A COMPARISON OF ACTIVITY OF QUININE AND QUINIDINE ON THE ISOLATED ELECTRICALLY STIMULATED RAT VENTRICLE STRIP

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In isolated and electrically stimulated rat ventricle strips, the activity of quinine and quinidine sulphate on excitability, rheobase and maximal rate of stimulation has been measured. By testing the two drugs on the same preparation at the same concentrations, from 5×10^{-6} to 3×10^{-5}, no statistically significant difference was detected in the relative potency of the two drugs. These findings are discussed in relation to the observed clinical inactivity of quinine.

THE first observations on the antiarrhythmia activity of cinchona alkaloids in man are attributed to Wenckebach (1923). Frey (1918) showed later the higher activity of quinidine. The superiority of quinidine over quinine in auricular fibrillation was thereafter generally accepted, but the experimental evidence for this superiority is scanty. Alexander, Gold, Katz, Levy, Scott and White (1947) reported a clinical trial on patients with cardiac arrhythmias in which quinine was clearly inferior to quinidine. More recently Benthe (1956) reported quinidine to be a little more active than quinine on conduction velocity and on absolute refractory time in the ventricle strip of the frog.

In the present work we have studied the relative activity of quinine and quinidine on excitability, rheobase and on the maximal rate of stimulation (Dawes, 1946) using the rat right ventricle strip.

METHOD

Strips of the right ventricle of adult albino rats (Feigen, Masuoka, Thienes, Saunders and Sutherland, 1952) were placed on the electrode unit of Alles and Ellis (1948) in a bath at 32° with Krebs-Henseleit solution, and stimulated by square pulses from a Grass stimulator. The displacement of an optical level was projected on a screen and used as an index of adequate stimulus. Recordings were made before and after 30 min. contact with the drug.

A complete curve of excitability was obtained by plotting the voltages of stimulation against duration (from 100 to 0·01 msec.). The equation of Weiss (1901) and Hoorveg (1892)

$$V = a/t + R \quad .. \quad .. \quad .. \quad .. \quad .. \quad .. \quad (1)$$

where V = voltage; t = duration (in msec.); a = constant; R = rheobase, was transformed in a linear equation as follows, to permit an easier calculation.

$$2 + \log (V - R) = A + B (2 + \log 1/t) \quad .. \quad .. \quad (2)$$

The slope B of the straight line (2) is not affected by the presence of an antifibrillatory drug; it is therefore possible to express the action of the

drug by measuring the displacement of the straight line (Libonati and Segre, 1960). The straight line (2) was calculated from the experimental values by the method of least squares (Figs. 1 and 2).

The per cent effect of a drug on the excitability is given by

$$100\ \frac{(V - R)' - (V - R)}{(V - R)}$$

where $(V - R)$ = the difference between voltage and rheobase, the voltage being calculated from equation (2) at 1 msec.; and $(V - R)'$ = the same difference in presence of the drug.

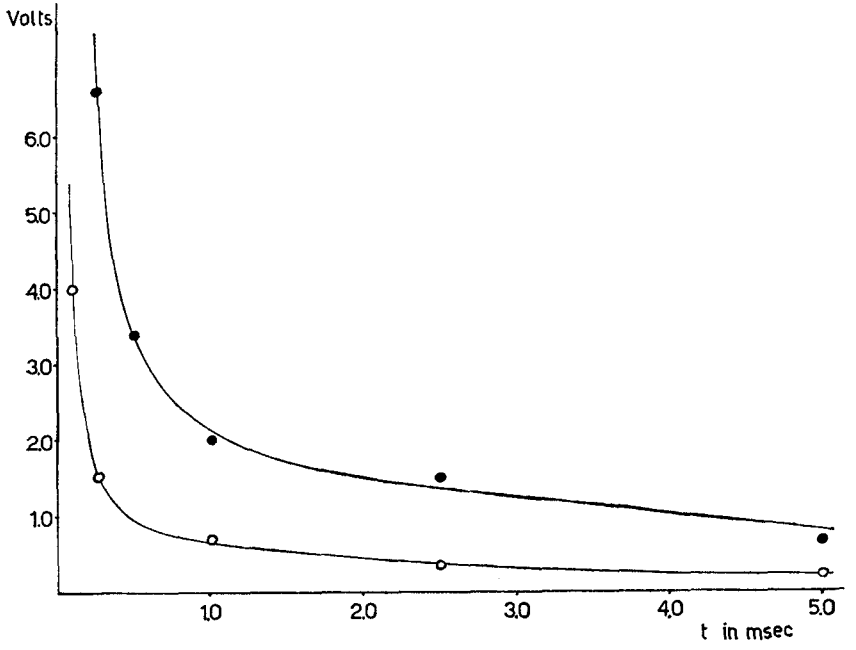

FIG. 1. Effect of quinidine sulphate (3×10^{-5}) ●—● on excitability curve ○—○.

The value of the rheobase was obtained by the same excitability curve and corresponds to the voltage applied for 100 msec.

