RESEARCH PAPERS

A COMPARATIVE STUDY OF THE ACTION OF OCTAVERINE, PERPARINE AND PAPAVERINE ON THE CIRCULATORY AND RESPIRATORY SYSTEMS

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A PREVIOUS communication[1] reported a comparative study of some pharmacodynamic properties of papaverine and two synthetic analogues, octaverine and perparine. It was shown that octaverine and perparine have a lower systemic toxicity and greater spasmolytic activity than papaverine when examined against spontaneous contractions of uterus and induced spasm in isolated guinea-pig ileum. The present investigation compares the activities of the three alkaloids on the circulatory and respiratory systems.

The literature on papaverine is extensive and has been reviewed by Kruger, Eddy and Sumwalt[2] but perparine has received much less attention. Langecker and Starkenstein[3] observed a diminution in blood pressure and increase in respiration in rabbits, and Pouchet[4] recorded a reduction in blood pressure both in man and in the cat after intravenous injection of perparine. Octaverine, on the other hand, has apparently only been mentioned once in the literature; Ellinger, Koschara and Seeger[5] record that octaverine in a dose of 2 mg./kg. by the intravenous route effected a small reduction in blood pressure of long duration in the vagotomised, atropinised cat under urethane anæsthesia. No account, however, of a direct comparison between the hypotensive properties of octaverine or perparine with those of papaverine exists.

The purpose of the present work was to compare the activities of octaverine and perparine with those of papaverine under identical conditions. The following properties have been examined, (i) the action on the blood pressure, heart rate, depth and rate of respiration in the rabbit under urethane anæsthesia, (ii) the action against adrenaline induced hypertension in rabbits, (iii) the adrenolytic activity as shown by the rise in threshold toxicity of adrenaline in mice, and (iv) the action on the coronary flow, amplitude and heart rate in the perfused isolated heart. The solutions used were those previously described[1] and all doses and concentrations are expressed in terms of the free alkaloid bases.

ACTION OF THE ALKALOIDS ON THE BLOOD PRESSURE AND RESPIRATION OF RABBITS

Heparinised rabbits weighing 1·75 to 2·0 kg. were anæsthetised by the intravenous administration of 1250 mg./kg. of urethane as the 25 per cent. aqueous solution. Blood pressure was measured in the carotid artery

with a mercury manometer; respiration was recorded with a tracheal cannula by Gaddum's[6] method using a tight tambour membrane. The alkaloids were injected into the cannulated jugular vein and four animals used for each compound. The following is representative of the results obtained; the blood pressures given are the average systole-diastole pressure.

Octaverine (1 mg./kg.) rapidly effected a 30 per cent. decrease in blood pressure (from 85 to 60 mm.); this was sustained for 15 seconds and then steadily rose during 15 minutes back to its normal value. There was a slight increase in the depth of respiration but the rate remained normal. A dose of 2 mg./kg. caused a similar immediate 30 per cent. decrease in blood pressure (from 85 to 60 mm.) but even after 30 minutes it was still only 75 mm., i.e., 10 per cent. below normal. As the blood pressure fell there was a noticeable increase both in depth and rate of respiration but after 15 minutes these had regained their former rhythm. At the highest dose (4 mg./kg.) there was a 40 per cent. reduction in blood pressure (from 85 to 52 mm.) of considerable duration; after 30 minutes the pressure had risen to 75 mm., i.e., 10 per cent. below its normal value. The respiratory rate increased 27 per cent. from 45 to 65 p.m., while the increase in depth of respiration was 40 per cent.; these levels were maintained throughout the period of the lowering of the blood pressure. The blood pressure and respiration rate and depth returned to normal after one hour.

Perparine (1 mg./kg.) caused a 17 per cent. reduction in blood pressure (from 90 to 75 mm.) lasting for 15 seconds and returning to normal in one minute; there was a simultaneous increase in depth of respiration, the rate remaining unchanged. With 2 mg./kg. of perparine there was a 30 per cent. fall in blood pressure, lasting for 60 seconds; the pressure had returned to 90 mm. after 1 minute. Coincident with the fall in blood pressure was a noticeable slowing of the heart and an increase in amplitude of the myocardium; this was not observed with a similar dose of octaverine. There was an increase in depth of respiration, the rate remaining normal. The highest dose of the alkaloid (4 mg./kg.) induced a 50 per cent. fall in blood pressure (from 90 to 45 mm.); after 2 minutes this had risen to 80 mm. and returned to 90 mm. after the lapse of a further 4 minutes. There was a 10 per cent. decrease in respiratory rate together with a 40 per cent. increase in respiratory depth.

