Brit. J. Pharmacol. (1949), **4**, 197.

SOME PHARMACOLOGICAL PROPERTIES COMMON TO ATROPINE, PETHIDINE, PROCAINE, AND QUINIDINE

BY

N. K. DUTTA

From the Department of Pharmacology, Oxford

(Received March 14 1949)

In earlier papers from this laboratory attention has been drawn to the similarity in the pharmacological properties of substances which are used in medicine for quite different purposes. In examining compounds for a quinidine-like action, Dawes (1946) pointed out that quinine, quinidine, and procaine resemble one another in antagonizing acetylcholine in all forms of muscle. Dews and Graham (1946) showed that the antihistamine substance neoantergan was quinidine-like on heart muscle and had a local anaesthetic action like procaine. Elío (1948) examined the actions of atropine, procaine, and quinidine (and also other local anaesthetics) on the frog rectus, the rabbit intestine, and the rabbit vessels; he found that these substances antagonized the action of acetylcholine in all three preparations; he also observed a parallelism between the inhibiting action of these drugs on the frog rectus and their local anaesthetic action. This parallelism was extended to conessine and its derivatives by Stephenson (1948).

Another way in which the similarity of these substances was revealed was in their action on body temperature. Glaubach and Pick (1931) observed that procaine caused a fall of body temperature. I therefore studied (Dutta, 1948) the action of atropine, benadryl, pethidine, and quinidine, and found that they, like procaine, reduced body temperature in mice. Finally, Burn and Dutta (1948) have shown that these substances also resemble one another in being able to reverse the constrictor action of adrenaline on the vessels of the rabbit's ear.

The present paper describes the action of these substances on some other preparations; viz., on the perfused superior cervical ganglion of the cat, on the phrenic nerve-diaphragm preparation of the rat, and on the bronchioles of the guinea-pig. Thus they have been examined for curariform activity, both in the ganglion and at the motor endplate, and also for antihistamine activity.

Action on superior cervical ganglion

The superior cervical ganglion of the cat, anaesthetized with chloralose (80 mg./kg.), was perfused according to the method of Feldberg and Gaddum (1934) (originally introduced by Kibjakow, 1933). Locke's solution at 35° C. was introduced into the ganglion through the common carotid artery at a

TABLE I

ACTION ON SUPERIOR CERVICAL GANGLION

Exp. No.	Substance	Amount injected in μg.	Height of contraction of the nictitating membrane in mm.		Percentage inhibition
			Before addition of drug	After addition of drug	
5	Atropine sulphate	50	44	23	48
7	,,	50	52	0	100
8	,,	50	30	16	47
1	Pethidine hydrochloride	800	52	0	100
2	,,	200	46	39	15
2	,,	400	43	22	50
5	,,	600	42	31	26
8	,,	250	33	4	88
3	Quinidine hydrochloride	500	50	0	100
4	,,	500	38	22	42
5	,,	250	45	36	20
5	,,	500	39	8	80
3	Procaine hydrochloride	500	58	33	43
3	,,	750	58	0	100
5	,,	250	43	39	9
5	,,	400	43	32	26
7	,,	100	46	43	7
8	,,	250	41	18	56

perfusion pressure round about 110 mm. Hg, maintained with a small pump designed by Dr. E. J. Schuster. The preganglionic fibres were stimulated maximally at the rate of 16 per second for 10 seconds at 3-minute intervals. The contractions of the nictitating membrane were recorded with an isotonic lever. The substances were dissolved in Locke's solution, and not more than 0.2 ml. was injected at any time into the arterial cannula. Each of the compounds was tested on several preparations.

The results in different experiments are given in Table I, and an illustration of the action of pethidine, atropine, and quinidine is given in Fig. 1. Harvey

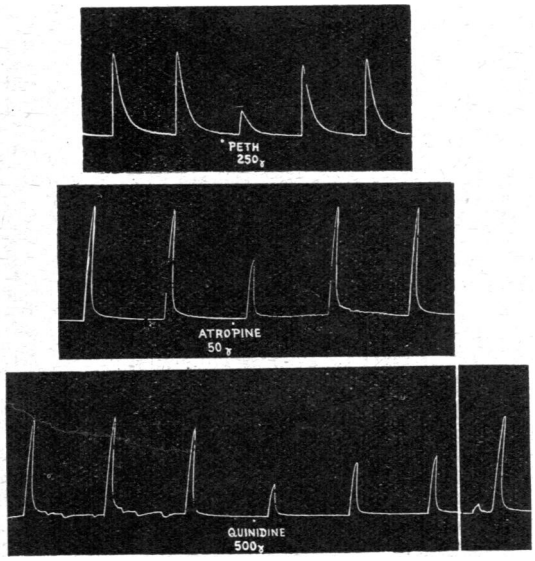

FIG. 1.—Superior cervical ganglion of the cat perfused with Locke's solution. Contractions of the nictitating membrane in response to preganglionic stimuli, 16 per sec. for 10 sec. every 3 minutes. Partial blocking of the ganglionic transmission by 250 μg. pethidine hydrochloride (upper tracing), 50 μg. atropine sulphate (middle tracing), and 500 μg. quinidine hydrochloride (lower tracing).

