Negative Chronotropic and Antiarrhythmic Properties of Atropine and Other Tropane Analogues on Isolated Cat Heart Preparations

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SUMMARY **This study was undertaken to characterize pharmacologically the negative chronotropic and antiarrhythmic action of atropine and other tropane analogues. Insight into the site of action of these drugs was obtained by comparing the effects on isolated heart preparations. Dose-response curves were constructed for the negative chronotropic action on the cat Langendorff preparation and refractory period prolongation determined by alteration in the maximal driving frequency of cat papillary muscles. In decreasing order, the relative potencies found in both preparations were: quinidine, *l*-atropine, *d,l*-atropine, *d,l*-homatropine, and *l*-scopolamine, and, with the exception of *l*-scopolamine, were quantitatively similar both for the production of bradycardia and for refractory period prolongation. At concentrations which produced a 20% decline in heart rate, tropane analogues reduced the rate of aconitine-induced tachycardia in cat Langendorff preparations to approximate the pre-aconitine control values. The similarity of potencies, found to be effective in all preparations, suggests that a prolongation of refractory period may be the basis for tropane-induced bradycardia as well as for its anti-aconitine action in cats. In contrast, neither tropine nor tropic acid, in concentrations as high as 10^{-3} to 10^{-2} M, altered the maximal driving frequency, nor did cocaine (8.8×10^{-8} to 8.8×10^{-5} M) influence either automaticity or rate of papillary muscles exposed to aconitine. Thus, at least part, if not all, of the negative chronotropic and antiarrhythmic effects of tropanes appears to be the result of a direct action upon the myocardium. The concentrations of tropane alkaloids required to obtain these actions on cat myocardial preparations suggest they are probably within the therapeutic range.**

IN DOSES LESS THAN 0.3-0.6 mg, atropine produces bradycardia in humans. Atropine-induced bradycardia was first described by Cushney[1] in 1904 who, using anesthetized cats, also noted the occurrence of a dose-dependent tachycardia as dosage was increased. For many years the mechanism of the bradycardia was attributed solely to central stimulation of the vagal nucleus.[2] However, in 1968, Kottmeier and Gravenstein[3] reported that atropine methylbromide, which does not diffuse across the blood-brain barrier, also decreases heart rate in man. Yet, in both cats and dogs, atropine-induced bradycardia is indistinguishable from that produced by acetylcholine.[4]

Clinically, atropine is used both in the treatment of postinfarction bradyarrhythmias and, on occasion, in the presence of ventricular tachyarrhythmias in an attempt to produce overdrive suppression. It also increases the refractory period and diminishes spontaneous firing of cardiac muscle.[5] In addition, both scopolamine and homatropine are capable of producing bradycardia in man.[6, 7]

It is a pharmacological axiom that substances whose principal action is that of a cholinergic antagonist may stimulate receptors for which they have an affinity during the initial act of combining with them.[8] Yet, regardless of dose, the tachycardia after scopolamine and homatropine administration is either absent or negligible, while the bradycardia is both pronounced and persistent. Thus, tropane-induced bradycardia may not be related to its anticholinergic properties.

The present study was undertaken in an attempt to characterize pharmacologically the dose-response effects of the principal tropane alkaloids with respect to their negative chronotropic and antiarrhythmic actions and to more clearly define the site of these actions.

Methods

We used the whole isolated cat heart (Langendorff) preparation, described by Anderson and Craver[9] and modified in this laboratory.[10] Perfusate was continuously recycled and heart rate determined by placing fine needle electrodes in the right atria and left ventricular epicardium. Following a 30-minute equilibration period, perfusate with drug was introduced into the system which contained a known volume. Thus drug concentration remained constant. Within 20 minutes after drug exposure, a chronotropic effect was observed, which reached a peak and leveled off at a constant rate 30-60 minutes later. When three consecutive rates obtained at 5-minute intervals from the electrogram did not vary by more than ±5%, the experiment was terminated. Only one drug and one concentration were used for each preparation. Perfusate for all preparations was maintained at 37.5°C.

Use of the cat papillary muscle preparation in this laboratory has previously been described in detail.[11] Briefly, individual muscles from the right ventricle were mounted on separate muscle holders and placed in identi-

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cal chambers. Electrical stimulation of individual muscles was accomplished by two platinum point electrodes in the shaft of the muscle holder which were in direct contact with the base of the muscle on either side. Grass Ft.03C force-displacement transducers mounted on racks and pinions were used to record isometric contractions for the sole purpose of determining rate and rhythm. During the equilibration period (30-minute), a strength-tension curve was determined for each muscle. The resting tension which produced the maximum recorded contractile force was equated to 100% peak (diastolic) tension, and the muscle was maintained at that tension throughout the experiment.

