.v. and i.c.v. data was recorded Fig.(1).

2- Effect on Heart Rate:

Trp (2.5 mg/kg) did not alter the heart rate either when injected i.v. or i.c.v. Also there was no significant difference between the data obtained with the two routes, Fig. (2).

3- Effect on ECG:

The present work revealed that Trp i.v. significantly decreased the amplitude of P, QRS, and T waves, while prolonging the duration of the P-R interval, P, QRS and T waves. Intracerberoventricular injection produced low voltage of P, QRS and T wave (decreased amplitude), while the duration was shortened. There was a significant difference between i.v and i.c.v at P<0.01 at time 10, 15 and 20 minutes Table (1).

4- Effect on Respiratory Rate:

It was found that i.v and i.c.v. injection of Trp significantly enhanced respiratory rate of rabbits. Significant differences between i.v. and i.c.v. data were obtained after 60 and 90 minutes, from 42.6±0.08 to 94.0±2.213 at 60` after i.v and 79.6±1.122 at 60` after i.c.v, and from 42.8±2.13 to 99.9±1.59 at 90 minutes after i.v, and 86.8±2.31 at 90 minutes after i.c.v, Fig (3).

5- Effect on Serum Electrolytes Level:

Intravenous and i.c.v injection ofTrp showed a non significant effect in Na^+ and Ca^{++} ions but significantly elevated serum K^+ ion level. Marked significant difference between i.v and i.c.v. findings was obtained statistically regarding K^+ level, (Table 2).

6- Effect on Liver Functions:

Trp injection either i.v. or i.c.v. signficiantly raised the serum GOT and GPT levels at P<0.01 No marked difference between the data recorded by the two routes of injection occured (Table 3).

7- Effect on Kidney Functions :

Intravenous or i.c.v injection of Trp resulted in a significant elevation of serum urea level and non significant effect on serum creatinine level. No significant difference was recorded between i.v and i.c.v routes Table (4).

DISCUSSION

The present study revealed that i.v. administration of Trp elicited significant long lasting hypertension without significant effect on heart rate. These findings were in aggreement with those of Terry and Robert[17]. They reported that, Trp reduced 77% of active

Table (1): Effects of I.V. and I.C.V. injection of tripelennamine (2.5 mg/kg) on ECG pattern of adult conscious rabbits. (Mean ± S.E., n=6)

Items	P wave				P - R		QRS complex				T wave			
	Amp. mm. volt		Duration Sec.		Interval sec.		Amp. mm. volt		Duration Sec.		Amp. mm. volt		Duration Sec.	
Time (min)	I.V.	I.C.V.	I.V.	I.C.V.	I.V.	I.C.V.	I.V.	I.C.V.	I.V.	I.C.V.	I.V.	I.C.V.	I.V.	I.C.V.
0 (min) (Control)	0.25±0.015		0.122±0.009		0.107±0.004		0.98±0.012		0.061±0.003		0.4±0.015		0.121±0.003	
5	0.62±0.23	0.09±0.011*	0.114±0.003	0.11±0.005	0.11±0.002	0.11±0.004	0.58±0.03*	0.3±0.02*	0.05±0.002	0.03±0.001*	0.25±0.016*	0.123±0.02*	0.12±0.004	0.14±0.034
10	0.5±0.002	.048±0.001*	0.108±0.004	0.1±0.002	0.113±0.002	0.13±0.002•	0.22±0.05*	0.13±0.008*	0.03±0.002*	003±0.001*	0.04±0.004	0.040.001*	0.13±0.003	0.103±0.1833*
15	0.064±0.022*	0.1±0.0018	0.115±0.002*	0.1±0.001*	0.1±0.003*	0.13±0.002•	0.04±0.08*	0.4±0.12*	0.08±0.002	0.4±0.009	0.35±0.015	0.13±0.006*	0.12±0.005	0.07±0.0012
20	0.02±0.011*	0.104±0.002*	0.12±0.003	0.12±0.004	0.119±0.002	0.132±0.001	0.02±0.04*	0.5±0.02*	0.4±0.002	0.05±0.002•	0.32±0.001*	0.24±0.014*	0.13±0.009	0.0770.001
30	0.016±0.004*	0.11±0.002*	0.11±0.006	0.11±0.014	0.83±0.002*	1.13±0.003	0.61±0.01*	0.55±0.02*	0.04±0.004*	0.05±0.002	0.52±0.003*	0.26±0.014	0.124±0.002	0.07±0.003*
60	0.19±0.04	0.107±0.003*	0.104±0.004*	0.123±0.01	0.122±0.001	0.113±0.002	0.012±0.04*	0.54±0.02*	0.04±0.002	0.05±0.002	0.24±0.018	0.27±0.017	0.13±0.012	0.77±0.001
90	0.480.08	0.1±0.002	0.119±0.002*	0.11±0.003*	0.104±0.004*	0.13±0.002*	0.04±0.004	0.6±0.02*	0.06±0.004	0.04±0.001*	0.22±0.04	0.24±0.02	0.136±0.006	0.086±0.001

