Pharmacology of Antiarrhythmics: Quinidine, Beta-Blockers, Diphenylhydantoin, Bretylium*

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The electrophysiologic effects of the antiarrhythmic drugs, presented elsewhere in this symposium, form only one of the bases for the selection of a therapeutic agent in any given clinical situation. The final choice depends at least on the following factors:

1. The specific arrhythmia
2. Underlying heart disease, if any
3. The degree of compromise of the circulation, if any
4. The etiology of the arrhythmia
5. The efficacy of the drug for that arrhythmia due to that etiology
6. The toxicity of the drug, especially in the given patient with possible alterations in volume of distribution, biotransformation, and excretion
7. The electrophysiologic effects of the drug
8. The routes and frequency of administration available for that drug

As no one drug meets, or even approaches, the criteria for the ideal antiarrhythmic, a knowledge of several drugs is essential. Unfortunately, adequate, controlled clinical comparisons are virtually nonexistent.

A complete presentation of the non-electrophysiologic pharmacology would include the following considerations:

1. Absorption and peak effect times
2. Biotransformation
3. Rate of elimination or half-life ($t_{1/2}$)
4. Drug interactions
5. Toxicity
6. Clinical usefulness
7. Therapeutic drug levels
8. Dosage schedules

As all of the above data cannot be presented in the limited space available, only selected items will be discussed. Much of the preceding information is available, however, in standard texts (17, 10). (See Addendum 1)

Quinidine. Quinidine is principally transformed in the liver by hydroxylation, but some 10-50% is excreted unchanged in the urine. This variation in the quantity excreted in the urine is of considerable importance, and it is influenced by both glomerular filtration and by urine pH.

Bellet *et al.* (3) measured the serum levels of quinidine in three groups of ten subjects after 600 mg of oral quinidine. Normal subjects had, af-

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ter two hours, significantly lower serum quinidine levels than the subjects with congestive heart failure (creatinine clearances of 35-80 ml per minute), or the subjects with renal disease and azotemia. While this study does not consider alterations in the volume of distribution, liver function, and so forth, the correlation between the peak level of quinidine and the rate of fall of the serum levels with glomerular filtration is evident. Thus, we must consider renal function much in the same way as when we use digoxin.

In addition to renal function, the pH of the urine is important in the excretion of quinidine. As urine pH rises, more of the urinary tubular quinidine is nonionized and, hence, more readily passes across the tubular epithelium, thus decreasing the quantity of filtered quinidine excreted in the urine.

Figure 1 is taken from the study of Gerhardt *et al.* (9). In normal subjects, urine pH was raised by administering acetazolamide and sodium bicarbonate. As shown, serum quinidine levels rise as urine pH increases and, furthermore, the pharmacologic significance of the higher serum quinidine levels is indicated by progressive increase in the Q-T interval.

Molar sodium lactate has been recommended as a means of treating the arrhythmic abnormalities associated with quinidine toxicity. While such alkalizing therapy may improve the arrhythmias, it surely will also delay the excretion of quinidine and might prolong the duration of the toxicity. Also a large segment of the population has been consuming a very effective urinary acidifier, ascorbic acid, in a huge dose. The doses of quinidine needed to establish an antiarrhythmic effect might be titrated in such an individual, who then discontinues the ascorbic acid. A considerable increase in serum quinidine could occur with a significant chance of serious toxicity.

Thus the physician must consider glomerular filtration rate and urine pH when prescribing quinidine. Alterations in liver function and the apparent volume of distribution are probably also important but less quantifiable.

The serum half-life ($t_{1/2}$) is known for all of the available antiarrhythmic drugs, and this simplified concept is useful in understanding the necessity for loading doses, the frequency of dosing, the duration of toxicity, and the timing of clinical observations of the patient.

The serum half-life is defined as the time required to reduce the serum level of a drug to one-

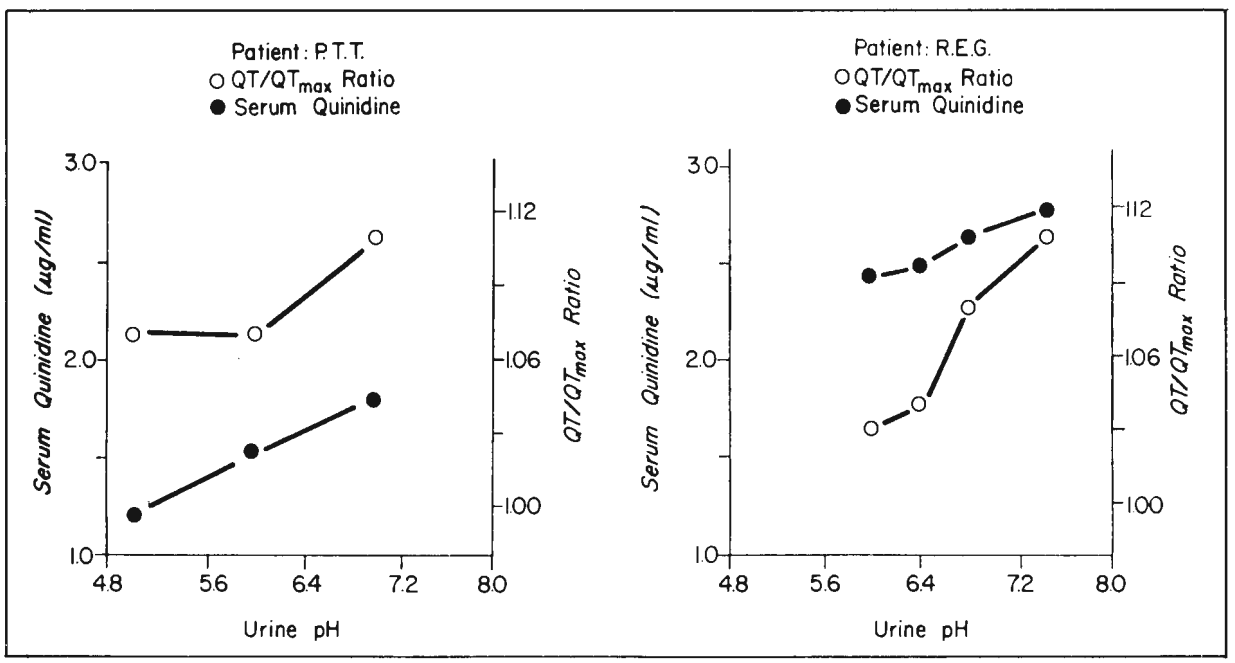

Fig. 1—Change of serum quinidine and change of ratio of measured Q-T interval to the maximum normal Q-T interval at measured heart rate (expression of quinidine effect), plotted relative to urine pH, for two subjects. (Reproduced by permission of *Annals of Internal Medicine*, 71:929, 1969, and R. E. Gerhardt).