Papaverine (1 mg./kg.) induced a small fall in blood pressure (from 100 to 90 mm.) lasting for 5 seconds, followed by a rise of 10 mm. above normal (to 110 mm.) of the same duration as the depressor effect. Accompanying these transient changes in the blood pressure there was a brief but definite increase in depth of respiration, the respiratory rate retaining its normal rhythm. With 2 mg./kg. of the drug this biphasic response was more pronounced than with the smaller dose; there was a 15 per cent. fall (from 100 to 85 mm.) lasting for 10 seconds followed by a rise above normal, with a maximum of 106 mm., lasting for 30 seconds. This was followed by a fall to 85 mm. at which level it remained for 3 minutes returning to the normal level after a further 5 minutes. The

respiration became deeper and the respiratory rate rose. With 4 mg./kg. of papaverine the secondary rise in blood pressure above the normal value was absent; there was an immediate 20 per cent. decrease in blood pressure (from 98 to 78 mm.) which was maintained at this level for 2 minutes before slowly climbing back to the original 98 mm. after 8 minutes. The effect upon respiration was more pronounced than with perparine; there was a 65 per cent. increase in depth of respiration and a decrease of 50 per cent. in respiratory rate but both frequency and depth regained their normal values in 9 minutes.

The experimental evidence from 12 kymograph records showed that octaverine and perparine possess a hypotensive activity approximately twice as great as that of papaverine. The depressor action of octaverine is of longer duration than that of the other two compounds. The fall in blood pressure followed by a secondary rise above normal has been observed in the dog[7] and in man[8] after administration of papaverine and it has been suggested by Delphant[8] that this may be due to induced release of adrenaline which is either central or reflex in origin. In the present work this secondary rise was observed with 0·5 mg./kg. of perparine but not with higher doses; it did not occur with 0·5 mg./kg. of octaverine or with any of the higher doses of this alkaloid. It is significant in this connection that both papaverine and perparine are 1-benzyl*iso*quinolines[1], whereas octaverine is a 1-phenyl-*iso*quinoline.

All three alkaloids exerted a noticeable effect on respiration during the hypotensive state and it is of interest to compare the ventilation rate at the top dose (4 mg./kg.) of each compound. The degree of ventilation may be considered within biological limits to be directly proportional to the respiratory rate and the depth of respiration, i.e., the ventilation rate is approximately proportional to the *product* of the depth and rate of respiration. When this was determined and averaged from all the records, before and after the administration of 4 mg./kg. of the alkaloids, it was found that octaverine gave an increase of about 50 per cent., perparine an increase of about 25 per cent. and papaverine a *decrease* of about 10 per cent. in the normal ventilation rate. Issekutz, Nyary and Botz[9] record that intravenous doses of 5 to 20 mg./kg. of papaverine effect an increase in respiration in rabbits but they probably refer to depth of respiration and not to the product of respiratory depth and rate.

Action of the Alkaloids on the Pressor Action of Adrenaline in Rabbits

It has previously been shown that the rise in blood pressure in dogs caused by intravenous adrenaline was at least partly obliterated by papaverine whether the alkaloid was given first[10], after[11], or simultaneously[12] with the adrenaline. Platz[13] and also Cespai[10,11], however, record that in human subjects papaverine does not influence the pressor effect of injected adrenaline. No work in this connection has been carried out previously with octaverine or perparine.

Adult rabbits weighing 1·75 to 2·0 kg. under urethane anæsthesia (1250 mg./kg.) were heparinised (10 mg./kg.), the blood pressure measured

with a mercury manometer and the respiration by the method of Gaddum[6]. The solutions of adrenaline and of the three alkaloids were injected into the cannulated jugular vein. Before administering the alkaloids, successive doses of 10 μg./kg. of adrenaline, as the aqueous solution of the tartrate, were given in order to ascertain the degree and duration of the pressor response. When a reproducible response was obtained, a further dose of adrenaline was given followed after 15 seconds by the alkaloid. In all, nine rabbits were used, three for each compound.