At the end of the 30-minute equilibration period, the maximal driving frequency was determined by increasing the frequency of stimulation[12] until 2:1 rhythm occurred. The rate of change was similar for all determinations and was equivalent to one additional stimulus/9 seconds. The muscle at this point was no longer able to respond to every stimulus applied, because the interval between consecutive stimuli was now less than the refractory period. The frequency at which 2:1 rhythm occurs is an easily discernible end point which can be quantified and is readily reproducible. Readings were taken at 5-minute intervals. Prior to each reading, threshold was determined to ensure that the stimulus was exactly 2 times threshold. Between readings, the stimulus was returned to a frequency of 1/sec.

An end point was reached when three consecutive readings were within a frequency of 0.3/sec. After the control (2:1) frequency was established, the test substance was added to the bathing medium at a specific concentration and allowed to remain in the bath until a new (2:1) end point was attained. A substance that prolongs the refractory period reduces the frequency at which 2:1 rhythm occurs, and the percent prolongation of the refractory period can then be calculated in comparison to the untreated control. Only one drug concentration was examined with each preparation.

Reversal of aconitine-induced tachycardia was examined in separate studies on whole isolated cat heart (Langendorff) and papillary muscle preparations. Automaticity and/or tachycardia was produced by the addition of aconitine nitrate to the bathing medium in a constant concentration for the duration of each experiment. In the studies on papillary muscle, diastolic tension was maintained at that tension which produced a maximum systolic contraction, and aconitine nitrate, 0.5 μg/ml, was added to the medium. In the cat Langendorff preparation, the addition of 0.05 μg/ml was sufficient to produce a pronounced tachycardia. Krebs-Ringer-bicarbonate enriched with glucose (5.56 mmol/liter), maintained at 37.5°C, and gassed with 95% O_2 and 5% CO_2 was used as the perfusing medium for all in vitro studies. The only difference between the two was that the papillary muscle medium contained $NaHCO_3$, 12.5 mmol/liter whereas the Langendorff perfusate contained 25 mmol/liter.

The following substances, with their monomeric anhydrous molecular weights, were used in this study: procaine amide·HCl (mol wt, 271.79; E. R. Squibb & Sons), cocaine·HCl (mol wt, 339.81; Mallinckrodt), aconitine·NO_3 (mol wt, 707.72; K & K Laboratories), *d,l*-atropine·$^1/_2$ SO_4 (mol wt, 338.41; Sigma Chemical Co.), *l*-hyoscyamine·$^1/_2$ SO_4 (*l*-atropine; mol wt, 338.4; Sigma), *l*-scopolamine·HBr (mol wt, 384.3; Sigma), *d,l*-homatropine·HBr (mol wt, 356.26; Sigma), quinidine·$^1/_2$ SO_4 (mol wt, 373.5; Sigma), *d,l*-tropic acid (mol wt, 166.2; Sigma), and tropine (mol wt, 141.2; Sigma). Dose-response curves were calculated as the concentration of each substance expressed as the salt-free base.

All drug solutions were prepared just prior to use, and statistical analysis was accomplished by use of Student's *t*-test, with a P value of <0.05 taken to indicate a statistically significant difference. The results presented were obtained on 140 cat Langendorff and 117 cat papillary muscle preparations.

Potency calculations given in Table 1 were obtained by equating the concentration of quinidine that elicited a 20% response to 1.0 and comparing it to the drug concentration that elicited a similar response. The relative potency of drug to quinidine was then determined by the relationship, [quinidine]:1.0::[drug]:1/x.

Results

Bradycardia

Mean results showing the relationship between the concentration of quinidine, *l*-scopolamine, *d,l*-homatropine, *l*- and *d,l*-atropine, and the ability of these alkaloids to produce bradycardia in the cat Langendorff preparation, are depicted in Figure 1. As illustrated, the dose-effect curves obtained are parallel to each other. However, figure 2 illustrates the nonparallel nature of the dose-effect curve obtained with procaine amide in the

TABLE 1 *Concentrations and Relative Potencies of Tropane Alkaloids Producing a 20% Decrease in Heart Rate and a 20% Prolongation of the Refractory Period (RPP_{20}), in Comparison to Quinidine*

Substance	Bradycardia		RPP_{20}		Ratio	
	× 10^{-6} M (A)	Potency (B)	× 10^{-6} M (C)	Potency (D)	(A/C)	(B/D)
Quinidine	6.0	1.0	4.3	1.0	1.4	1.0
Cocaine			4.6	0.935		
l-Atropine	59.0	0.102	44.0	0.098	1.34	1.04
d,l-Atropine	69.0	0.087	50.0	0.086	1.38	1.01
d,l-Homatropine	85.0	0.071	68.0	0.063	1.25	1.13
l-Scopolamine	205.0	0.029	92.0	0.047	2.22	0.62