half its initial level. As the great majority of drugs follow first-order kinetics (the amount eliminated is proportional to the quantity present), the following "rules" of half-life are widely applicable:

1. The serum half-life is independent of the quantity of drug present. In figure 2, the disappearance curve declines 50% each half-life, decreasing from 100% to 50% the first half-life, from 50% to 25% the second half-life, and so forth.
2. The half-life concept is independent of the mechanism of elimination; urinary or intestinal excretion, hepatic transformation, and so forth.
3. The dosing interval must be shorter than the half-life to avoid wide fluctuations in serum levels and body stores of a drug.
4. Essentially complete elimination of a drug is achieved after five half-lives and conversely, with regular dosing, at frequencies of the half-life, or more often, equilibrium levels are achieved after five half-lives (see accumulation curve). After 3.3 half-lives, 90% of equilibrium levels are achieved. This would then be an appropriate time to make clinical observations on the pharmacologic effects of the drug.

For quinidine, the half-life is about 4-6 hours. Doctors Richardson, Zee, and Wyso (21) from our institution reported on studies in which quinidine was given at 9 A.M., 1, 5, and 9 P.M. While the serum levels before the next day's dose were still adequate, they were achieved at the expense of excessive levels one and one-half hours after the 9 P.M. dose. A six-hour schedule would have avoided the potentially toxic levels at bedtime.

In a study to be described further below, Bloomfield *et al.* (7) gave patients quinidine 300 mg at 0, 3, and 6 hours, as a loading attempt and then gave 300 mg every 6 hours thereafter. Figure 3 shows that the serum concentrations did not reach equilibrium levels until after 24 hours, in keeping with the principles noted above.

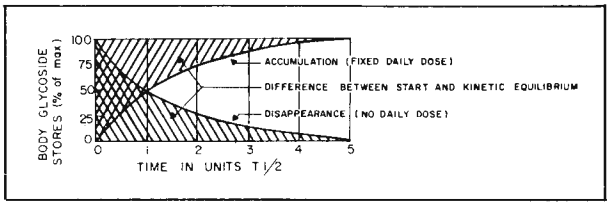

Fig. 2—The accumulation and disappearance of a drug is depicted in terms of its half-life.

In summary, application of the rules of $t_{1/2}$ to quinidine suggests that where prompt action is needed, a loading dose should be given and that quinidine should be given every six hours to avoid peaks and troughs of serum levels and associated toxicity and subtherapeutic concentrations.

"Quinidine Syncope" is the name employed by Selzer and Wray (23) to describe recurrent ventricular fibrillation, usually self-terminating, seen in patients treated with quinidine. It usually occurs after the first few doses, and it may be noted in patients with normal or even low serum quinidine levels. While tachyarrhythmias and ventricular fibrillation are well-known toxic effects of quinidine, these individuals seem to be unusually susceptible to this serious adverse effect. While most patients receiving quinidine have underlying heart disease, quinidine syncope can occur in patients with no detectable organic heart disorder.

Some clinicians are attempting close monitoring of patients during the initiation of quinidine therapy. The effectiveness of such monitoring will be difficult to assess because of the infrequency of this syndrome. Selzer and Wray estimated that 3-5% of patients treated with quinidine may develop this idiosyncratic toxicity, but Bjerkelund (6) reported only 1+% and Lown (16) reported only 0.5% sudden deaths in his series of 650 patients.

Finally, in regard to quinidine, some note of its efficacy need be made. Bloomfield *et al.* (7) studied 53 patients with acute myocardial infarction in a placebo controlled, randomly allocated prospective

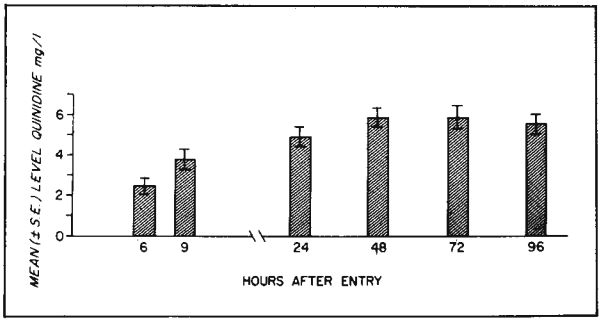

Fig. 3—Blood quinidine concentrations at various intervals during five days of prophylactic quinidine therapy in 27 patients with acute myocardial infarction. (Reproduced by permission of the *New England Journal of Medicine*, 285: 981, 1971, and S. S. Bloomfield).

trial of oral quinidine (*vide supra*). Because of the lag in achieving therapeutic serum quinidine levels, there was no difference between the treated and placebo groups in the first six hours, but thereafter (see fig. 4), there was a statistically significant reduction in premature ventricular and supraventricular contractions and in "serious ventricular arrhythmias." As has also been true of the studies of other antiarrhythmics in acute myocardial infarction, there was no difference in mortality between the treated and control groups.

Beta Adrenergic Receptor Blockers. The serum half-life of oral propranolol (Inderal®) is 3-4 hours. Successful management with less frequent dosing intervals is likely due to the fact that the large doses used result in blood levels which remain above the therapeutic level for a longer period of time.

