Phenytoin in Post-operative Cardiac Arrhythmias

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Harris and Kokernot (1950), using the rationale that the mechanism of formation of ectopic cardiac rhythms might be analogous to seizure activity in the central nervous system, successfully showed the anti-arrhythmic action of phenytoin in experimentally induced ventricular arrhythmias. Its value in experimental arrhythmias was later confirmed by Mosey and Tyler (1954), Covino, Wright, and Charleson (1955), White, Megirian, and Swiss (1955), Scherf *et al.* (1960), and Bose, Saifi, and Sharma (1963).

Leonard (1958) reported the first successful documented clinical use of phenytoin in the treatment of recurrent ventricular tachycardia complicating myocardial infarction which proved refractory to other treatment. Clinical interest lay dormant till Osborne in 1964 mentioned its use in the treatment of arrhythmias occurring after cardiac operations and cardiac catheterization. More recently, Bernstein *et al.* (1965), Conn (1965), Ruthen (1965), Karliner (1967), Bashour *et al.* (1968), and Bigger, Schmidt, and Kutt (1968) have shown its success in the treatment of clinical cardiac arrhythmias particularly associated with digitalis toxicity. The purpose of this presentation is to report on the clinical use of phenytoin in the management of arrhythmias after cardiac operations.

SUBJECTS AND METHODS

The effect of the drug was tried on 14 patients who developed a variety of arrhythmias after open heart surgery. The group included 5 men and 9 women, whose ages ranged from 22 to 65 years. Thirteen of them had Starr Edwards prosthetic valve replacement (7 mitral, 3 aortic, 1 mitral and aortic, 1 mitral and tricuspid, and 1 triple valve), and 1 of them had closure of secundum atrial septal defect. Four patients were in sinus rhythm and the rest had atrial fibrillation before operation. The arrhythmias occurred from 2 to 30 hours after operation. Only 2 patients were on small maintenance doses of digoxin, and probably this was

not related to the development of the arrhythmia. Serum potassium was measured in all cases, and its level ranged between 3.0 to 5.5 mEq/litre.

Phenytoin in a dose of 250 mg. was diluted in 5 ml. solvent and 1 ml. was intravenously administered every minute until the satisfactory response was achieved. The electrocardiogram was monitored during and after administration of the drug. If the arrhythmia recurred after a good response, a further dose of 250 mg. was slowly injected. The patients who needed a dose larger than 250 mg. of intravenous phenytoin were put on an oral maintenance daily dose of 400 mg. for a period of 48 hours. Success was defined as the cessation or unequivocal amelioration of the arrhythmia, with the return of the electrocardiogram to the normal or pre-arrhythmic state.

RESULTS

Eleven patients had multiple ventricular extrasystoles; in 2 of these it produced bigeminy and in 1 it was associated with short runs of ventricular tachycardia. Of the remaining 3 patients, 1 had recurrent ventricular tachycardia and 2 had nodal tachycardia. The therapeutic response (Fig.) was satisfactory in all but one. In general the response was rapid, frequently occurring during the administration of the drug but in some patients success was not obtained until after the full dose had been given. In 2, the response was seen about 5 minutes after the injection. One patient only required a total intravenous dose of 175 mg. and 5 needed 2 separate intravenous doses of 250 mg. each because of the recurrence of arrhythmia. In these 5 patients the period of freedom from arrhythmia varied from 30 minutes to 3 hours, and they received oral maintenance therapy for 48 hours. In patients with pre-operative persistent atrial fibrillation, administration of phenytoin only suppressed the ventricular arrhythmias without any effect on atrial fibrillation. One patient with recurrent ventricular tachycardia did not respond to the drug; she had irreversible shock and persistent anoxia due to severe respiratory infection.