(1939a) has already shown that procaine diminishes the effect of preganglionic stimulation because of its action on the ganglion. The most powerful of the four substances was found to be atropine, which in a dose of 50 μg. abolished the effect of stimulation in one observation, and reduced the effect to half in two other observations in different experiments. Since *d*-tubocurarine chloride produces a similar effect in a dose of 5–10 μg., it follows that atropine has from 10–20 per cent of the inhibitory action of *d*-tubocurarine on the ganglion. From the results shown in Table I, it is difficult to give a figure for the other substances, though it is clear that they are weaker; pethidine and quinidine seem on the whole more active than procaine, but the effect of quinidine, illustrated in Fig. 1, is more prolonged.

Phrenic nerve-diaphragm preparation

The rat diaphragm method described by Bülbring (1946) was used; Tyrode solution containing double the amount of glucose was the bathing fluid and the 50-ml. bath was maintained at 37° C. and aerated with oxygen containing 5 per cent CO_2. The nerve was stimulated by a pair of platinum electrodes kept submerged in the solution. The muscle was excited directly with a pair of electrodes which consisted of insulated copper wires with silver tips. One electrode was placed near the centre of the base of the fan-shaped diaphragm, while the other was fixed at the apex of the muscle. Shocks were delivered from an electronic square wave stimulator at a desired strength, frequency, and duration.

The observations were most definite when pethidine was used; they are illustrated in Fig. 2 (*a*) to (*f*). When stimulation was applied through the nerve, the addition of pethidine to make a concentration of 10^{-4} resulted in an increase of muscle contractions by 67 per cent, as shown in (*a*). A similar effect was obtained when direct stimulation was used, as shown in (*b*). After the pethidine had been washed out again, 100 μg. *d*-tubocurarine chloride were added to the bath during the application of stimuli to the nerve and allowed to remain in contact until complete curarization was obtained (*c*). Direct stimulation was applied to the muscle; the addition of the same concentration of pethidine again increased the muscle contractions (*d*). This effect was obtained during full curarization, because when indirect stimulation was applied just before the bath was washed out there was at first no response. The earliest return of the response is shown at the right hand of the record (*d*).

Fig 2 (*e*) shows a similar increase caused by pethidine (4×10^{-5}), and Fig. 2 (*f*) shows the change from augmentation to depression when a much higher concentration (2.6×10^{-4}) was used. Both these effects (*e* and *f*) were obtained with nerve stimulation.

The actions of atropine and quinidine were much less striking than that of pethidine. Atropine sulphate in a concentration of 1.2×10^{-4} increased the effect of indirect stimulation by 12 per cent, and increased the effect of direct stimulation by 14 per cent. After full curarization, the same concentration increased the effect of direct stimulation by 16 per cent, at the end of which full curarization was still present. Atropine sulphate in larger concentration