The major concern in beta-blocker therapy is the marked cardiovascular depression which these agents induce. In three separate series of dogs, we (19) determined the mean doses of three antiarrhythmic drugs required to convert ouabain (a cardiac glycoside)-induced ventricular tachycardia to normal sinus rhythm. Alprenolol is an effective beta-blocker, the dose of which (intravenously) does not differ from propranolol. These doses of the three antiarrhythmics were then studied in a new series of paced, open chest dogs, and the electrocardiographic and hemodynamic effects of these drugs given in "equi-antiarrhythmic" doses are depicted in figure 5. The beta-blocker significantly prolonged the P-R and Q-T intervals and depressed blood pressure, cardiac output (aortic flow via an electromagnetic flow transducer), and left ventricular contractility (dp/dt, peak left ventricular rate of pressure rise). Directionally similar but less marked alterations occurred with procainamide, while diphenylhydantoin did not affect these or any of the other measured cardiovascular functions. Beta-blockers are, therefore, the most likely of the antiarrhythmics to induce cardiac depression, and even in low doses, a worsening of heart failure or the precipitation of pulmonary edema may result. While it is true that the correction of an arrhythmia by the beta-blocker may so improve the heart's overall function as to counteract any direct myocardial depression, such therapy is fraught with the danger that should the beta-blocker not affect the arrhythmia, its negative inotropic action will still be manifest.

Except where an arrhythmia is caused by adrenergic mechanisms, beta-blockers are best avoided in patients with myocardial disease unless other therapy has failed and the situation is desperate.

Diphenylhydantoin. Diphenylhydantoin (DPH) is

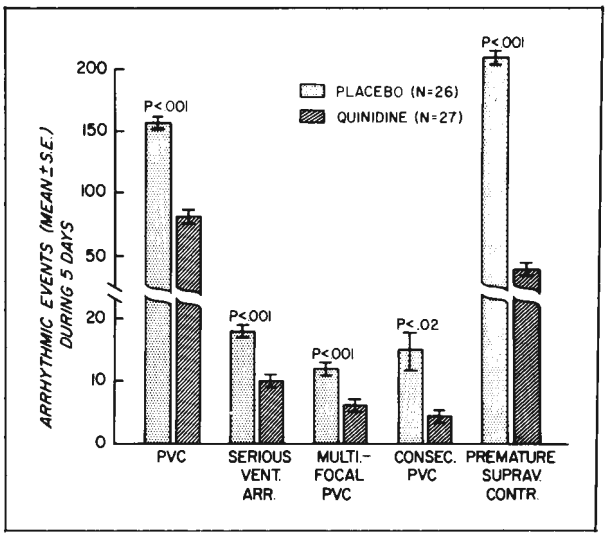

Fig. 4—Occurrence of arrhythmias during five days of prophylactic quinidine or placebo therapy in 53 patients with acute myocardial infarction. (Reproduced by permission of the *New England Journal of Medicine,* 285:984, 1971, and S. S. Bloomfield).

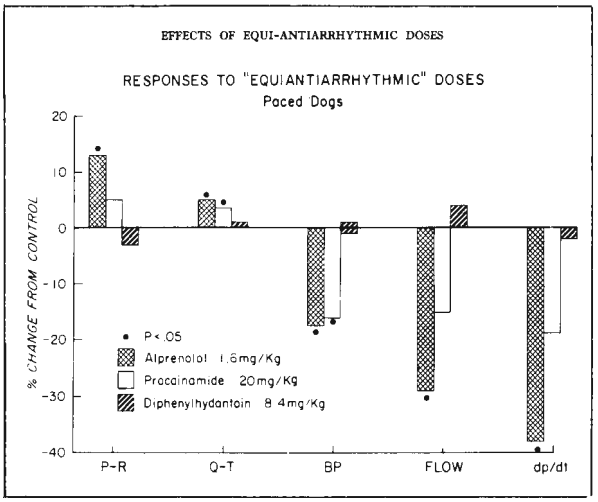

Fig. 5—The responses to equi-antiarrhythmic doses of alprenolol, diphenylhydantoin, and procainamide are shown. Statistically significant ($P < .05$) changes from control are indicated. (Reproduced by permission of *Archives Internationales de Pharmacodynamie et de Therapie,* 190:354, 1971, and J. D. Proctor).

of particular interest. The differences in its electrophysiologic effects have already been noted elsewhere. Also, any consideration of DPH must include information about its pharmacokinetics and biotransformation.

Diphenylhydantoin is slowly absorbed by mouth, peak levels not being achieved for hours. This drug should not be given intramuscularly since its absorption is erratic. Even intravenously, DPH effect requires 1-5 minutes, and rapid (bolus) injections must be avoided.

The biotransformation of DPH is shown in figure 6. Diphenylhydantoin is parahydroxylated by oxidizing enzymes in the liver microsomes, converting DPH to HPPH (hydroxyphenyl, phenylhydantoin or 5 phenyl 5'parahydroxyphenylhydantoin). It is this enzyme which is so susceptible to both enzyme inhibition and enzyme induction, accounting for the large number of reported DPH drug interactions (see addendum 2). Hydroxyphenyl, phenylhydantoin, the inactive metabolite, is conjugated with glucuronide, and its excretion in the urine normally accounts for about 75% of the elimination of DPH. Letteri *et al.* (15) have found that patients with uremia have *lower* serum levels of DPH than do normal subjects receiving the same dose, and that furthermore, the $t_{1/2}$ in uremia is shorter (more rapid DPH disappearance). This, of course, is quite the opposite from most drugs where renal failure results in higher serum levels and longer $t_{1/2}$. The mechanism whereby lower DPH levels are seen in uremia has not been completely elucidated, but several possible mechanisms have been suggested. It is known that HPPH levels are higher in uremic patients. It might be that something in the uremic state induces the parahydroxylating enzyme, hence more rapidly converting DPH to HPPH, or it may be

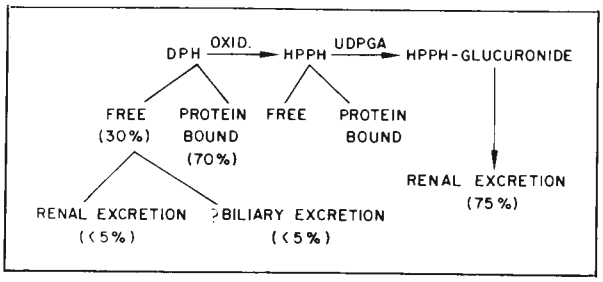

Fig. 6—Major route of metabolism of DPH. (Reproduced by permission of the *New England Journal of Medicine*, 285:651, and Joseph M. Letteri).

that the renal failure blocks the excretion of HPPH which competes with DPH for serum protein binding sites (see fig. 6). The unbound, free DPH would be more accessible to enzymatic conversion to HPPH and also more accessible to its receptor site. Thus, while total DPH would be reduced, the free (active) portion might be normal. Finally, it is known that serum protein binding is altered in uremia and this, too, could account for the lower total DPH and its more rapid conversion to HPPH due to more of the serum DPH existing in the free, unbound form.