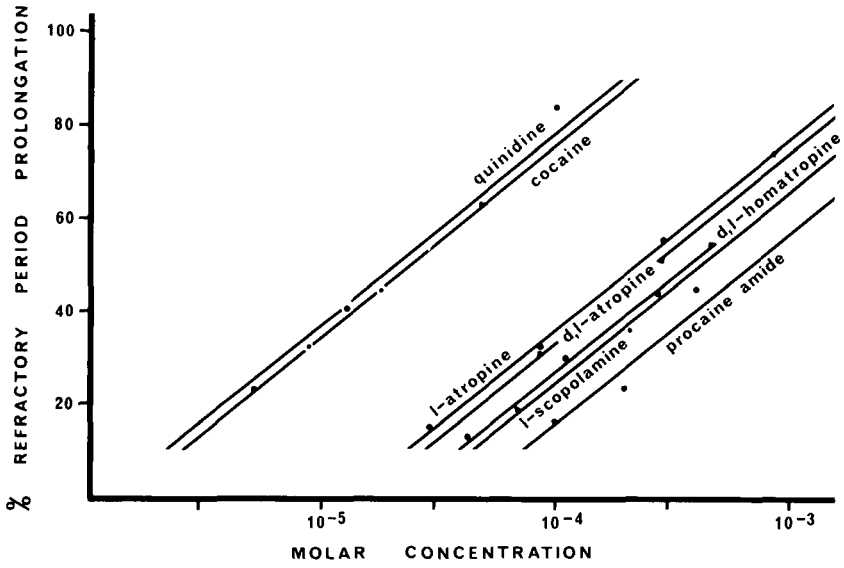

FIGURE 1 *Dose-effect curves obtained on the whole isolated cat heart preparation illustrating the diminution of heart rate produced by quinidine (13), l-atropine (20), d,l-atropine (13), d,l-homatropine (18), and l-scopolamine (9) (number of individual determinations in parentheses).*

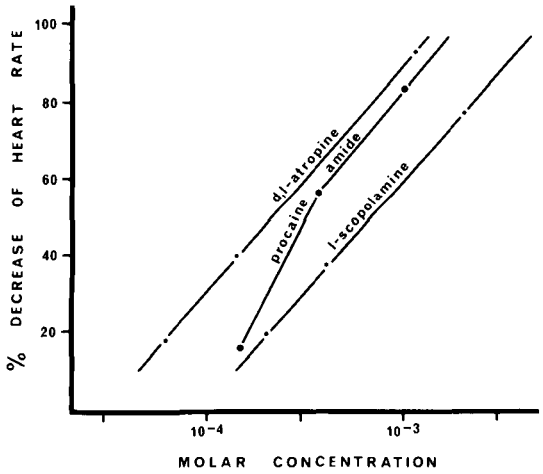

FIGURE 2 *Dose-effect curves obtained on the whole isolated cat heart preparation illustrating the diminution of heart rate produced by procaine amide (16), in comparison to d,l-atropine and scopolamine (from Fig. 1).*

same preparation in comparison to *d,l*-atropine and *l*-scopolamine. The addition of cocaine to give a similar range of concentrations usually produced tachycardia, although, on occasion, bradycardia was observed. A tabulation of the drug concentrations that produced a 20% decrease in heart rate is shown in Table 1 (Column A). The order of potencies found (Column B) was: quinidine $\gg$ *l*-atropine $\simeq$*d,l*-atropine $\simeq$*d,l*-homatropine > *l*-scopolamine.

Refractory Period Prolongation

We used the maximal driving frequency of cat papillary muscles as an indirect measure of refractory period. Figure 3 illustrates the results obtained with five tropane alkaloids as well as quinidine and procaine amide. The order of potency showed quinidine $\simeq$ cocaine >> *l*-atropine $\simeq$ *d,l*-atropine > *d,l*-homatropine $\simeq$ *l*-scopolamine > procaine amide (see also Table 1, Column D). The concentrations required to produce a 20% response, as well as the relative potencies compared to quinidine, are

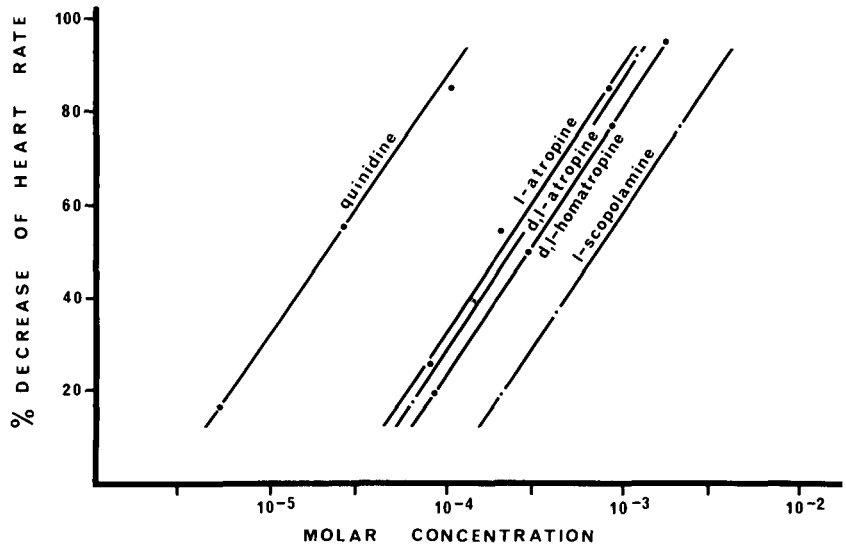

FIGURE 3 *Dose-effect curves obtained on the cat papillary muscle preparation illustrating the prolongation of refractory period of quinidine (20), cocaine (11), l-atropine (12), d,l-atropine (14), d,l-homatropine (18), l-scopolamine (14), and procaine amide (10).*