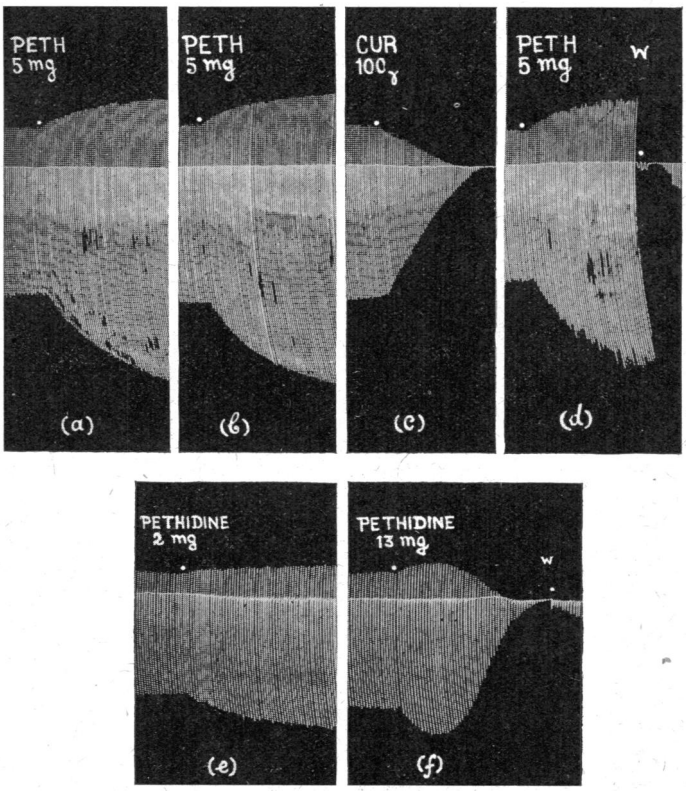

FIG. 2.—Rat phrenic nerve diaphragm preparation in Tyrode, 37° C., 50 ml. bath. *Upper tracing:* single, maximal shock, 7 per minute, 0.7 millisecond. Tyrode solution was changed between (*a*) and (*b*); (*b*) and (*c*). (*a*) Indirect stimulation: 5 mg. pethidine hydrochloride increased the muscle contractions. (*b*) Direct stimulation: 5 mg. pethidine had the same effect as before. (*c*) Indirect stimulation: progressive paralysis of the muscle after 100 μg. *d*-tubocurarine chloride. (*d*) Direct stimulation: 5 mg. pethidine still produced increased muscle tension. Just before wash-out (W) indirect stimulation was applied, but the muscle gave no response. The contractions began to return after washing out the tubocurarine as shown in the right-hand side of the record. *Lower tracing:* single, maximal shock, 7 per minute, 0.5 millisecond delivered through the nerve. Effect of pethidine hydrochloride 2 mg. (*e*) and 13 mg. (*f*). Tyrode solution was changed between (*e*) and (*f*).

(3.2×10^{-4}) caused augmentation of the contractions followed by depression, as shown for pethidine in Fig. 2 (*f*).

Similar results were obtained for quinidine in concentrations $\frac{1}{8}$ and $\frac{1}{4}$ of those of atropine. With procaine the augmentor action was less easily observed, for the depressor action was more powerful; both, however, were recorded, the former when a concentration of 10^{-5} was present in the bath, and the latter when higher concentrations were used.

Antihistamine action on bronchioles

The antihistamine action was observed by the method described by Konzett and Rössler (1940). Guinea-pigs were used, anaesthetized with urethane (1.8 g. per kg.) injected into the peritoneal cavity, the lungs being ventilated by a small Starling respiration pump driving air into the trachea. The excess air which did not enter the trachea operated a lever which recorded a vertical line on a kymograph. The lever rose during the period of insufflation and fell back to zero when insufflation ended. When the bronchioles constricted, the lever rose higher, so that the length of the vertical line was a measure of the constriction. Injections of substances affecting the bronchioles were made through a cannula into the jugular vein.

TABLE II

ANTIHISTAMINE ACTION ON BRONCHIOLES

Bronchoconstriction measured by rise of lever in mm.

Dose (μg.) histamine acid phosphate	Substance	Dose mg.	Broncho-constriction		Percentage inhibition
			Before	After	
2	Antistin hydrochloride	0.005	34	9	73
2	Atropine sulphate	0.05	45	6	86
12	,,	0.075	33	2	94
2	Benadryl	0.002	42	13	69
2	,,	0.002	39	13	67
4	,,	0.008	28	7	75
4	,,	0.004	15	6	60
2	Pethidine hydrochloride	0.05	27	7	74
5	,,	0.1	28	5	82
2	Procaine hydrochloride	1.0	38	12	68
4	,,	0.5	31	7	77
2	Quinidine hydrochloride	2.0	35	15	57

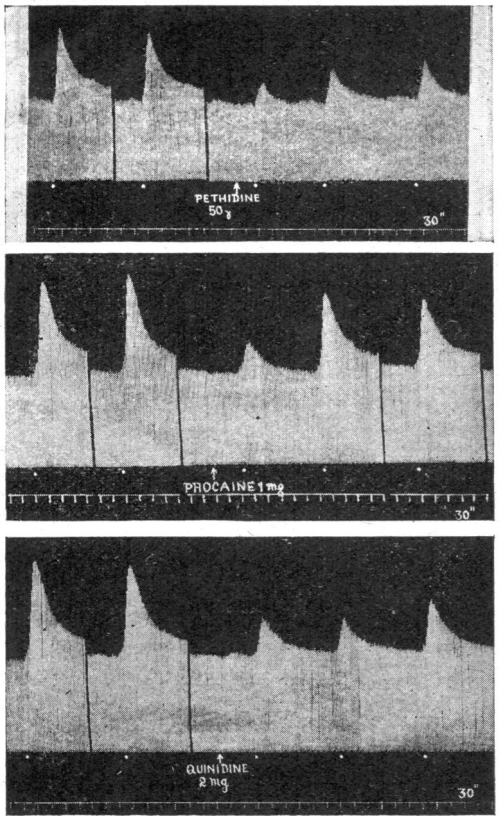

FIG. 3.—Records of the bronchoconstriction produced in the guinea-pig by the intravenous injection of 2 μg. histamine acid phosphate at each white spot. The first two successive injections were made at 8-min. intervals. The effect of histamine was diminished by the intravenous injection of 0.05 mg. pethidine hydrochloride (upper tracing), 1 mg. procaine hydrochloride (middle tracing), and 2 mg. quinidine hydrochloride (lower tracing). Interruption of the records indicates where the drum was stopped.