The clinical role of DPH is receiving more attention. Lown and Wolf (16) report studies in which ventricular fibrillation was induced in dogs by occluding, and if necessary, later releasing the occlusion, of the anterior descending coronary artery. About 75% of untreated dogs developed ventricular fibrillation, and pretreatment with DPH had no effect. On the other hand, pretreatment with procainamide reduced the incidence of ventricular fibrillation to about 20%; quinidine, lidocaine, practolol (a beta-blocker), and bretylium tosylate reduced it to about 35%; and dextro-propranolol and ajmaline reduced ventricular fibrillation to about 50%.

Last year an Australian cooperative group reported a clinical trial of DPH prophylaxis in patients discharged from the hospital after their first acute myocardial infarction (8). Diphenylhydantoin, 300-400 mg per day, was given to 283 patients while the control group received 3-4 mg per day. Although the high dose DPH group had less palpitations and less documented arrhythmias than the control group, survival was unaffected.

Mercer and Osborne (18) in 1967, noted that the etiology of the arrhythmia was a significant factor in predicting its response to DPH. Where the arrhythmia was due to digitalis intoxication, one-half of the patients were successfully managed with DPH, but where the arrhythmia was due to coronary heart disease, only about one-fourth responded. (These percentages may not represent the maximum efficacy of DPH as the dosage schedules suggested below were not employed.)

From these data, it would appear that digitalis intoxication is the prime indication for DPH and that its usefulness in coronary heart disease is likely to be limited.

The effective serum concentration of DPH was

established by the elegant studies of Bigger and his colleagues (5) (fig. 7). These data indicate an effective level of about 6-18 μg per ml, the same range as that established for anti-convulsant efficacy (10–20 μg per ml).

Diphenylhydantoin does not follow first-order kinetics as even usual doses approach saturation of the parahydroxylating enzyme system. Thus, the "rules" of half-life do not, strictly speaking, apply to DPH. In the effective serum level range, however, DPH serum levels decline by one-half over 18-24 hours. It is evident then, that without a loading dose, several days will be needed to achieve equilibrium levels. Kutt and McDowell (14) and Bigger *et al.* (5) have recommended the following dose schedule for prompt DPH effect:

Day	Dose (mg)
1	1,000
2	500–600
3	500–600
Thereafter	400–500

Where urgent indications exist, DPH may be given intravenously, 50-100 mg at 5 minute intervals until a therapeutic effect, a toxic effect, or 1,000 mg is given (5). If less than 1,000 mg is given IV, the rest of the loading dose may be given slowly IV or orally over the next 6-18 hours. Where less urgency exists, the 1,000 mg should be given orally over 6-18 hours.

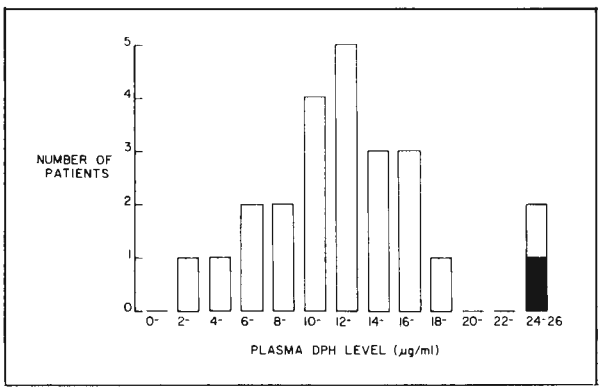

Fig. 7—Plasma levels at which ventricular arrhythmias were abolished. Plasma DPH concentrations are plotted on the abscissa. The number of patients whose arrhythmia was abolished in each range of plasma level is represented on the ordinate as unfilled bars. The one patient whose arrhythmia was unaffected by DPH is represented by the filled bar; this unresponsive arrhythmia was a typical ventricular parasystole. Seventy percent of the conversions occurred at plasma concentrations between 10 and 18 μg/ml. Only one patient required a plasma concentration above 18 μg/ml before conversion occurred. (Reproduced by permission of the American Heart Association from *Circulation,* 38:367, 1968, and J. T. Bigger, Jr.).

One last point needs to be made in regard to DPH. This is one of the very few currently available drugs for which generic non-equivalence exists. (Digoxin is the other important example.) Generic brands of DPH have been shown to result in *higher* serum levels than the first marketed product, Dilantin®. An "epidemic" of DPH toxicity occurred when the source of supply of DPH was changed to a generic product and its greater bioavailability resulted in toxic effects in previously stable patients with convulsive disorders (25). Patients on DPH should receive a single manufacturer's product.

Bretylium Tosylate. Bretylium tosylate, BT, is a drug of considerable current interest. It is available only on an investigational basis, *viz.,* it is not approved for marketing in this country.

Much of the action of bretylium can be understood in light of its effects on the sympathetic neuron. Norepinephrine is present in the terminal sympathetic neurons in two pools, a larger storage pool and a smaller labile pool. Bretylium tosylate does not affect the former, but its acute administration causes a sudden release of norepinephrine from the latter. This release of norepinephrine accounts for a number of the early effects of parenterally administered BT, such as the early transient hypertension, enhanced automaticity, and increased conduction velocity. The initial positive inotropic effect (increased myocardial contractility) is largely, if not totally due to this norepinephrine release. Chronic bretylium therapy does, however, cause a supersensitivity to circulating and infused epinephrine and norepinephrine since BT blocks the sympathetic neuronal uptake of these catecholamines, the major route of modulating the catecholamine-receptor action. This same uptake mechanism also accounts for a number of bretylium drug interactions as BT competes with tyramine, amphetamines, and metaraminol (Aramine®) for uptake. The tricyclic anti-depressants also block BT uptake and antagonize its effect, as they do, too, for guanethidine (Ismelin®).