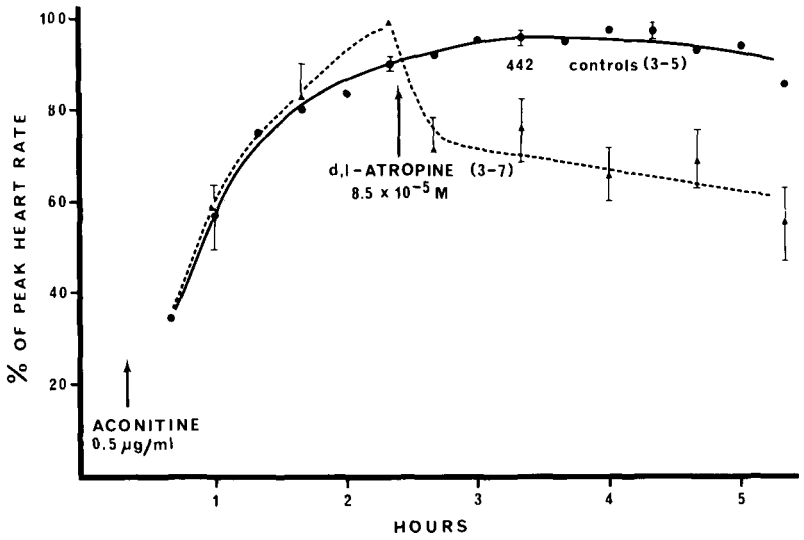

FIGURE 4 *Time-action curves of aconitine-induced automaticity and tachycardia in the cat papillary muscle preparation; d,l-atropine (8.5 × 10⁻⁵ M, dotted curve), added at 2 hours 22 minutes, resulting in a significant decline in rate. (Vertical lines = ± SEM; numbers in parentheses = number of individual experiments.)*

presented in Table 1. Ratios relating both the concentration and potency (in terms of bradycardia) to the prolongation of refractory period also are presented in Table 1. With the exception of scopolamine, the ratios for quinidine and the tropane alkaloids are remarkably constant, varying up to a maximum of 10.7% (A/C) (e.g., [(1.4 − 1.25) ÷ 1.4] × 100) and 13% B/D). In six additional studies, neither tropine nor tropic acid in concentrations of 10^{-2} and 10^{-3} M altered the refractory period.

Aconitine-Induced Tachycardia

The addition of aconitine (0.5 µg/ml) to the medium for bathing electrically stimulated cat papillary muscles results in the development of automaticity in about 9 minutes, as evidenced by the appearance of extrasystoles; at this time, stimulation was discontinued.[11] Twenty minutes after the addition of aconitine, an automatic rate of 156 beats/min was present. The progression from this rate to a persistent and reasonably stable tachycardia peaking at a mean of 442 beats/min is depicted in Figure 4. This figure also illustrates the effect on rate observed after the addition of *d,l*-atropine (8.5 × 10^{-5} M) to the medium containing aconitine. Within 20 minutes, there was a statistically significant decrease which persisted until the experiment was terminated at 320 minutes. Concentrations of *d,l*-atropine (8.5 × 10^{-7} and 8.5 × 10^{-6} M) produced results qualitatively similar to those at 8.5 × 10^{-5} M, but were less consistent. However, a concentration of 8.5 × 10^{-8} M failed to affect aconitine-induced tachycardia. Thus, concentrations of atropine greater than 8.5 × 10^{-7} M apparently do little, if anything, to enhance the anti-aconitine action of *d,l*-atropine, though the effect becomes more consistent as concentration approaches 8.5 × 10^{-5} M.

The ability of aconitine (0.05 µg/ml to produce tachycardia when added to the medium perfusing the cat Langendorff preparation is shown in Figure 5. A mean peak heart rate of 387 beats/min occurred 100 minutes after exposure to aconitine and declined slightly until experiments were terminated at 4 hours.

Data were obtained for concentrations required to decrease the heart rate by 20% (Table 1). Figures 6 and 7 illustrate the anti-aconitine action of *l-*, *d,l*-atropine, *d,l*-homatropine, and *l*-scopolamine upon the aconitine-treated cat Langendorff preparation. At plus 4 hours, the difference between aconitine-treated controls and *l*-atropine yielded a P value of < 0.01; for *d,l-* -atropine and *d,l*-homatropine, P values of < 0.005, and for *l*-scopolamine, a P value of < 0.001. The results show a statistically significant decline in heart rate produced by all four alkaloids in the aconitine-treated preparation at plus 4 hours, about 2 hours after drug administration. Moreover, at that time heart rates had returned to approximately their pre-aconitine levels.