The per cent effect of a drug on the rheobase was

$$100\ \frac{R' - R}{R}$$

where R = rheobase and R′ = rheobase in presence of the drug.

The maximal rate of stimulation (MRS) was determined at 5 V and 1 msec.; MRS can be accurately estimated because of an abrupt change in the rhythm of the contractions by overcoming the maximal rate.

The per cent effect of a drug on MRS was calculated as

$$100\ \frac{MRS - MRS'}{MRS}$$

where MRS′ = MRS in presence of the drug.

COMPARISON OF ACTIVITY OF QUININE AND QUINIDINE

The drugs used were commercial samples of quinidine sulphate and quinine sulphate. No difference in relative potency was detected whether quinine or quinidine was first introduced into the bath.

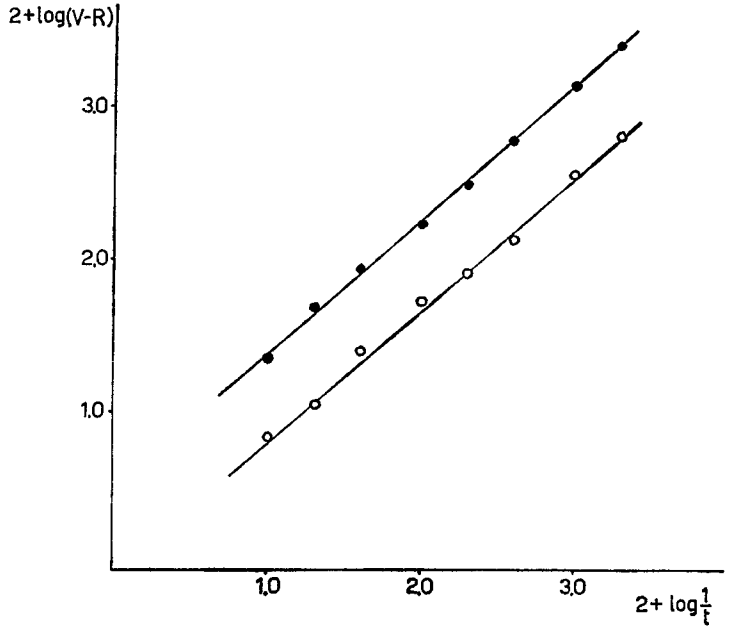

FIG. 2. Linear transformation of the values of the experiment of Fig. 1.

TABLE I

EFFECTS OF QUINIDINE AND OF QUININE ON THE EXCITABILITY CURVE

Concentration	Effect of quinidine (per cent) (A)	Effect of quinine (per cent) (B)	A − B	t	P
5×10^{-6}	0·00	0·00	0·00		
	15·93	12·23	+3·70		
	33·13	64·25	−31·12		
	10·17	0·00	+10·17		
	42·41	62·60	−20·19		
	31·60	4·47	+57·13	0·26	>0·8
1×10^{-5}	18·16	17·90	+0·26		
	25·30	43·48	−18·18		
	7·20	8·94	−1·74		
	12·83	0·00	+12·83		
	96·25	34·57	+61·68	0·80	>0·4
2×10^{-5}	15·82	17·13	−1·31		
	95·07	279·83	−184·76		
	124·56	163·56	−39·00		
	36·65	132·44	−95·79		
	58·68	97·15	−38·47		
	47·36	13·47	+33·89		
	500·66	26·03	+474·63	0·27	>0·7
3×10^{-5}	289·50	106·25	+183·25		
	656·00	57·81	+598·19		
	671·70	370·47	+301·23	2·32	>0·1
		On the total		1·41	>0·1

RESULTS

Tables I, II and II show the effects produced in 21 experiments on each parameter by the two drugs. (A — B) indicates the difference (per cent) of the effect between the two drugs on the same preparation. These differences were statistically analysed by the Student's "*t*" test at each concentration and for all the values of the tables. The levels of significance do not show difference ($P > 0.05$) between quinine and quinidine as far as the three parameters are concerned.

By using the Lineweaver and Burk (1934) double reciprocal transformation, the values obtained for excitability and MRS enable the best

TABLE II

EFFECTS OF QUINIDINE AND OF QUININE ON RHEOBASE

Concentration	Effect of quinidine (per cent) (A)	Effect of quinine (per cent) (B)	A − B	*t*	P
5×10^{-6}	8·69	0·00	+8·69		
	17·07	0·00	+17·07		
	23·81	25·00	−1·19		
	100·00	95·83	+4·17		
	26·47	35·29	−8·82		
	17·39	13·64	+3·75	1·10	>0·3
1×10^{-5}	4·35	0·00	+4·35		
	46·70	0·00	+64·70		
	12·19	6·00	+6·19		
	118·51	139·28	−20·77		
	88·57	76·47	+12·10	0·95	>0·3
2×10^{-5}	7·14	20·00	−12·86		
	11·54	0·00	+11·54		
	72·73	68·00	−4·73		
	500·00	28·00	+472·00		
	9·37	21·05	−11·68		
	65·91	44·44	+21·47		
	5·26	0·00	+5·26	1·02	>0·3
3×10^{-5}	247·83	190·91	+56·92		
	400·00	58·82	+341·18		
	284·61	233·33	+51·28	1·56	>0·2
		On the total		1·81	<0·05 >0·1

straight line to be calculated between 1 ÷ per cent effect (y) and 1 ÷ concentration $\times 10^5$ (x) for the two drugs; one obtains:

	Quinidine	Quinine
Excitability ..	$y = 0.01374 + 0.02303x$	$y = 0.006271 + 0.04072x$
MRS	$y = 0.00633 + 0.02439x$	$y = 0.00163 + 0.03757x$

Putting now $y = 0.04$, the concentrations giving 25 per cent effect may be derived.

	Quinidine	Quinine
Excitability ..	$x = 0.8770 \times 10^{-5}$	$x = 1.2074 \times 10^{-5}$
MRS	$x = 0.7244 \times 10^{-5}$	$x = 0.9025 \times 10^{-5}$

It is seen that these values are very similar, agreeing with the estimate non-significance yielded by the *t* test.

At high dosage levels it was noticed that quinidine displayed a more marked negative inotropic effect.

Discussion

The effects of quinidine on excitability, rheobase and MRS correspond to those found in this laboratory with the same method (Libonati and Segre (1960).

The findings of Benthe (1956) on the ventricular strips of the frog show that quinidine is a little more active than quinine at two concentrations, 10^{-5} and 10^{-4}, on the absolute refractory period; however, the experimental

TABLE III

EFFECTS OF QUINIDINE AND OF QUININE ON MAXIMAL RATE OF STIMULATION

Concentration	Effect of quinidine (per cent) (A)	Effect of quinine (per cent) (B)	A − B	t	P
5×10^{-6}	25·00	13·95	+11·05		
	11·82	16·00	−4·18		
	17·39	34·78	−17·39		
	30·00	35·94	−5·94		
	38·23	7·69	+30·54		
	12·76	8·00	+4·76	0·75	>0·4
1×10^{-5}	37·50	30·23	+7·27		
	34·40	40·00	−5·60		
	29·09	40·95	−11·86		
	34·00	35·13	−1·13		
	16·00	17·64	−1·64	1·31	>0·2
2×10^{-5}	54·00	100·00	−46·00		
	32·29	60·00	−27·71		
	52·17	100·00	−47·83		
	100·00	40·42	+59·58		
	44·17	30·00	+14·17		
	92·64	100·00	−7·36		
	82·76	55·00	+27·76	0·48	>0·7
3×10^{-5}	89·23	58·26	+30·97		
	100·00	100·00	0·00		
	100·00	100·00	0·00	0·81	>0·5
		On the total		0·08	>0·9

conditions and the test used were different from ours and he did not investigate the relative activities of the two drugs on the parameters investigated by us.

Only one clinical trial has been reported, in which the activity of the two drugs has been compared in man (Alexander and others, 1947); this trial showed no appreciable therapeutic activity of quinine. On the other hand it must be remembered that in the standard books of pharmacology and therapy no mention is made to the use of quinine in cardiac arrhythmias which is also true of a recent review on the clinical treatment of atrial fibrillation (Migheli, 1958).

The experimental results of the present work do not show differences in potency between quinine and quinidine on the excitability parameters in isolated rat ventricle. To explain the discrepancy between the experimental and the clinical findings it might be worth while to make a controlled clinical trial in which the absorption rate, the distribution in blood and myocardium, the excretion and the inactivation rate of quinine and quinidine were compared.

REFERENCES

Alexander F., Gold H., Katz, L. N., Levy, R. L., Scott, R. and White, P. D. (1947). *J. Pharmacol.*, **90**, 191–201.
Alles, C. A. and Ellis, C. H. (1948). *Ibid.*, **94**, 416–425.
Benthe, H. F. (1956). *Arch. exp. Path. Pharm.*, **299**, 82–91.
Dawes, G. S. (1946). *Brit. J. Pharmacol.*, **1**, 90–112.
Feigen, G. A., Masuoka, D. T., Thienes, C. H., Saunders, P. R. and Sutherland, G. B. (1952). *Stanford Med. Bull.*, **10**, 27–31.
Frey, W. (1918). *Klin. W.*, **55**, 849–853.
Hoorveg, J. L. (1892). *Pflüger's Arch.*, **52**, 87–108.
Libonati, M. and Segre, G. (1960). *Arch. Ital. Sci. Farmacol.*, **25**, 166–180.
Lineweaver, H. and Burk, D. (1934). *J. Amer. chem. Soc.*, **56**, 658–666.
Migheli, B. (1958). *Omnia Therapeutica*, **9**, 225–267.
Weiss, M. G. (1901). *C.R. Soc. biol., Paris*, **53**, 466–468.
Wenckebach, K. F. (1923). *J. Amer. med. Ass.*, **81**, 472–474.