Bretylium is excreted unchanged in the urine. Its serum half-life is unclear. Kuntzman *et al.* (13) studied four normal subjects and found a nonexponential decline of serum levels with the rate of

disappearance quite rapid early ($t_{1/2}$ = ±1 hour) and somewhat slower later ($t_{1/2}$ = ±5 hours). Romhilt and associates (22), using the serum method established by Kuntzman, studied eight patients. They found an exponential decline of serum levels with a $t_{1/2}$ = 10 hours (fig. 8). There was no apparent relationship between the $t_{1/2}$ and the levels of BUN in this latter study, and personal communication failed to resolve this discrepancy. The $t_{1/2}$ value for bretylium tosylate may not be critical, however, since, as shown in figure 8, there is a temporal disparity between the serum levels and the antiarrhythmic efficacy. Bretylium tosylate may, therefore, be one of the so-called "hit-and-run" drugs (12). On the other hand, there appears to be an excellent correlation between the hypotensive effects and the serum levels of this "peripheral sympathetic blocker." This temporal dispersion of hypotensive and antiarrhythmic action prompted these authors (22) to suggest that BT's antiarrhythmic effect may not be related to its action on the sympathetic neuron.

There are both animal and human data to suggest that other antiarrhythmic drugs antagonize the effects of bretylium. Bernstein and Koch-Weser (4) found that patients concurrently receiving other antiarrhythmic drugs were less likely to respond to BT, confirming the observations of Bacaner (2) in experimental animals. Therefore, it would appear wise to discontinue all other antiarrhythmics when initiating bretylium therapy.

Bernstein and Koch-Weser (4) noted the following incidence of adverse effects:

Side Effects of Short-Term Bretylium Therapy in 30 Patients

	%
Hypotension	63
Hypertension	17
Initial increase in arrhythmias	13
Nausea or vomiting	10
Involuntary head movements	3
Headache	3

In only one of the 19 patients with hypotension did the decline in blood pressure exceed 20 mm Hg. As these patients were recumbent and as the hypotensive effect of BT is largely orthostatic, such results could be anticipated (*vide infra*). Transient hypertension and transient enhanced automaticity (increase in arrhythmias) were surely related to the initial release of norepinephrine. Nausea and vomiting are rare with intramuscular administration, but common if bretylium is given intravenously.

Chronic oral administration commonly produces severe, persistent parotid pain during mastication. This pain is of sufficient magnitude to be the major cause for discontinuing chronic oral therapy. Postural hypotension is a problem early, but tolerance to this action develops fairly promptly.

The clinical role of bretylium is still unclear, but the drug may find a place in the management of recurrent severe ventricular tachyarrhythmias, *viz.*, ventricular tachycardia, and ventricular fibrillation. Bacaner reviewed 250 reported cases of ventricular tachyarrhythmias (1). Eighty-five percent re-

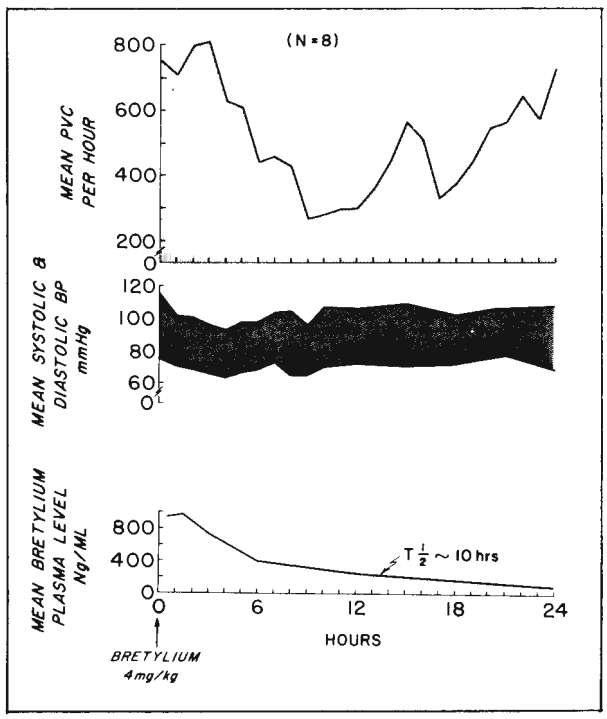

Fig. 8—Comparison of the onset and duration of action of bretylium, 4 mg/kg, on PVC frequency and arterial pressure in relation to blood levels. On the average, hypotensive effect was present in the first hour, when mean plasma concentration of bretylium was at its peak, and continued until the ninth hour after administration. By contrast 50% suppression of mean PVC frequency began at the sixth hour and continued until the 18th hour. The mean elimination half-life of bretylium was about 10 hours. N refers to number of patients. (Reproduced by permission of the American Heart Association from *Circulation,* 45:804, 1972, and D. W. Romhilt).

sponded favorably. Romhilt *et al.* (22) continuously monitored eight patients with frequent premature ventricular contractions (fig. 9). The effectiveness of bretylium tosylate, 4 mg per kg intramuscularly, is evident after a six-hour lag. Bernstein and Koch-Weser (4) found an excellent response in 18 of 30 patients with ventricular tachycardia unresponsive to other drugs. Five patients had a partial response and in seven, no response was evident. Those failing to respond were more often receiving other antiarrhythmic drugs concurrently and were more likely to have had the arrhythmia for a longer period of time. These authors rightly caution against an over zealous interpretation of these data, noting that had these patients been first treated with bretylium, the failures could well have responded to whatever the second drug might have been.

One negative report is noteworthy. Taylor *et al.* (24) studied 101 patients during acute myocardial infarction. Sixty-three patients received bretylium, 300 mg IM every 6 hours. In 25 of the 63, therapy was discontinued because of adverse effects, four due to nausea and vomiting and 21 due to hypotension. In these 21 patients, blood

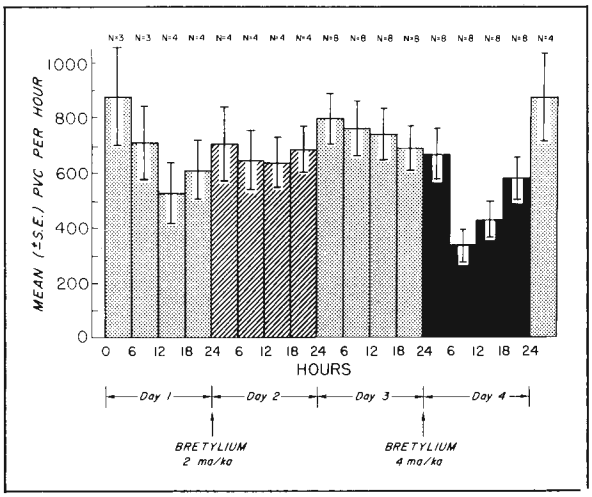

Fig. 9—Mean PVC frequency during treatment days compared with control days. There was 50% supression of mean PVC frequency in the second and third 6-hour intervals following bretylium 4 mg/kg (solid bars), while no suppression was seen after 2 mg/kg (shaded bars). Control days are shown in stippled bars. N refers to number of patients. On day 1, data were not obtained in one patient during the first 12 hours due to recording-equipment failure. (Reproduced by permission of the American Heart Association from *Circulation,* 45:805, 1972, and D. W. Romhilt).