In single cat papillary muscle preparations, the administration of cocaine · HCl (4.4 × 10^{-6} M) 1 hour previously failed to antagonize aconitine-induced automaticity and tachycardia. Similarly, the addition of cocaine (8.8 × 10^{-8} to 8.8 × 10^{-5} M) failed to reverse automaticity and tachycardia in a muscle previously exposed to aconitine.

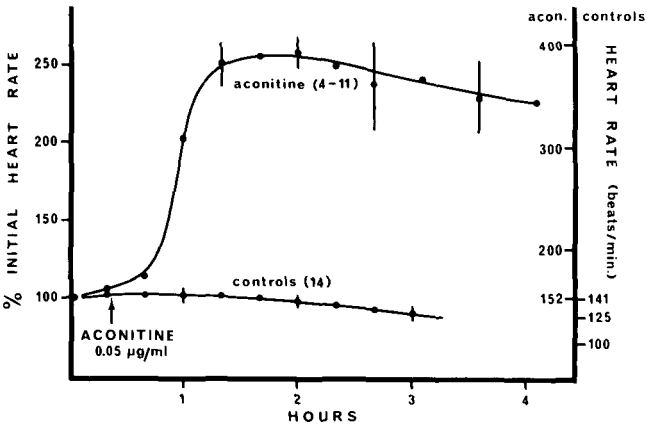

FIGURE 5 *Time-action curves showing the alteration in heart rate produced by the addition of aconitine (0.05 µg/ml) to the medium perfusing the whole isolated cat heart preparation. (Vertical lines = ± SEM; numbers in parentheses = number of individual experiments.)*

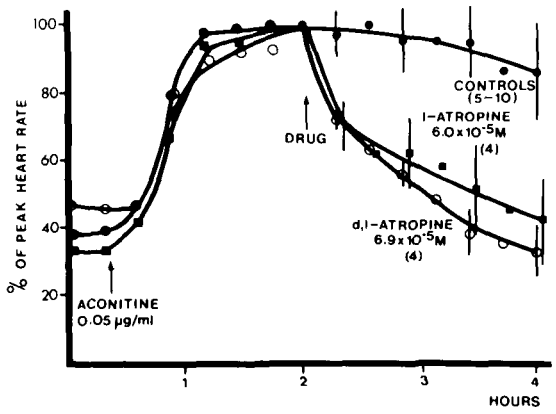

FIGURE 6 *Time-action curves showing the alteration in heart rate produced by d,l- and l-atropine on the aconitine-treated whole isolated cat heart preparation. All values are expressed as a percentage of the peak heart rate obtained following the addition of aconitine. Drug concentrations were those that produced a 20% decline in heart rate (Table 1). (Vertical lines = ± SEM; numbers in parentheses = number of individual experiments.)*

Discussion

These studies demonstrate that homatropine and scopolamine, as well as *l-* and *d,l-*atropine, possess negative chronotropic and "quinidine-like" activity in isolated cat myocardial preparations, but that tropine and tropic acid do not.

The ability of small doses of atropine to produce bradycardia in animals and man,[1, 2] as well as its ability to potentiate the depressor effect of injected acetylcholine,[4] has been recognized for some time. Following these early reports, several investigators studied the antiarrhythmic properties of atropine. For example, DiPalma and Mascatello,[5] using isolated cat myocardial preparations, noted that atropine slowed spontaneous rate and prolonged the refractory period. Others have commented on its ability to antagonize catecholamine-induced arrhythmias, alone or in association with inhalation anesthetics,[13-16] as well as those produced by calcium and aconitine.[17] Similarly, atropine has been shown to protect mice against ventricular fibrillation induced by halogenated hydrocarbon anesthesia in doses that exceed those necessary to induce a maximal mydriasis;[18] but, as in the results we obtained, the antiarrhythmic potency of atropine was found to lie between that of quinidine and procaine amide. To date, the most extensive pharmacological characterization of the antiarrhythmic properties of atropine has been by Viana and Osswald,[19] who demonstrated that doses of 0.2 mg/kg and higher protect anesthetized dogs against tachyarrhythmias produced by epinephrine, $BaCl_2$, digoxin, and aconitine.

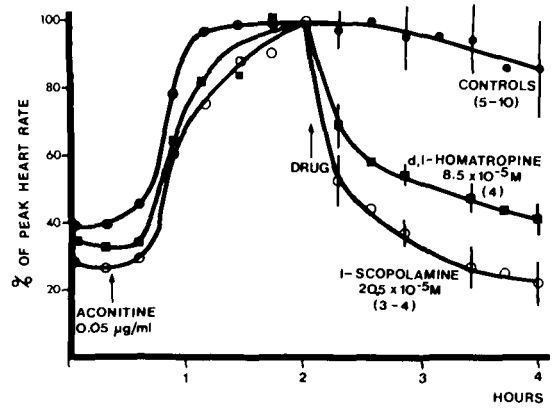

FIGURE 7 *Time-action curves showing the alteration in heart rate produced by d,l-homatropine and l-scopolamine on the aconitine-treated whole isolated cat heart preparation. All values are expressed as a percentage of the peak heart rate obtained following the addition of aconitine. Drug concentrations were those that produced a 20% decline in heart rate (Table 1). (Vertical lines = ± SEM; numbers in parentheses = number of individual experiments.)*