TABLE I

ACTIONS ON BLOOD PRESSURE

Before adrenaline	After (*a*) adrenaline	Dose of alkaloid mg./kg.	After (*b*) alkaloid	Percentage fall after alkaloid
		OCTAVERINE		
80	130	0·5	80	38
80	125	1·0	70	44
90	130	2·0	54	57
		PERPARINE		
90	150	0·5	110	27
90	150	1·0	90	40
90	150	2·0	70	53
		PAPAVERINE		
90	135	0·5	135	0
85	130	1·0	115	12
85	130	2·0	100	23

(*a*) Maximum blood pressure 10 to 20 seconds after end of injection.
(*b*) Minimum blood pressure 10 to 20 seconds after end of injection.

TABLE II

ACTIONS ON RESPIRATION

Respiration before adrenaline		Respiration after adrenaline (*a*)		Dose of alkaloid	Respiration after alkaloid (*b*)	
Depth	Rate	Depth	Rate	mg./kg.	Depth	Rate
				OCTAVERINE		
100 (*c*)	36	60	33	1	160 (*d*)	50
100	38	60	35	2	160	41
				PERPARINE		
100	50	70	50	1	110	55
100	50	70	50	2	110	55
				PAPAVERINE		
100	38	70	46	1	130	44
100	38	70	46	2	140	40

(*a*) 10 to 20 seconds after injection.
(*b*) 10 to 20 seconds after injection.
(*c*) Normal depth as measured in mm. on kymograph records.
(*d*) 160 per cent. of normal, i.e., an increase of 60 per cent. in depth of respiration.

The standard response obtained with 10 μg./kg. of adrenaline was as follows: there was an immediate increase in blood pressure rising to a maximum of 75 per cent. above normal 20 seconds after the end of the adrenaline injection; the level was 50 per cent. above normal 40 seconds after the injection, smoothly returning to its original value 80 seconds after the injection. The respiratory rate remained unchanged and the depth of respiration decreased 30 to 40 per cent. during the hypertensive period.