pressure averaged 65/40 mm Hg, a marked degree of hypotension for patients with acute infarction. It is likely that the unstable state of the circulation in such patients and their use of bedside commodes, thus enhancing orthostasis, accounts for the strikingly higher incidence of significant degrees of hypotension than those noted in the table above. Furthermore, among those who continued BT therapy, there was no decrease in ventricular arrhythmias. Supraventricular arrhythmias, however, were less in the treated group. Again, one patient died in each of the treated and control groups.

Finally, the role of bretylium tosylate in the management of digitalis-induced ventricular tachyarrhythmias should be considered. Our group (20) infused ouabain in a group of ten dogs. In half, the ouabain was continued until stable ventricular tachycardia was established. Bretylium was then given in incremental doses, beginning with 5 mg per kg and increasing to 40 mg per kg total dose. In every dog, the ventricular tachycardia not only persisted, but indeed, the ventricular rate accelerated. Furthermore, when the ouabain infusion was stopped at the time frequent ventricular premature contractions had occurred, bretylium, in each of the five dogs, promptly induced ventricular tachycardia (fig. 10). This augmentation of automaticity by BT was also noted by Kleiger and Shander (11). They produced ventricular tachycardia in dogs with acetylstrophanthidin (another cardiac glycoside). When the tachycardia had subsided spontaneously after cessation of the glycoside, they administered bretylium and a recurrence of the ventricular tachycardia ensued. Both of these animal studies were completed before the time of maximal antiarrhythmic efficacy of BT, but they indicate the potential danger during the period of initiation of such therapy.

In conclusion, time and space have not allowed a classical pharmacological discussion of these four important antiarrhythmic drugs. In order to use a drug rationally so as to obtain a maximum efficacy:toxicity ratio, one must understand the drug's absorption, its route and mechanism of biotransformation, and its effective half-life. Such data are available for the antiarrhythmic drugs.

Where the achievement of one's therapeutic goal is so readily measurable, as it is with antiarrhythmic drugs, we must demand of ourselves a more knowledgeable and rational therapeutic approach.

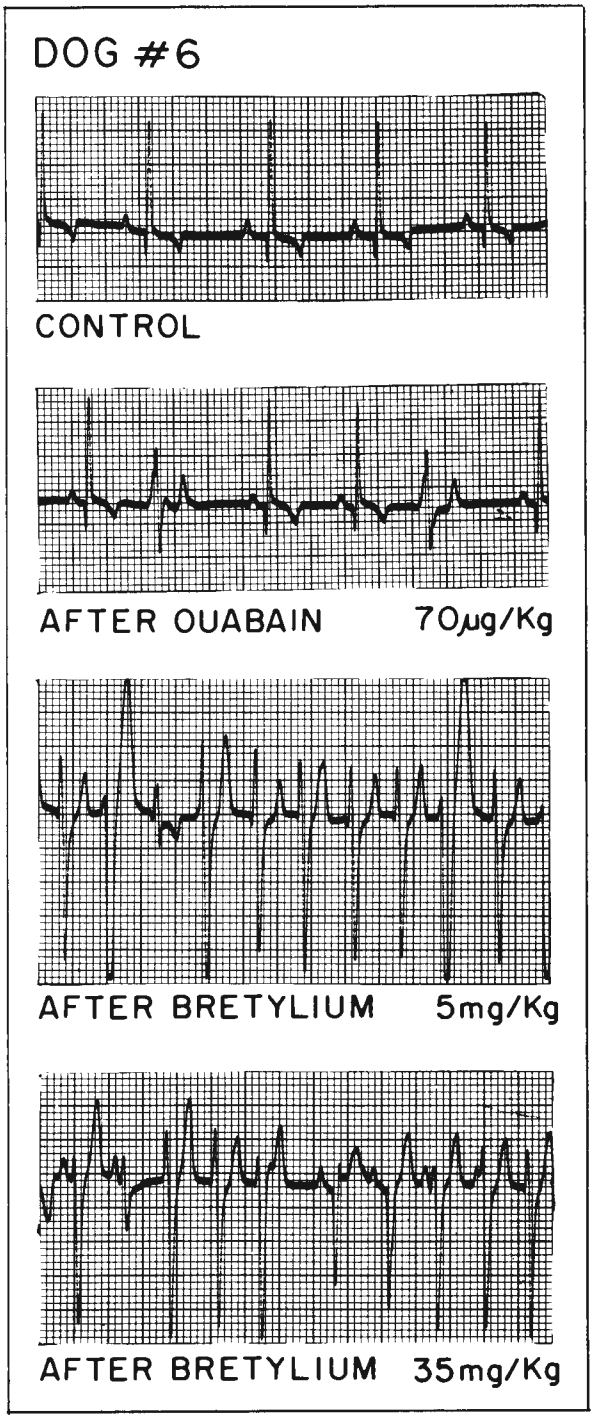

Fig. 10—Ouabain was given to this dog until frequent premature ventricular contractions developed. Treatment, then, with bretylium induced ventricular tachycardia.

REFERENCES

1. BACANER, M. Experimental and clinical effects of bretylium tosylate on ventricular fibrillation, arrhythmias, and heart-block. *Geriatrics* 26:132–148, 1971.

2. BACANER, M. B. Quantitative comparison of bretylium with other antifibrillatory drugs. *Amer. J. Cardiol.* 21:504–512, 1968.

3. BELLET, S., ROMAN, L. R., AND BOZA, A. Relation between serum quinidine levels and renal function. *Amer. J. Cardiol.* 27:368–371, 1971.