Between species, dose-effect relations differ with respect to the ability of atropine to produce muscarinic, antimuscarinic, and perhaps weak local anesthetic activity, and therefore it is often difficult to extrapolate from the literature the dose needed to produce a specific effect. Sensitivity to the antimuscarinic action of atropine, for example, varies considerably, with man, dogs, and cats apparently showing the greatest effect, and goats, rats, and rabbits, the least.[20]

The effective unbound plasma quinidine concentration in man ranges between 2.4 and 4.9 × 10^{-6} M, based on a therapeutic plasma level of 2–4 mg/liter, of which 60% is bound to albumin. We have been unable to locate in the literature "therapeutic" plasma levels of atropine in man. Anticholinergic activity in cats requires parenteral administration of atropine in a dose greater than 0.5 mg/kg.[21] According to Tonnesen,[22] approximately 50% of parenterally administered atropine is loosely bound to plasma albumin in humans. In cats, since 5.5% of body weight is blood, an intravenous administration of 0.5 mg/kg would yield an unbound atropine blood concentration of 1.66 × 10^{-5} M. In studies on isolated cat myocardial preparations, we found that a 20% reduction in heart rate was produced by 6 × 10^{-6} M quinidine and 5.9 × 10^{-5} M atropine; to prolong the refractory period by 20%, a quinidine concentration of 4.3 × 10^{-6} M and an atropine concentration of 4.4 × 10^{-5} M were needed. Thus, the calculated in vivo concentrations for quinidine and atropine are very similar to their in vitro therapeutic concentrations. In the case of the calculated in vivo atropine concentration, it must be noted that neither its volume of distribution nor its binding affinity for heart is known.

Some investigators have attributed atropine's antifibrillatory effects to antimuscarinic properties; others have emphasized a nonspecific quinidine-like action in either parasympatholytic or subparasympatholytic concentrations. Thus, Szekeres and Papp[23] noted that, in low concentrations (0.1 µg/ml), it prolongs the duration of the action potential of the isolated dog heart but, in doses higher than 0.5 mg/ml, it exerts both parasympatholytic and quinidine-like effects which modify both Purkinje fiber and ventricular action potentials in the same manner as local anesthetics.

The ability of atropine to induce bradycardia in doses less than 0.6 mg, sc, in man has been noted previously[24, 25]

and has been confirmed following intravenous[26-28] and oral[24, 25] administration. In man, atropine (0.2 mg, iv) shortens the P wave and lengthens both the P-R and R-T intervals, and at times during the height of bradycardia, some P waves completely disappear.[29, 30] Since stimulating the peripheral end of the cut right vagus accomplishes the same thing, it suggests that small doses of atropine are parasympathomimetic. Although many have suggested that atropine-induced bradycardia is the result of stimulation of the central vagal nucleus,[31, 32] atropine methylbromide, which is unable to cross the blood-brain barrier, also produces bradycardia.[3] Moreover, since neostigmine and acetylcholine enhance the bradycardia produced by atropine, it was concluded that small doses display agonistic activity at cholinergic cardiac receptors.[3] Our observations on the cat Langendorff preparation agree with the suggestion that atropine-induced bradycardia results from a direct action on the heart. The nature of atropine's negative chronotropic effect is still in doubt. Under certain conditions, however, it has been demonstrated that atropine may inhibit the activity of cholinesterase leading to an increased receptor response to acetylcholine.[33] Although we have no direct evidence in support, it is our belief that at low doses these tropane alkaloids produce a cholinergic agonistic effect and at higher doses, a quinidine-like action.

The present study also compared the racemate to *l*-atropine because anticholinergic activity resides in the *l*-isomer,[32, 34] and it has been claimed that the *l*-isomer is twice as potent insofar as its chronotropic action is concerned.[35] Our results, however, suggest that atropine isomers are equipotent in the production of bradycardia on cat myocardium.

The production of bradycardia following administration of homatropine and scopolamine also has been reported.[6, 19, 26, 27, 34] Hayes and Katz[6] showed that homatropine produced a dose-dependent bradycardia in humans in doses ranging between 0.5 and 2.0 mg, sc, with a ceiling effect between 2 and 4 mg. In contrast to atropine, however, homatropine never elicited tachycardia. It is of interest that, although homatropine is considerably less potent as an anticholinergic agent than atropine,[32] the dose-effect curves for negative chronotropic effect and refractory period prolongation lie very close to each other. Again this suggests that we are witnessing a mechanism unrelated to the anticholinergic action of these substances.