Table I shows the typical effect upon blood pressure; the second column

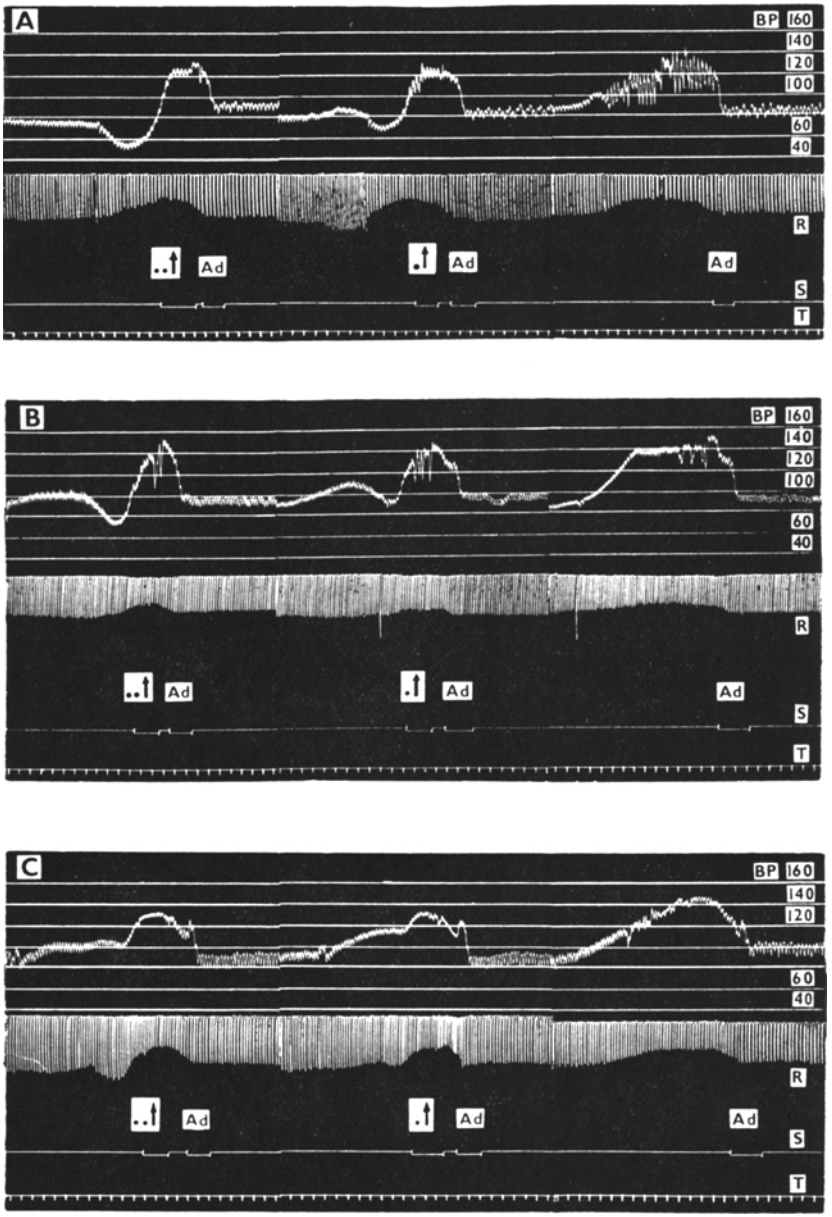

FIG. 1. Action of octaverine (A), perparine (B) and papaverine (C) on adrenaline-induced hypertension in rabbits. Records read from right to left.

B.P. Blood pressure in mm. of mercury; R. Respiration; S. Drug dose signal; Ad. Adrenaline; T. Timer: 5 second beats; ·↑ 1 mg./kg. of alkaloid.; ··↑ 2 mg./kg. of alkaloid.

gives the blood pressure maximum occurring 10 to 20 seconds after the adrenaline injection and the fourth column the blood pressure minimum occurring 10 to 20 seconds after the alkaloid; Table II records the observed effects upon respiration. Figure 1 comprises a typical set of kymograph records.

Examination of the tables and kymograph records showed that octaverine and perparine are more powerful adrenolytic reagents than papaverine and that octaverine is slightly superior to perparine. At the 1 mg./kg. dose octaverine and perparine are about 3 times as active as papaverine in counteracting the pressor effects of adrenaline; at the 2 mg./kg. dose they have about twice the activity of papaverine. It is of interest that octaverine and perparine not only obliterate the pressor effect of adrenaline but at the 1 and 2 mg./kg. dose levels they effect a transitory reduction in blood pressure below normal; this was not observed with papaverine. There was a secondary rise in blood pressure above normal with 1 mg./kg. of perparine but not with the higher doses; the same effect was usually observed with 4 mg./kg. of papaverine and with the lower doses it was evident from the shape of the curves that, although there was no rise above the normal value, there was a transient impedance to the fall in blood pressure. Octaverine exhibited no secondary rise and the hypotensive action lasted longer than with the other two alkaloids. Octaverine also has a greater activity in counteracting the adrenaline-induced hypopnœa than the other two alkaloids.

It is of interest to record that sodium nitrite (4 mg./kg. and 8 mg./kg.) did not have any action on the pressor effect of 10 μg./kg. of adrenaline. Theophylline at a dosage level of 4 mg./kg. likewise had no effect; at 8 mg./kg. and at 16 mg./kg. the percentage reduction in blood pressure was 23 and 60 per cent. respectively.

Protective Action of the Alkaloids against Adrenaline Toxicity in Mice

Adrenaline, in the form of the tartrate, was administered to 20 g. mice, in groups of four, by the intraperitoneal route in doses ascending by 5 mg./kg. intervals from 20 to 50 mg./kg. At the higher doses the mice had intermittent convulsions and died of prolonged apnœa; the approximate LD50 and LD100 figures thus obtained were 25 mg./kg. and 50 mg./kg.

Groups of 4 mice were given an intraperitoneal injection of 50 mg./kg. of octaverine, perparine or papaverine followed after an interval of 5 or 10 minutes by 50 mg./kg. of adrenaline by the same route. The protective activity of the alkaloid was assessed by its ability to reduce mortality due to the adrenaline. All survivors were kept under observation for 7 days; the results are shown in Table III.

Both octaverine and perparine have greater activity than papaverine in raising the threshold of adrenaline toxicity in mice and octaverine is superior to perparine. The figures agree with the relative activities observed (v.s.) for the three alkaloids on the ventilation rate in rabbits.

TABLE III

No. of mice	Alkaloid	Time interval (minutes)	Observations
4	Octaverine	5	1/4 died in 4 hours. No apnœa or convulsions. Fast breathing. Protection 75 per cent.
4	Perparine	5	2/4 died, 1 in 5 minutes and 1 in 3 hours. Two had apnœa and 1 had convulsions. Protection 50 per cent.
4	Papaverine	5	4/4 died in 5 minutes. All had apnœa and powerful convulsions. Protection 0 per cent.
4	Octaverine	10	0/4 died. Fast breathing but no apnœa or convulsions. Protection 100 per cent.
4	Perparine	10	1/4 died within 24 hours. Fast breathing but no apnœa or convulsions. Protection 75 per cent.
4	Papaverine	10	2/4 died in 10 minutes; another died in 2 hours and the other in 24 hours. All had apnœa and convulsions. Protection 0 per cent.