* Data Considered to be significantly different from control value at P<0.01.
• Data of I.C.V. group considered to be significantly different from I.V. group at P<0.01.

Table (2): Effect of I.V. and I.C.V. injection of tripelennamine (2.5 mg/kg) on serum electrolyte levels of adult conscious rabbits. (Mean±S.E., n=6)

Parameters	Na^+ mEq/L		K^+ mEq/L		Ca^{++} mEq/L	
	I.V.	I.C.V.	I.V.	I.C.V.	I.V.	I.C.V.
Control	156.0±1.581		4.82±0.312		9.97±0.146	
Tripelennamine	149.5±1.208	157.4±2.158	8.28±0.265**	6.16±0.261**	9.63±0.18	12.20±1.322

* Data considered to be significantly different from control value at P<0.01.
* Data considered to be significantly different from I.V. group at P<0.01.

Table (3): Effects of I.V. and I.C.V. injection of tripelennamine (2.5 mg/kg) on serum transaminases level of adult conscious rabbits. (Mean ±S.E., =6.

Parameters	Serum GOT U/L		Serum GPT U/L	
	I.V.	I.C.V.	I.V.	I.C.V.
Control	20.0±0.612		5.0±0.790	
Tripelennamine	24.5±0.707*	31.0±1.816*	21.6±1.133*	21.2±0.860*

* Data considered to be significantly different from control value at P<0.01.

Table (4): effects of i.v. And i.c.v. Injection of tripelennamine (2.5 mg/kg) on serum urea and creatinine level of adult conscious rabbits. (Mean±S.e., N=6)

Parameters	Serum GOT U/L		Serum GPT U/L	
	I.V.	I.C.V.	I.V.	I.C.V.
Control	38.882±2.22		0.97±0.191	
Tripelennamine	55.102±2.144*	83.64±2.087*	1.88±0.182	1.92±0.191

* Data considered to be significantly different from control value at P<0.01

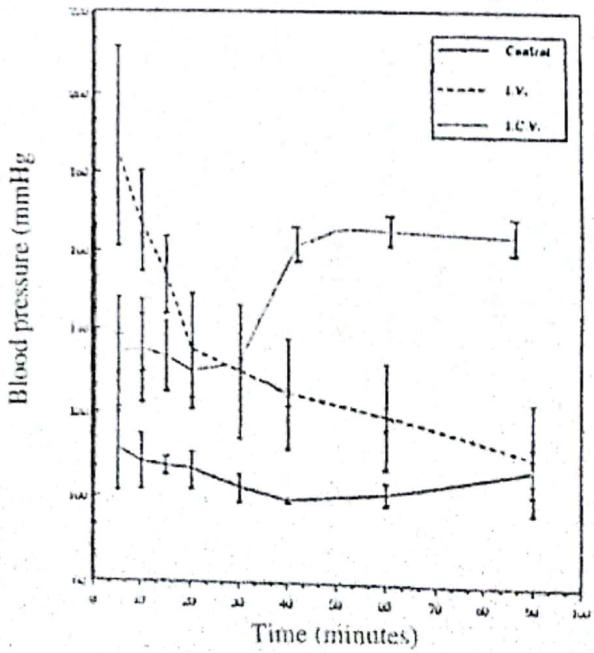

Fig. (1) Effect of intravenous and intracerebroventricular injection of tripelennamine (2.5mg/kg) on mean arterial blood pressure of adult conscious rabbits.