Examples of the results obtained are given in Fig. 3, which shows the antihistamine action of pethidine, procaine, and quinidine. Histamine acid phosphate was injected at each white spot below the record. The bronchoconstriction produced by at least two successive injections was recorded, the injections being made at 8-minute intervals. Before the third injection, shown in each part of Fig. 3, pethidine or another substance was given, and the effect of histamine was thereby diminished as shown. The results are summarized in Table II. In the table results with two recognized antihistamine substances, "Antistin" (Ciba) and "Benadryl" (Parke, Davis, and Co.), are included in order that a better judgment may be formed of the potency of the other substances. Atropine and pethidine have about one-tenth the potency of antistin, procaine has about one-hundredth the potency of antistin, and quinidine has about one four-hundredth the potency of antistin.

DISCUSSION

The observations provide further evidence that no sharp line of distinction is possible between the actions of atropine, pethidine, procaine, and quinidine, although these four substances are classified quite differently for medical purposes. All of them depress the response of the perfused cervical ganglion to preganglionic stimulation, acting in this way like *d*-tubocurarine.

The powerful action of atropine in blocking the preganglionic stimulation in the perfused superior cervical ganglion is contrary to the general belief that the nicotine-like action of acetylcholine is not influenced by atropine. Abdon (1940) has shown that the difference in the antagonism of atropine to nicotine-like and muscarine-like actions of acetylcholine is quantitative rather than qualitative.

The actions of atropine, procaine, pethidine, and quinidine on the skeletal muscle (diaphragm) of the rat are complex. In small concentrations these substances increase the contraction to a single maximal stimulus, but in higher doses they exert a curare-like effect; procaine, pethidine, and quinidine depress the muscle in concentrations much less than that required for atropine. The augmentation of the muscular twitches in response to direct stimulation by any one of these substances was not affected by *d*-tubocurarine: therefore, the point of attack was directly on the muscle itself. Procaine acts on skeletal muscle at several points; it interferes with the liberation of acetylcholine at the motor nerve endings (Harvey, 1939a), depresses the motor endplate, and also acts directly on the muscle (Kubota and Macht, 1919; Macgregor, 1939). Harvey (1939b) showed that quinine exerts its action on the motor endplates as well as on the muscle itself. Quinidine, a stereoisomer of quinine, probably acts in the same way. Like tubocurarine, atropine raises the threshold of the skeletal muscle to stimulation, and it has been suggested that it prevents the action of acetylcholine at the nerve terminals (Brown, 1937; Bülbring, 1946). Since these substances block ganglionic transmission, it may be that they interfere with the action of acetylcholine at the motor nerve terminals of the skeletal muscle.

Loew, Kaiser, and Moore (1946) compared the relative potency of benadryl, pethidine, and atropine in reducing the mortality rate of guinea-pigs exposed

to histamine aerosol. They found that pethidine had about a quarter of the activity of benadryl, but it was three times more potent than atropine. Using a similar technique, Graham (1947) showed the superiority of benadryl over antistin. Frommel, Favre, and Vallette (1947) had to use a large amount of procaine to protect their guinea-pigs from the effect of histamine given in the form of spray. Thus a fair amount of correlation exists between the results obtained by the above investigators and the findings in the present experiments, though the modes of administration of histamine were different. It is remarkable that quinidine also possesses some antihistamine activity.

Summary

Atropine, pethidine (demerol), procaine, and quinidine have the following properties in common:

(1) When injected into the fluid perfusing the superior cervical ganglion they depress the contraction of the nictitating membrane in response to preganglionic stimulation.

(2) They augment the contractions of the isolated rat diaphragm, both when it is stimulated through the nerve and when it is stimulated directly after curarization. Very high concentrations depress the contractions.

(3) They depress the bronchoconstrictor action of histamine in the guinea-pig.

I am most deeply indebted to Professor J. H. Burn for the guidance and encouragement which he has given throughout and for the facilities provided.

The work was carried out during the tenure of a fellowship from the Government of India.

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