4. BERNSTEIN, J. G. AND KOCH-WESER, J. Effectiveness of bretylium tosylate against refractory ventricular arrhythmias. *Circulation* 45:1024–1034, 1972.

5. BIGGER, J. T., JR., SCHMIDT, D. H., AND KUTT, H. Relationship between the plasma level of diphenylhydantoin sodium and its cardiac antiarrhythmic effects. *Circulation* 38:363–374, 1968.

6. BJERKELUND, C. AND SKALAND, K. Quinidine-induced paroxysmal ventricular fibrillation. *Nord. Med.* 77: 76–81, 1967.

7. BLOOMFIELD, S. S., *et al.* Quinidine prophylaxis of arrhythmias in acute myocardial infarction. *New Eng. J. Med.* 285:979–986, 1971.

8. Collaborative Group. Phenytoin after recovery from myocardial infraction. *Lancet* II:1055–1057, 1971.

9. GERHARDT, R. E., *et al.* Quinidine excretion in aciduria and alkaluria. *Ann. Int. Med.* 71:927–933, 1969.

10. GOODMAN, L. S. AND GILMAN, A. *The Pharmacological Basis of Therapeutics.* 4th edition, New York, The Macmillan Company, 1970.

11. KLEIGER, R. E. AND SHANDER, D. Bretylium tosylate in acetylstrophanthidin-induced ventricular tachycardia. *Circulation* (suppl. III):III–174, 1970.

12. KOCH-WESER, J. Drug therapy: serum drug concentrations as therapeutic guides. *New Eng. J. Med.* 287: 227–231, 1972.

13. KUNTZMAN, R., *et al.* Disposition of bretylium in man and rat. *Clin. Pharmacol. Ther.* 11:829–837, 1970.

14. KUTT, H. AND MCDOWELL, F. Management of epilepsy with diphenylhydantoin sodium. *JAMA* 203:167–170, 1968.

15. LETTERI, J. M., *et al.* Diphenylhydantoin metabolism in uremia. *New Eng. J. Med.* 285:648–652, 1971.

16. LOWN, B AND WOLF, M. Approaches to sudden death from coronary heart disease. *Circulation* 44:130–142, 1971.

17. MELMON, K. L. AND MORRELLI, H. F. *Clinical Pharmacology*. New York, The Macmillan Company, 1972.

18. MERCER, E. N. AND OSBORNE, J. A. The current status of diphenylhydantoin in heart disease. *Ann. Int. Med.* 67:1084–1107, 1967.

19. PROCTOR, J. D., ALLEN, F. J., AND WASSERMAN, A. J. Cardiovascular effects of equi-antiarrhythmic doses of alprenolol (a beta-adrenergic receptor antagonist), diphenylhydantoin, and procainamide. *Arch. Int. Pharmacodyn.* 190:354–367, 1971.

20. PROCTOR, J. D., BAIRD, C. L., AND WASSERMAN, A. J. Adverse effect of bretylium in ouabain-induced ventricular tachyarrhythmias. *Circulation* (suppl. III): III–190, 1970.

21. RICHARDSON, D. W., ZEE, M. E., AND WYSO, E. M. Maintenance quinidine therapy. Value of enteric-coated quinidine tablets. *Amer. J. Cardiol.* 5:417–420, 1960.

22. ROMHILT, D. W., *et al.* Evaluation of bretylium tosylate for the treatment of premature ventricular contractions. *Circulation* 45:800–807, 1972.

23. SELZER, A AND WRAY, H. W. Quinidine syncope. *Circulation* 30:17–26, 1964.

24. TAYLOR, S. H., *et al.* Bretylium tosylate in prevention of cardiac dysrhythmias after myocardial infarction. *Brit. Heart J.* 32:326–329, 1970.

25. TYRER, J. H., *et al.* Outbreak of anticonvulsant intoxication in Australian city. *Brit. Med. J.* 4:271–272, 1970.

PANEL DISCUSSION

Dr. Surawicz: I use quinidine less, and some people have stopped using it. This is actually the only true antiarrhythmic drug because it is the only drug that will reasonably consistently convert atrial fibrillation to sinus rhythm. As Dr. Hoffman pointed out, its effect on conduction would have predictable effects on the electrocardiogram in terms of prolongation of the QRS complex and the P-R interval, and with increasing concentration of the drug, which is increasing the dose, we have evidence of increasing

Addendum 1

ANTIARRHYTHMIC DRUGS

Name of Drug	EFFECT OF DRUG ON HEART: Automaticity Atrium	Automaticity Ventricle	Conduction Velocity	Refractory Period	Inotropic State	Autonomic Effects	Therapeutic Plasma Levels μg/ml
Quinidine	↓	↓	↓	↑	↓	Vagolytic	3–6
Procainamide (Pronestyl®)	↓	↓	↓	↑	↓	Vagolytic	4–8
Lidocaine (Xylocaine®)	0	↓	0	↓	0	0	2–5
Propranolol (Inderal®)	↓	↓	↓	↓	↓↓	Beta-adrenergic Blocking	.05–.15
Diphenylhydantoin (Dilantin®)	↓	↓	↑	↓	0	0	6–18
Bretylium (Darenthin®)	Initial↑	Initial↑ then↓(?)	Initial↑ then O	Initial↓ then↑	Initial↑	NE Release Followed by Sympath Block	—

prolongation of P-R and QRS intervals. This is a dose related toxicity that we can avoid by keeping our doses down. Dr. Wasserman discussed the quinidine induced ventricular fibrillation and pointed out that this is not necessarily a dose related effect. This occurs when the concentrations are therapeutic and the QRS interval is not widened and the P-R is not prolonged. Therefore, we have no warning, and that is much more frightening because this cannot be avoided. Now, does that mean that we should stop using quinidine? I, of course, asked that question and observed some quinidine syncope, the same kind of record as was shown from Dr. Selzer's and Dr. Wray's paper. Then I reviewed all available data on quinidine toxicity and came to the conclusion that all published reports that I have been able to review showed three things: first, all people had severe heart disease; second, all people were treated with digitalis; and third, in spite of quinidine syncope not being dose related, they all received more than 1.2 g of quinidine per day. I concluded that I have not had any evidence that lower doses will induce fibrillation. On that basis I still use quinidine, and I wonder whether you would like to comment on that.