Summarizing his experience with scopolamine in 250 patients, Pedersen[7] reported that in doses between 0.3 and 0.5 mg, sc, tachycardia was never observed; either initial rate was unchanged or bradycardia resulted. In man, intravenous doses of scopolamine between 0.3 and 0.6 mg/kg may produce an initial tachycardia, although invariably it is followed by a long-lasting bradycardia.[26, 27, 36] On isolated cat heart preparations, our results confirm the dose-dependent bradycardia following exposure to homatropine and scopolamine. These tropane analogues also prolong the refractory period of ventricular muscle (i.e., maximal driving frequency) and antagonize aconitine-induced tachycardia.

Similarly, cocaine prolongs the refractory period of cat papillary muscle but, because it produces tachycardia in the Langendorff preparation by blocking catecholamine re-uptake, it was not possible to separate the two actions (bradycardia and tachycardia) by our methods. Nevertheless, others[37] have shown that, in the intact cat with a denervated heart, cocaine does produce a profound bradycardia, as well as in isolated cat and rabbit auricles,[38] and the Starling heart-lung preparation.[39] In man, after 0.6 mg, sc, of cocaine, heart rate remains well below control for several hours,[40] as it does in the dog.[41] Moreover, Weidman[42] has observed the ability of cocaine to abolish spontaneous activity of sheep Purkinje fibers, slow the rate of rise of phase 0 of the action potential, decrease the resting membrane potential, and diminish the action potential amplitude, suggesting that the sodium-carrying system may be inactivated. Our results on refractory period prolongation show that quinidine and cocaine are very similar, their RPP_{20} (20% prolongation of the refractory period) potencies being 1.0 and 0.935, respectively.

With the exception of scopolamine, the potency ratios comparing the 20% decrease in heart rate to a 20% prolongation of the refractory period were remarkably consistent for quinidine, *l*- and *d,l*-atropine, and homatropine. This suggests that an intimate relation exists between these two phenomena, namely, that the negative chronotropic effect is a result of refractory period prolongation. The fact that drug concentrations extrapolated from the 20% decrease in heart rate were effective to approximately the same extent in reversing aconitine-induced tachycardia in the cat Langendorff preparation again suggests that a fundamental relationship exists between anti-aconitine activity and refractory period prolongation. In a previous study,[10] we were able to demonstrate the existence of the same type of relationship with respect to propranolol, lidocaine, procaine amide, and practolol.

Cocaine, however, does not fit the results obtained with the other tropane analogues, because, with the exception of its ability to prolong the refractory period, we were unable to demonstrate that it could antagonize aconitine over a wide concentration range. Neither tropine nor tropic acid in high concentrations (10^{-3} and 10^{-2} M) displayed activity.

In the presence of ventricular tachycardia, atropine is occasionally administered in hopes of producing overdrive suppression. Sometimes the ventricular tachycardia worsens and terminates in fibrillation. We do not know whether the administration of atropine is related to this terminal event. However, if it possesses the ability to produce local conduction blocks, it could contribute to the formation of reentrant arrhythmias.

References

1. Cushney AR: Atropine and the hyoscyamines—A study of the optical isomers. J Physiol (Lond) **30:** 176-194, 1904
2. Pilcher JD, Sollmann T: Quantitative studies of vagus stimulation and atropine. J Pharmacol Exp Ther **5:** 318-340, 1913-1914
3. Kottmeier CA, Gravenstein JS: The parasympathomimetic activity of atropine and atropine methylbromide. Anesthesiology **29:** 1125-1133, 1968
4. Cohn AE, MacLeod AG: Effect of acetylcholine on the mammalian heart. Am Heart J **21:** 356-364, 1941
5. DiPalma JR, Mascatello AV: Analysis of the actions of acetylcholine, atropine, epinephrine and quinidine on heart muscle of the cat. J