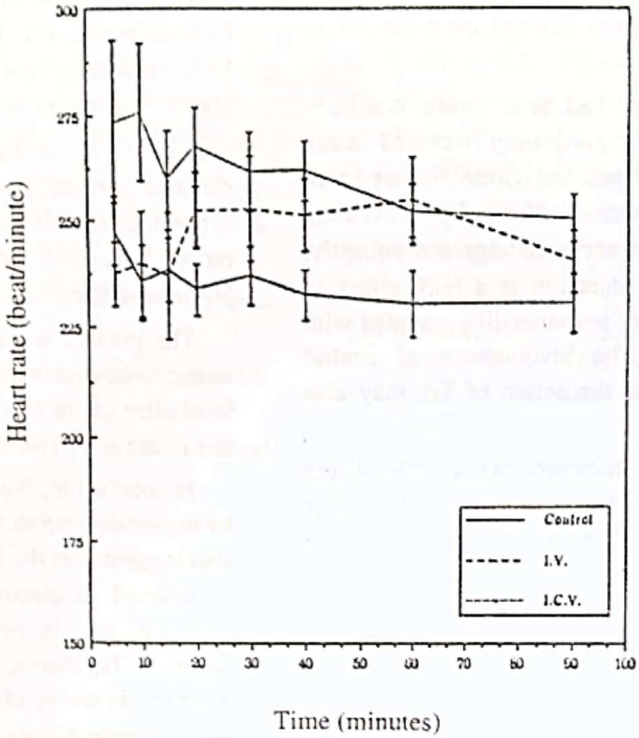

Fig. (2) Effect of intravenous and intracerebroventricular injection of tripelennamine (2.5 mg/kg) on heart rate of adult conscious rabbits.

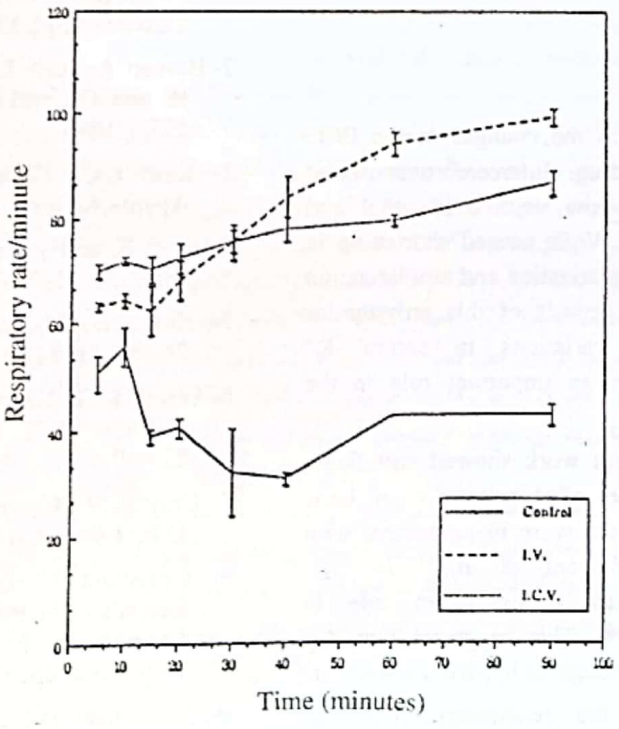

Fig. (3) Effect of intravenous and intracerebroventricular injection of tripelennamine (2.5mg/kg) on respiratory rate of adult conscious rabbits.

vasodilatation provoked by vascular-stored histamine in rats. This effect was related to a cocaine-like action in neuronal reuptake of noradrenaline[5]. Also our results are in harmony with Owen[18], McNeill and Verma[19]. They reported that, H_1-antihistaminics reverse the diminution in arterial tension induced by histamine in cat and dog.

In the present study, it had been shown that i.c.v. injection of Trp could significantly elevated mean arterial blood pressure. Issac and Goth[20] found that Trp potentiated catecholamie effects by preventing noradrenaline uptake into nerve endings consequently, hypertension due to i.v. injection is a bulk effect of peripheral neurotransmitter noradrenaline, coupled with α-excitatory receptors. The involvement of central dopaminergic receptors in the action of Trp may also explain this effect[21].

Data from the present study proved that both i.v. and i.c.v injection of Trp, did not significantly affect heart rate, confirming our previous findings using mepyramine[22].

On the other hand i.v. injection of Trp in man caused myocardial infarction related to coronary artery spasm secondary to excessive catecholamine stimulation[23].

