A study has been made of the antifibrillatory activity and acute cardiac toxicity of pentaquine phosphate, quinacrine hydrochloride, chloroquine phosphate, chlorguanide hydrochloride and pyrimethamine (Daraprim) as compared with quinidine sulfate and procaine amide. Such an investigation might uncover useful cardiac agents among the commonly available antimalarial drugs.

**Methods**

The procedure used to assay the potency of antifibrillatory drugs has been described by DiPalma and colleagues. A brief summary will suffice for this report. Cats weighing between 2 and 3 kg were anesthetized with intraperitoneal Dial (Ciba). Artificial respiration was maintained at an even level with a suitable pump, and the heart was exposed and suspended in a pericardial cradle. Clip electrodes were attached to the right atrium. A current of 600 impulses per minute was supplied by a thyratron stimulator. The current was conducted through a calibrated and variable resistance unit which permitted the determination of the liminal amount of current which would just induce atrial fibrillation. On the average this varied between 2 and 5 milliamperes.

In a typical assay the control fibrillation threshold expressed in milliamperes of current was determined at five-minute intervals until variation was not more than 5 per cent. The drug to be assayed was then injected in the femoral vein. Individual doses of each drug given are shown in table 1. Following the injection the fibrillation threshold was determined immediately and after 10 and 20 minutes. It was usually possible to test the same drug in the same animal once or twice more, but in no instance was one animal used for more than one drug. After the assay of antifibrillatory potency, it was possible to determine the acute cardiac toxicity of the drug under study by injecting the antifibrillatory dose intravenously at intervals of one minute until cardiac arrest occurred.

**Results**

The results are summarized in table 1. Quinidine and procaine amide serve as standards of comparison and, as shown, both have considerable antifibrillatory potency. Quinidine caused
a rise in electrical fibrillation threshold of 88 per cent. This may be contrasted to a rise of 151 per cent for procaine amide. The intravenous toxicity of procaine amide is much less than that of quinidine. Since the antifibrillatory action of quinidine is established, its therapeutic index is arbitrarily set at one and, using the formula,

\[
\text{Therapeutic Index} = \frac{\text{Potency of Quinidine}}{\text{Toxicity of Quinidine}} \cdot \frac{\text{Toxicity of Unknown}}{\text{Potency of Unknown}}
\]

it may be seen that, compared to quinidine, procaine amide ought to be a superior drug for atrial fibrillation. However, this method of analysis applies only to intravenous use and does not apply to the oral use where absorption and distribution factors might alter the outcome. Also to be noted is the fact that the effective dose of procaine amide is double that of quinidine.

The next group of drugs which can be considered together are quinacrine, chloroquine and pentaquine. All are essentially similar in side-chain substitution. Quinacrine differs in that the aromatic portion is an acridine instead of a quinoline ring. In table 1, it is shown that, on the average, quinacrine increased the fibrillation threshold 221 per cent, chloroquine 349 per cent and pentaquine 347 per cent. It is thus seen that these drugs have very high antifibrillatory potentials. However, their intravenous toxicity for the heart is also great, and hence their therapeutic index is low compared to procaine amide.

The third group of drugs include chlorguanide and Daraprim. These compounds differ markedly in chemical structure from the other antimalarials studied and, as shown in table 1, their antifibrillatory potency is negligible.

**Discussion and Summary**

The results indicate quite clearly that, at the dose level used, quinacrine hydrochloride, chloroquine diphosphate and pentaquine phosphate are very effective against atrial fibrillation in the cat when compared to procaine amide and quinidine. However, their acute intravenous toxicity is also quite high. Chlorguanide hydrochloride and Daraprim are equally effective drugs against the Plasmodia, but are ineffective antifibrillatory agents. In this regard it may be pointed out that the former drugs are regarded as owing their therapeutic effectiveness to their ability to inhibit carbohydrate and respiratory metabolism of the malarial parasite, while the latter drugs are considered to affect folic acid metabolism. This might provide a clue to the mechanism of action of antifibrillatory drugs, suggesting that the desirable effect might reside in inhibition of carbohydrate metabolism of heart muscle.

**Reference**

Comparison of Antifibrillatory Potency of Certain Antimalarial Drugs with Quinidine and Procaine Amide
FRANK BURNO, FRANK BURSTEIN and JOSEPH R. DIPALMA

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