Pharmacol Exp Ther **101:** 243-248, 1951
6. Hayes AH Jr, Katz RA: Homatropine bradycardia in man. Clin Pharmacol Ther **11:** 558-566, 1970
7. Pedersen JEP: Scopolamine as sole pre-anesthetic medication. Acta Anaesthesiol Scand **7:** 121-129, 1963
8. Paton WDM: The principles of drug action. Proc R Soc Med **53:** 815-820, 1960
9. Anderson FF, Craver BN: A pyrex apparatus for the perfusion of the coronary circulation of mammalian hearts. J Pharmacol Exp Ther **93:** 135-141, 1948
10. Tanz RD: Pharmacology of aconitine-induced automaticity on in vitro cat myocardial preparations. II. Effects of refractory period prolongation, reduced sodium and tetrodotoxin. J Pharmacol Exp Ther **191:** 232-240, 1974
11. Tanz RD, Robbins JB, Kemple KL, Allen PA: Pharmacology of aconitine-induced automaticity of cat papillary muscle. I. Effect of dose, tension, rate and endogenous catecholamines. J Pharmacol Exp Ther **185:** 427-437, 1973
12. Tanz RD, Cavaliere TA: Modified method for determining myocardial refractory period. Proc Soc Exp Biol Med **120:** 66-68, 1965
13. Lees P, Tavernor WD: Influence of halothane and catecholamines on heart rate and rhythm in the horse. Brit J Pharmacol **39:** 149-159, 1970
14. Riker WF, Depierre F, Roberts J, Roy BB, Reilly J: The epinephrine and hydrocarbon-epinephrine disturbance in the cat. J Pharmacol Exp Ther **114:** 1-9, 1955
15. Roberts J, Roy BB, Reilly J, Garb S, Riker WF Jr, Hashimoto K: Use of certain neuromuscular blocking drugs in an analysis of ventricular irregularities induced in the cat. J Pharmacol Exp Ther **117:** 279-288, 1955
16. Nickerson M, Toman JEP, Hecht HH: Effect of atropine on epinephrine-induced cardiac irregularities (abstr). Fed Proc **6:** 361, 1947
17. Malinow MR, Battle FF, Malamud B: Prevention of experimental ventricular arrhythmias in the rat by atropine. Arch Int Pharmacodyn Ther **99:** 458-466, 1954
18. Lawson JW: Antiarrhythmic activity of some isoquinoline derivatives determined by a rapid screening procedure in the mouse. J Pharmacol Exp Ther **160:** 22-31, 1968
19. Viana AP, Osswald W: Antiarrhythmic action of atropine. Arch Int Pharmacodyn Ther **192:** 238-246, 1971
20. Stowe CM: Parasympatholytic drugs in veterinary pharmacology and therapeutics, chap 26, ed 3, edited by LM Jones. Ames, Iowa, Iowa State University Press, 1965, pp 325-333
21. Barnes CD, Eltherington LG: Drug Dosage in Laboratory Animals: A Handbook. Berkeley, University of California Press, 1965
22. Tonnesen M: On the absorption of atropine to plasma proteins. Acta Pharmacol Toxicol **12:** 247-250, 1956
23. Szekeres L, Papp GyJ: Experimental cardiac arrhythmias and antiarrhythmic drugs. Budapest, Akademiai Kaido, 1971
24. McGuigan H: The effect of small doses of atropine on the heart rate. J Am Med Assoc **76:** 1338-1340, 1921
25. Rudolph RD, Blumer FMR: Some cardiac effects of atropine. Am J Med Sci **168:** 641-647, 1924
26. Gravenstein JS, Anderson TW, De Padua CB: Effects of atropine and scopolamine on the cardiovascular system in man. Anesthesiology **25:** 123-130, 1964
27. List WF, Gravenstein JS: Effects of atropine and scopolamine on the cardiovascular system in man. 2. Secondary bradycardia after scopolamine. Anesthesiology **26:** 299-304, 1965
28. Morton HJV, Thomas ET: Effect of atropine on the heart rate. Lancet **2:** 1313-1315, 1958
29. Gravenstein JS, Ariet M, Thornby JI: Atropine on the electrocardiogram. Clin Pharmacol Ther **10:** 660-666, 1969
30. Gravenstein JS: The belladonna drugs. Int Anesthesiol Clin **6:** 33-40, 1968
31. Henderson VE: On the sensitivity of different nerve endings to atropine. J Pharmacol Exp Ther **21:** 99-102, 1923
32. Goodman LS, Gilman A: The pharmacological basis of therapeutics, ed 5. New York, Macmillan, 1975, pp 516-519
33. Lullman H, Forster W, Westermann E: Uber eine "paradoxe" Atropinwirkung an isolierten Organen and ihre statistiche Erfassung. Arch Exp Pathol Pharmakol **215:** 8-15, 1952
34. Cushney AR: Optical isomers. VII. Hyoscines and hyoscyamines. J Pharmacol Exp Ther **17:** 41-61, 1921
35. Bagshaw H, Chamberlin DA, Turner P: Comparison of atropine and (-)-hyoscyamine on heart rate in man. Br J Pharmacol **40:** 600-601, 1970
36. Gravenstein JS, Thornby JI: Scopolamine on heart rates in man. Clin Pharmacol Ther **10:** 395-400, 1969
37. Rosenblueth A, Schlossberg T: The sensitization of vascular response to 'sympathin' by cocaine and the quantitation of 'sympathin' in terms of adrenalin. Am J Physiol **97:** 365-374, 1931
38. MacGregor DF: The relation of cocaine and of procaine to the sympathetic system. J Pharmacol Exp Ther **66:** 393-409, 1939
39. Wollenberger A, Krayer O: Experimental heart failure caused by central nervous system depressants and local anesthetics. J Pharmacol Exp Ther **94:** 439-443, 1948
40. Shearer WM: The effect of atropine and hyoscine on the pulse rate in human subjects. Anesthesia **6:** 76-82, 1951
41. Stewart DM, Rogers WP, Mahaffey JE, Witherspoon S, Woods EF: Effect of local anesthetics on the cardiovascular system of the dog. Anesthesiology **24:** 620-624, 1963
42. Weidman S: Effects of calcium ions and local anesthetics on electrical properties of Purkinje fibres. J Physiol (Lond) **129:** 568-582, 1955

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