The present work showed that i.v. injection of Trp significantly decreased the amplitude of P, QRS and T waves, while producing prolongation of duration of P-R interval and QRS complex. These effects may be attributed to the β-blocking activity of the drug[24]. Trp i.v. caused a significant elevation in serum K^+ level in the present study.

This effect may explain the changes in the ECG pattern induced by the drug. Intercerebroventricular injection of Trp showed low voltage in atrial and ventricular depolarization. While caused shortening in the period required for depolarization and repolarization of the myocardium. The genesis of this arrhythmias may be mediated by variations in serum K^+ concentration which plays an important role in the genesis of arrhythmia[25].

Results from the present work showed significant increase in respiratory rate after either i.v. or i.c.v. injection of Trp These rsults were in agreement with those reported by Valdamani et al.,[9] in rats. Baroreceptor reflexes play a significant role in regulation of respiration[26]. This suggestes that Trp may increase respiration through its hypertensive effect.

The automatism of the respiratory center is controlled by nerve impulses coming from many receptor pathways involving the vascular reflexogenic zone (baroreceptors), these receptors are stimulated by the rise in blood pressure, stimulating the respiratory center which elicits the increase in respiratory rate[27].

Data from the present study revealed that i.v. injection of Trp did not alter serum sodium or calcium ions concentration but significantly produced hyperkalaemia which may be the probable cause of ECG changes. These findings agreed with our pervious result[22] using mepyramine.

Either i.v. or i.c.v injection of Trp significantly elevated serum transaminases level. These results support those obtained by Dry and Pradlier[28] who reported hepatic insufficiency after large doses of H_1-antagonists.

The present work showed a significant increase in serum urea and insignificant rise in serum creatinine level after i.v. or i.c.v. injection of Trp This may be due to a direct action on the kidney.

In conclusion, the route of drug administration plays an important role in the effects induced Trp our results also suggest that the ECG changes induced by Trp may be referred to electrolytes imbalance which plays an important role in cell membrane stability and action potential. Trp caused hypertension and changes in liver function shown by elevated serum GOT and GPT level, and disturbed kidney function as observed in the from of elevated serum urea level.

REFERENCES

1- Smith R.B., Rossi G.V. And Orzechevski R.F. **Toxicol. Appl. Pharmacol.**, 28.240-247. (1974)

2- Barnett A., Iorio L.C., Kreutner W., Tozzi S., Al.ter H. and Gulbenkian A. **Agents Actions,** 14: 590-597. (1984)

3- Iorio L.C., Cohen-Winstion M. and Barnett A. **Agents Actions,** 18:485-493. (1986)

4- Kraft E. and Zimmerman B.G. **Br. J. Pharmacol.** 53:51-58. (1975)

5- Holcslaw T.L. and Lassiter D. **Pharmacologist,** 26:157. (1984).

6- Sewell R.G., Nanry K.P. Kennedy J., Stiger T.R. and Harmon R.E. **Pharmacol. Biochem Behar.** 22:469-477. (1985)

7- Cray N.M., Contrerase P.C., Allen S.E. and Taylor D.P. **Life Sci.** 47 (2): 175-180. (1990).

8- Crossland J. Histamine and its **Antagonist**. In Lewis's Pharmacology. 5th edition. churchill Livingstone, Edinburg, London, Melbourne and New York, pp. 336-356. (1980).

9- Vadlamani N.L., Pontani R.B. andMisra A.L. **J. Pharm. Pharmacol,** 36:61-63 (1984).

10- Feldberg W. and Sherwood S.L. **J. Physol.** (Lond.) 120: 3-4. (1953).

11- Buden D.T., Blaber L.C. and Natoff I.L. **Pharmacol. Ther,** 5: 99. (1979).

12- Osman F.H., Ammar E.M., Affiti A.M. and Ahmed N.M. **Jap. J. Exp. Med.**, 46:1. (1975).

13- Reitman, S. and Frankel, S.; **Amer. J. Clin Path.**, 28: 56-60. (1957).

14- Fawcett J. K. and Scott J.E. **J. Clin. Path.**, 13: 156. (1960).

15- Husdan H. and Rapoport A. **Clin. Chem.**, 14: 222-238. (1968).

16- Snedecor, G.W.; **Statistical Methods**. Iowa state College, Amer. Iowa 4th ed. (1964).