Dr. Wasserman: Yes. In some of the cases it is clear that preceding the fibrillation there was prolongation of the Q-T interval; thus, whether or not this is predictable in the majority of cases, I do not know. It certainly would be in some, and it is for this reason that we are monitoring. I can tell you about a case in which a young lady who had no heart disease whatsoever was erroneously treated for VPC's which I am sure in retrospect were due to alcoholism. In the absence of digitalis and with standard doses she developed this syndrome. She was shocked 20 or 30 times with typical findings. We did not have a quinidine level in her, but her renal function was normal, her heart was normal, and we simply stopped the drug. Within the usual six hour period, actually four hours, she stopped having ectopic activity and stopped her recurrent bouts of ventricular fibrillation. Subsequently, we have found normal and even low levels of serum quinidine in patients exhibiting quinidine syncope, including cases where syncope followed a single usual initial dose of quinidine.

Questioner: Did your alcoholic patient have hypokalemia?

Dr. Wasserman: No, she did not. As a matter of fact, she came in with pelvic inflammatory disease but unfortunately was seen by a medical intern who was certain that he knew how to take care of her

Biotransformation	Plasma Half-Life $t_{1/2}$	Peak Effect Time		Dosage		Adverse Effects (See Heart Effects)
		p.o.	i.v.	p.o. (gm)	i.v. (mg)	
Renal 10–50% (↓if ↑urine pH) Liver	4–6 hr.	2–4 hr.	5 min.	0.4 × 1; 0.2–0.4q 6 hr.	25/min. to 1000	"Syncope"; Shock; Hemolysis; Thrombocytopenia; G-I Sx; Paralysis; Cinchonism
Renal 60% (↓if ↑urine pH)	3–4 hr.	1 hr.	Stat	1.0 × 1; 0.5q 3 hr.	50/min. to 1–2,000	Lupus; Shock; ? Syncope; Agranulocytosis; G-I Sx; Psychosis; Paralysis
Liver	2 hr.	—	Stat	—	50-100 Stat 1–4/min.	Twitching, Seizures; CNS Depression; Shock
Liver	±3 hr.	few hrs.	10 min.	.04 × 1; .01–.03q 6 hr. ?	0.1/min. to 10	Heart failure; Bronchospasm; Hypoglycemic Unresponsiveness; Rash; G-I Sx
Liver	18–24 hr. average	1–2 hr.	5 min.	1.0 first day 0.5 next day then 0.4/day	50–100mg 5/min. to 1,000	Ataxia; Sedation; Gums; Lymphoma: Lupus; Rash; Folate Def; Hepatitis; Osteomalacia; Thyroiditis Nystagmus
Renal	±10 hr.	hrs.	15 min.	.3–.6q 8–12 hr.	4–5 mg/Kg	Initial Tachycardia; Postural Hypotension; Parotid pain; Vomiting I.V.

Addendum 2

DIPHENYLHYDANTOIN DRUG INTERACTIONS

I. DRUGS LEADING TO INCREASED DPH EFFECT AND TOXICITY	
DRUGS	MECHANISM
A. Bishydroxycoumarin (Dicumarol®)	Inhibition of liver metabolism
B. Disulfiram (Antabuse®)	Inhibition of liver metabolism
C. Isoniazid	Not definite—probably inhibition of liver metabolism
slow-inactivators	
D. PAS	Unknown—Possibly due to its increased blood levels of concommitant INH
E. Phenylbutazone (Butazolidin®)	Binding displacement of DPH
F. Phenyramidol (Analexin®)	Inhibition of liver metabolism
G. Sulfaphenazole (Sulfabid®) and Sulthiame (Ospolot®)	Unknown
H. Salicylates	Binding displacement of DPH
I. Chloramphenicol	Inhibition of liver metabolism
J. Benzodiazepines	Unknown
K. Methylphenidate (Ritalin®)	Not definite—probably inhibition of liver metabolism
II. DRUGS LEADING TO DECREASED DPH EFFECT AND TOXICITY	
A. Phenobarbital	Increased hepatic microsomal metabolism
B. Amphetamines	Decreased absorption of DPH
C. Alcohol	Increased liver metabolism of DPH

III. DPH'S EFFECT ON OTHER DRUGS		
DRUGS	EFFECT	MECHANISM
A. Coumarin Anticoagulants	Enhancement	Not definite—probably binding displacement
B. Corticosteroids	Inhibition	Increased microsomal metabolism
C. Methotrexate	Enhancement	Binding displacement
D. Vitamin D	Inhibition	Increased liver metabolism of Vit. D

VPC's. Of course when she developed the first episode of ventricular fibrillation, he concluded that he simply had not given her enough. She received two doses of quinidine, but that was all.

Dr. Dreifus: I too use quinidine. I just want to mention two things. The first point Dr. Surawicz already inferred was low potassium, and this seems to be one of the settings in which I have seen this repetitive ventricular tachycardia with quinidine and with other antiarrhythmic drugs that prolong Q-T intervals. The second point, which is much more serious, is acute coronary insufficiency with very long Q-T intervals. It is usually seen on the basis of sinus bradycardia. These patients do worse with quinidine or procainamide because you may move the premature systole into the long Q-T interval. The VPC will bisect the T wave, and then ventricular fibrillation or runs of ventricular tachycardia occur. Actually, the only way to deal with such patients is to pace them. The reason I wanted to mention this is, if patients at high risk were on a prophylactic agent and quinidine or a congener of quinidine was one on these agents, the patients who were tending to develop long Q-T intervals with their bouts of coronary insufficiency might be more vulnerable to sudden death. This is a very serious problem, and I think when you use quinidine you have to take all these facts into consideration if you want to avoid mistakes.

Dr. Dreifus: I would like to ask Dr. Wasserman if he feels that bretylium has any membrane effects as an antiarrhythmic agent.

Dr. Wasserman: Yes. The problem of course has been to forget the initial articles, all of which were merely reflecting the release norepinephrine. I think it is quite clear that it does have direct myocardial effects. It certainly does so in the absence of norepinephrine depleted by pretreatment reserpine or guanethidine, and it has effects which differ from guanethidine in terms of the ventricular fibrillation threshold which suggests that it is not simply the depletion of catecholamines. Thus, I think it clearly must have some effect. I think its role is not yet clear, and I think we need to know more about it before we can use it wisely.