Coronary Dilator Activities of the Alkaloids on the Isolated Perfused Rabbit Heart

The action of papaverine on the rate and amplitude of the isolated heart has been studied by Macht[14], Sakussow[15], Gruber and Robinson[16], Micheew[17], Heathcote[18] and Lipschitz and Osterroth[19], but there appear to be no figures recorded for the action on the coronary flow. The results reported in the literature are not concordant; this lack of agreement is doubtless due to the biphasic action of the alkaloid at different concentration levels and also to the known variability of the isolated perfused heart preparation No work has previously been carried out on the activity of octaverine or perparine on the isolated heart.

The coronary dilator action of the alkaloids was evaluated by perfusing the isolated rabbit heart with oxygenated Ringer Locke solution at 36° to 38° C. using the Langendorff[20] method. The coronary outflow issuing from a calibrated dropper-nozzle was recorded with a Thorpe Impulse Drop Counter[21] with a silver drop tube connected to the valve relay. Heart rate was recorded by a pair of contacts on a Starling heart lever connected to a rotatory toothed mechanism which in turn activated a signal which registered every seventh heart beat on the kymograph drum. In this manner simultaneous records of coronary flow, heart rate, heart amplitude were made on a slow kymograph. All solutions used were in physiological saline adjusted so that every dose employed was contained in 0·5 ml.; injections were made through the rubber tubing connecting the perfusing system with the aortic cannula. Each drug was tested on a fresh heart and at least three records made for each drug. Table IV shows a typical set of values obtained and Figure 2 comprises a set of kymograph records.

The experimental figures obtained had the concordance to be expected of results from the isolated heart preparation. The nine records prepared showed that all three alkaloids have a powerful action on the coronary flow; octaverine is slightly more active both in degree and duration, while perparine is slightly less active than papaverine in effecting increase in the