17- Terry L.H. and Robret, D.R., **J. Pharm. Pharmacol.** 38:731-736. (1986).

18- Owen, D.A.A.; **Gen. Pharmacol**, 8:141-156. (1977).

19-McMeill, J.H. and Verma, S.C.; **Proc. West Pharmacol. Soc.**, 21: 99-101. (1978).

20- Issac, L. and Goth, A.; **Life Sci.**, 4:1899. (1965).

21- Hudzik, T.J. and Slifer, B.L.; **Pharmacol. Biochem. Behav.,** 36 (3): 547-554. (1990).

22- Abdel-Aziz, M.; Abdel-Aal, M.; Ahmed, A.F; Zakaria, M.N.M and Abdel Ghany, R.H. **J. Biochem. Med. Sci. Ther.,** 3 (1): 95-110. (1987).

23- McCwire, B.W., Alpert, M.A., Panayioteu, H., and Lambert, C.R.; **Chest,** 101 (6): 17301732. (1992).

24- Altura, B.M. and Altura B.T.; **J. Pharmacol. Exp. Ther,** 191 (2): 262-267. (1974).

25- Nayler, W.G.; **Acta. Med. Scand.,** 647 Suppl. 1:17-31. (1981).

26- Kirchheim, H.R., **Physiol Rev.**, 56: 160-176. (1976).

27- Babsky, E.B.; Khodorv, B.I.; Kositsky, G.I .and Zubkov, A.A., **Text Book of Human Physiology**. 5th ed. Mir publishers Moscow, Vol. 1, pp 197-199. (1985):.

28- Dry, L. and Pradalier, A.; **Histamine Antagonists**. Elsevier North. Holland Biomedical Antihormones, M.K. Agarwal editor, pp 319-330. (1979).

دراسة مقارنة لتأثير عقار الترايبلينامين المحقون مركزيا وطرفيا فى الأرانب

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تم فى هذا البحث دراسة تأثير عقار الترايبلينامين غالق مستقبلات الهستامين على ضغط الدم ورسم القلب الكهربائى ومحتوى الأكتروليتات فى مصل الدم وبخاصة الصوديوم والبوتاسيوم والكالسيوم ومعدل التنفس كما تم اجراء اختبارات على وظائف الكبد والكلى لمعرفة دور الدواء وآثاره الجانبية واجريت الدراسة على الأرانب البالغة الواعية حقنا بالوريد وكوسيلة للمقارنة حقنا ببطين المخ وأدى حقن الترايبلينامين فى الوريد أو فى بطين المخ إلى رفع ضغط الدم فى الأرانب بدرجة ملحوظة. ولم يلاحظ فرق بين الحقن فى الوريد أو مركزيا فى التأثير على ضغط الدم، ولم يؤثر حقن الترايبلينامين بالوريد والحقن مركزيا على معدل ضربات القلب بينما أثر بدرجة ملحوظة على رسم القلب الكهربائى وكانت هناك فروق جوهرية بين تأثير العقار المحقون بالوريد وتأثيره بعد الحقن مركزيا بعد ١٠، ١٥، ٢٠ دقيقة أدى حقن الترايبلينامين مركزيا وبالوريد إلى زيادة معدل التنفس بدرجة ملحوظة بينما لم يؤثر على نسبة الصوديوم أو الكالسيوم فى مصل الدم. أما محتوى المصل من البوتاسيوم فقد ارتفع ارتفاعا واضحا. ولوحظ أن هناك فرقا واضحا بين تأثير العقار المحقون مركزيا وتأثيره بعد الحقن فى الوريد أدى حقن الترايبلينامين مركزيا وبالوريد إلى رفع محتوى مصل الدم من الترانس أمينات والبوريا، ولم يلاحظ فرق بين تأثير الدواء بعد الحقن بكلا الطريقتين.

ومما سبق نستنتج أن اختلاف طريقة الحقن تؤدى الى اختلاف التأثير الفارماكولوجى لعقار الترايبلينامين. وقد أرجعنا التأثير على رسم القلب الكهربائى الى تأثير الترايبلينامين على محتوى الكتروليتات مصل الدم (وخصوصا البوتاسيوم) حيث أن لها دورا هاما فى نشاط عضلة القلب وما يترتب على وظائفها يؤثر عقار الترايبلينامين على وظائف كل من الكبد والكلى.