THE CLINICAL APPLICATION OF ERGOTAMINE (TYRAMINE)

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Ergotamine, also known as tyramine, is an organic base which can be produced from tyrosine by the action of certain bacteria, normally existing in the alimentary canal.¹ Recent writers² have shown that p. hydroxyphenylethylamine occurs in placental extracts, being probably formed by incipient putrefaction, and that this substance, together with other less active bases, is responsible for the pressor action which these substances produce when injected. Barger and Dale³ have proved that p. hydroxyphenylethylamine is responsible for nearly the whole of the pressor action of the liquid extract of ergot.

Dale and Dixon⁴ thoroughly investigated the action upon animal tissues of p. hydroxyphenylethylamine. The drug was found to produce a marked rise of blood pressure when injected intravenously into a pithed animal; this rise was produced partly by augmentations of the cardiac output, and partly by constriction of the arterioles. When injected into a normal animal the drug produced reflex inhibition of the heart through the vagi. The writers conclude that the action of the drug is very similar to that of adrenaline, but that the pressor action is slower and more sustained, whilst its local action is less intense. These differences are of great clinical importance, for owing to its feeble local action, the drug will produce its effects when administered either hypodermically or by the alimentary canal. Adrenaline on the contrary, as is well known, is destroyed in the stomach, and even when injected subcutaneously it is,

1. Barger and Walpole, *C.R. de Soc. de Biol.*, I, pp. 463, 530, 1906.

2. Dixon and Taylor, *Lancet*, II, p. 1158, 1907. Rosenheim, *Journal of Phys.*, XXXVIII, p. 337, 1909.

3. *Journal of Phys.*, *Proc. of Phys. Soc.*, May 15, 1909.

4. *Journal of Phys.*, p. 25, 1909.

in the majority of cases, oxidised locally without inducing systemic effects. These conclusions suggested that the drug might be of great clinical importance in the treatment of shock. Dale and Dixon¹ record one observation showing the action of the drug upon man. Ten milligrams of p. hydroxyphenylethylamine were given by mouth, and the blood pressure rose from 116 mm. to 149 mm. in fifteen minutes; after one hour the blood pressure still remained at 134 mm.

At the suggestion of Dr. Dixon the writer made observations to determine more fully the action of the drug when administered to man. The observations fall into three series:—

1. Effect of tyramine administered by mouth to healthy subjects.
2. Effect of tyramine injected hypodermically into healthy subjects.
3. Effect of tyramine administered to patients in the condition of shock or collapse.

The earliest experiments were made upon the writer; later the effects of the drug were tried upon hospital patients resting in bed after minor operations, the subjects being healthy young men between the ages of twenty and thirty. After the correct dose had been ascertained, the drug was used in certain cases of collapse. The subjects were always either lying in bed or else resting in a chair whilst observations were recorded. The blood pressure was measured by Martin's Riva Rocci sphygmometer.

I. A first series of observations was made to ascertain the effect of tyramine administered by mouth on healthy people. The drug was always taken upon an empty stomach. The experiments may be summarised as follows:—

Expt.	Subject	Dose	Blood pressure at 20 min. intervals after administration of drug									
			0	20	40	60	80	100	120	140	160	180
I ...	A.J.C.	15 mgm.	105	105	100	103	103	—	—	—	—	—
II ...	A.J.C.	30 mgm.	102	105	107	107	113	112	—	117	117	110
III ...	H.D.	30 mgm.	110	118	116	116	—	—	—	—	—	—
IV ...	H.D.	50 mgm.	110	118	120	118	—	120	120	—	—	112

A final experiment was made with a larger dose, two doses of 100 mgm. each being given by mouth; a record of the blood pressure of the subject was obtained on the preceding day to serve as a control.

1. *Loc. cit.*, p. 42.

Experiment V.—Subject A.M.

Time	...	...	10.30 a.m.	11	11.5	11.20	11.40	11.45	12 noon	12.10			
B.P.	...	...	105	105		107	105		103		dinner		
					100 mgm. tyra- mine admin- istered			100 mgm. tyra- mine admin- istered					
B.P. on previous day	105		104			—	102		102		„		
Time	...	...	12.30 p.m.	12.40	1.40	2	2.20	2.30	2.30	3.30	4.0	5.30	6.30
B.P.	...	...	103	105	109	109	107	109		118			113
								Got up for about one hour		tea			
B.P. on previous day	101		—	—	105	—	—	„	105		111	107	

From these results it will be seen that in nearly every case the administration of tyramine by mouth was followed by a slight rise of blood pressure. The rise was in all cases slight, and sometimes did not occur until one or two hours after the drug was taken; the rise persisted for some hours after it had commenced. A dose of 200 mgm. of tyramine did not produce any large rise of blood pressure. It will be seen that these results do not agree with the observations recorded by Dale and Dixon in their single experiment upon man, for they obtained a well-marked rise in blood pressure after 10 mgm. of tyramine had been taken: this result was probably due to some idiosyncrasy of the subject for the drug.