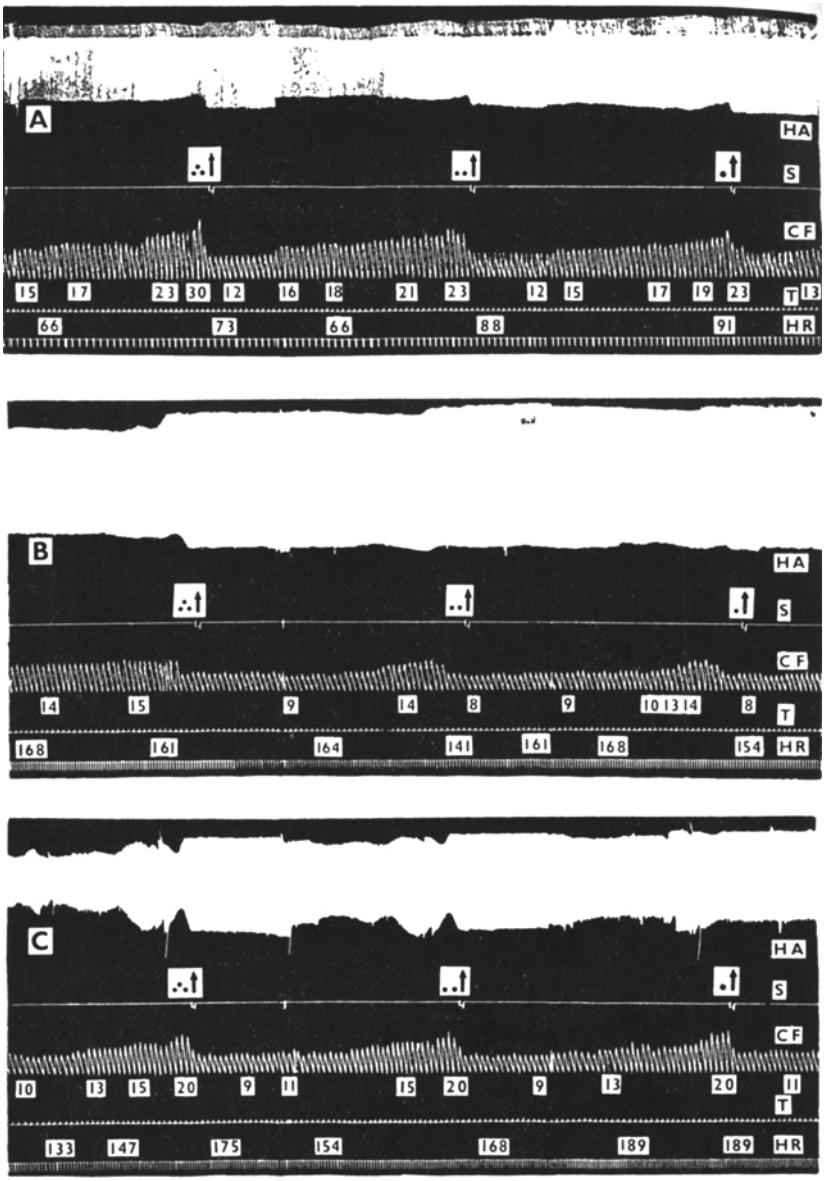

FIG. 2. Action of octaverine (A), perparine (B) and papaverine (C) on the perfused isolated heart. Record reads from right to left.

HA. Heart amplitude; S. Alkaloidal dose; CF. Coronary flow ml./minute; T. Timer: 5 second beats; HR. Heart rate; .↑ 0·04 mg. of alkaloid; ..↑ 0·08 mg. of alkaloid; .·.↑ 0·10 mg. of alkaloid.

TABLE IV

Coronary flow, ml./min.	Heart rate	Coronary flow per beat	Dose	Coronary flow ml./min.	Heart rate	Coronary flow per beat	Percentage increase in coronary flow per beat
Before drug			mg.	After drug			
			OCTAVERINE				
13·0	91	0·143	0·04	19 (*a*)	91	0·210	47
				16 (*b*)	91	0·175	22
				14 (*c*)	91	0·155	9
12·5	80	0·156	0·08	22 (*a*)	80	0·275	77
				19 (*b*)	70	0·270	74
				16 (*c*)	66	0·240	54
12·5	73	0·10	0·10	26 (*a*)	73	0·356	110
				18 (*b*)	73	0·250	47
				17 (*c*)	67	0·250	47
			PERPARINE				
8·5	154	0·55	0·04	12·5 (*a*)	154	0·081	47
				10 (*b*)	160	0·063	14
				9 (*c*)	168	0·054	nil
8·5	141	0·060	0·08	14·5 (*a*)	141	0·103	72
				11 (*b*)	164	0·067	12
				9·5 (*c*)	160	0·060	nil
9·5	161	0·059	0·10	15 (*a*)	161	0·094	60
				14 (*b*)	168	0·083	41
				10·5 (*c*)	155	0·068	15
			PAPAVERINE				
11·5	189	0·061	0·04	16 (*a*)	189	0·085	40
				13 (*b*)	189	0·069	13
				12 (*c*)	189	0·064	5
9·0	168	0·054	0·08	17 (*a*)	168	0·101	87
				14 (*b*)	154	0·091	70
				11 (*c*)	154	0·072	34
9·0	175	0·052	0·10	17 (*a*)	175	0·097	87
				13 (*b*)	147	0·088	69
				10 (*c*)	150	0·067	29

(*a*) Average during 1st 60 second interval after drug injection.
(*b*) " " 2nd " " " " " "
(*c*) " " 3rd " " " " " "

coronary flow per beat. The three compounds have approximately the same effect on the amplitude of the heart beat; thus at the top dose (0·1 mg.) the average decreases in amplitude for octaverine, perparine and papaverine were 18, 21 and 24 per cent. respectively.

SUMMARY

1. A comparative study has been made of the activities of papaverine and two synthetic analogues—octaverine and perparine—on the circulatory and respiratory systems in rabbits.

2. Octaverine and perparine possess a hypotensive activity approximately twice as great as that of papaverine. The depressor action of octaverine is of longer duration than that of the other two alkaloids and there is no secondary rise in blood pressure above the normal level.

3. Papaverine causes a slight decrease, while octaverine and perparine effect a substantial increase, in the ventilation rate as measured by the product of respiratory rate and amplitude.

4. Octaverine and perparine are twice to three times as active as papaverine in counteracting adrenaline induced hypertension. Octaverine has a higher adrenolytic activity than the other two compounds as shown by the rise in threshold toxicity of adrenaline in mice.

5. Perparine is slightly less active, while octaverine is slightly more active, than papaverine in increasing the coronary flow in the perfused isolated heart.

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