II. The effect of injecting the drug hypodermically into healthy subjects was next investigated. The site chosen for injection was found to be of importance. In all cases a marked local reaction followed the injection, but when the drug was injected into the arm or forearm little general reaction followed. The loose tissue around the clavicle was found to be the most favourable spot for hypodermic injection, and the drug was given dissolved in 2-3 c.c. of cold sterile water. Pallor and 'goose flesh' at once appeared around the site of injection, and after a few minutes the pale area was surrounded by a ring of hyperaemic tissue. The following systemic effects were observed: a marked rise of blood pressure, attended in some cases by slowing of the pulse. In some cases the subject mentioned feeling 'throbbing of the heart, and fulness in the head.' The observations recorded are as follows:—

Experiment I.—Subject A.J.C. 15 mgm. tyramine injected subcutaneously. After five minutes the blood pressure rose from 102 to 108; after fifteen minutes more it sank again to 102.

Experiment II.—Subject H.H. 20 mgm. tyramine injected subcutaneously. The blood pressure rose immediately from 124 to 140, and after five minutes sank to 130; after fifteen minutes more it sank again to 124. The pulse was unaltered.

Experiment III.—Subject A.H. 30 mgm. tyramine injected subcutaneously. After five minutes the blood pressure commenced to rise; after ten minutes it had risen from 122 to 138; after ten minutes more it sank again to 122. The pulse rate was unaltered.

Experiment IV.—Subject A.M. 40 mgm. tyramine injected subcutaneously.

FIG. 1. *Experiment IV.*—Subject A.M., age 28. Record of pulse and blood pressure. Effect of 40 mgm. tyramine injected subcutaneously.

As will be seen from the chart, the blood pressure commenced to rise after six minutes, and after thirteen minutes rose from 108 to 136 mm., and then quickly fell. In this case the pulse increased in frequency when the blood pressure commenced to rise.

Experiment V.—Subject A.U. 50 mgm. tyramine injected subcutaneously.

FIG. 2. *Experiment V.*—Subject A.U., age 27. Record of pulse and blood pressure. Effect of 50 mgm. tyramine injected subcutaneously.

The subject of this experiment (A. M.) was also the subject in Experiment V in the first series. As will be seen, 200 mgm. of tyramine when given by mouth only caused a slight rise in blood pressure, whereas 40 mgm., given subcutaneously, produced a very marked reaction.

This dose of the drug caused a very marked rise in the blood pressure, and this was accompanied by considerable diminution in the frequency of the pulse.

Experiment VI.—Subject W.S. 60 mgm. tyramine injected subcutaneously.

FIG. 3. *Experiment VI.*—Subject W.S., age 25. Record of pulse and blood pressure. Effect of 60 mgm. tyramine injected hypodermically.

In this case the rise in blood pressure was very sudden and very great; the diminished frequency of the pulse during the rise in blood pressure was well marked.

From these observations it was concluded that the most suitable dose of tyramine for clinical purposes was 20-60 mgm., dissolved in 2-3 c.c. of water, and injected subcutaneously into the more connective tissue around the clavicle. As is shown by the observations recorded above, this dose will produce a great rise in the blood pressure in a healthy subject. In no case was the frequency of the pulse much increased; on the contrary, in those cases in which the rise of blood pressure was most marked there was a diminution in the frequency of the pulse. From

the work of Dale and Dixon¹ it appears that the rise in blood pressure observed is chiefly due to constriction of the arterioles; the diminution in the frequency of the pulse is probably due to stimulation of the vagi.

III. The drug was administered to a few patients in a state of collapse; in three cases it was possible to obtain records of the state of the blood pressure after administering the drug.

Case (i). Collapse following trephining and exploration of the brain for a cerebral abscess. Here the blood pressure was 86 mm. Three doses of 20 mgm. of tyramine were given by mouth; the drug had no apparent effect, and the blood pressure continued to sink slowly without interruption.

Case (ii). Collapse following ruptured gastric ulcer. At 11.30 p.m. the ulcer ruptured, and at 4 p.m. next day laparotomy was performed and the ulcer sutured, the operation lasting forty-five minutes. After the operation the patient suffered from severe shock and was treated with saline injections; these had no apparent effect, and tyramine was administered.

FIG. 4. Subject B.S., age 25. Patient in condition of collapse. Effect of doses of 40 mgm. and 70 mgm. tyramine injected hypodermically.

As will be seen from the appended chart the injection of tyramine was twice followed by a slight rise in blood pressure, with slight general improvement; the effect, however, was only temporary, and at 11.50 p.m. the patient died.

Case (iii) Collapse following haemorrhage from a septic wound. At 8.20 a.m. the haemorrhage occurred.

11.0	a.m.	P. 140	B.P. 100
12.20	midday	P. 160	B.P. 100
12.24	50 mgm. tyramine injected hypodermically		
12.27		P. 160	B.P. 110
12.30			B.P. 112
12.35			B.P. 100

1. *Loc. cit.*, pp. 29-31.

The patient died three days later.

In this case it will be seen that there was a slight but transient rise in blood pressure following the administration of the drug.

Further clinical evidence is required before pronouncing finally upon the value of tyramine in the treatment of shock. From the few cases recorded it appears that tyramine, when injected hypodermically, will produce a slight rise in blood pressure, even in cases of extreme collapse; the drug may therefore prove useful in the treatment of such cases.

CONCLUSIONS

1. Tyramine, when given by the mouth to a healthy subject, in doses from 30-100 mgm., causes a slight rise in blood pressure; the rise lasts for some hours.

2. Tyramine, when injected hypodermically into a healthy subject, in doses from 20-50 mgm., causes a rapid and well-marked rise in the blood pressure, lasting for about twenty minutes.

3. Tyramine, when injected hypodermically in doses of 20-50 mgm., into patients in a condition of shock, causes a slight rise in blood pressure.