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FIG.—Electrocardiograms showing the effect of intravenous phenytoin on cardiac arrhythmias. (A) Multiple ventricular extrasystoles with short runs of nodal tachycardia reverting to slow nodal rhythm. (B) Multifocal ventricular extrasystoles (upper tracing) disappearing, and establishment of nodal rhythm (lower tracing). (C) Disappearance of ventricular ectopic beats after administration of phenytoin.

DISCUSSION

The results of this study confirm the usefulness of phenytoin in cardiac arrhythmias. Though it is effective in controlling both supraventricular and ventricular arrhythmias, particularly those resulting from digitalis toxicity (Osborne, 1964; Lang *et al.*, 1965; Conn, 1965; Bashour, Jones, and Edmondson, 1965; Karliner, 1967; Bashour *et al.*, 1968; Bigger *et al.*, 1968), it does not appear to have any place in the treatment of atrial flutter and fibrillation (Scherf *et al.*, 1960; Conn, 1965; Bigger *et al.*, 1968). However, Bashour *et al.* (1968) have shown

that it suppresses atrial fibrillation and restores sinus rhythm only when the former is of recent origin.

The pharmacological actions of phenytoin resemble those of quinidine and procainamide, with the exception that phenytoin does not seem to be effective against chronic atrial flutter and fibrillation, and that it may greatly augment vagal tone. The latter is helpful as the increased vagal influence results in a subsequent reduction in the ventricular response to a rapid supraventricular arrhythmia.

The untoward effects include bradycardia, hypotension, and transient atrioventricular block (Bernstein *et al.*, 1965; Conn, 1965; Karliner, 1967). Ventricular standstill has also been reported due to rapid administration of the drug (Goldschlager and Karliner, 1967). No serious arrhythmia was produced during the administration of phenytoin, and none of these side-effects, nor those that occur when it is used in epileptic convulsions, were noted. As the drug is known to produce bradycardia, atrioventricular dissociation, and hypotension, slow intravenous administration, continuous electrocardiographic monitoring, and repeated measurement of blood pressure are of paramount importance. For the same reasons, its use should be avoided in patients with bradycardia and high degree of atrioventricular block.

Bigger *et al.* (1968) have documented a relation between the plasma level of phenytoin and its antiarrhythmic effect. Three-quarters of the responsive arrhythmias were abolished at plasma levels of 10 to 18 $\mu\text{g./ml.}$, and 90 per cent responded at a level below 18 $\mu\text{g./ml.}$ Central nervous system symptoms were encountered only when the plasma level of phenytoin exceeded 20 $\mu\text{g./ml.}$ An arrhythmia which has shown no sign of responding when these symptoms appear during administration of phenytoin is therefore unlikely to respond to further doses of the drug.

Phenytoin is parahydroxylated in the liver and excreted as glucuronic acid conjugate (Maynert, 1960). Phenobarbitone accelerates (Maynert, 1960; Cucinell *et al.*, 1965), while isonicotinic acid hydrazide, para-amino salicylic acid (Kutt, Winters, and McDowell, 1966), and bishydroxycoumarin (Hansen *et al.*, 1966) decrease its hepatic metabolism. Dose adjustment may therefore be necessary when phenytoin is used in conjunction with these drugs.

The mechanism of action of phenytoin in arrhythmias is not clear. Experiments have shown that, by lowering the coronary resistance, it causes an increase in coronary blood flow (Gupta *et al.*, 1966; Nayler *et al.*, 1968). Gupta *et al.* (1966) postulated that the increased coronary flow might account for the antiarrhythmic effects of this drug. Radio-sodium turnover studies by Woodbury (1955) have shown that, as in brain cells, but not to the same extent, it actively extrudes sodium ions from myocardial muscle cells, thus raising the membrane threshold and decreasing the excitability of the myocardium (Ruthen, 1965). Much like quinidine, it also causes decreased conduction velocity between myocardial fibres (Dreifus, Rabbino, and Watanabe, 1964). Lang and associates (1965), using an auto-transplanted heart, lung, and cerebral venous shunt preparation, showed that the antiarrhythmic effects

of phenytoin were due to its direct action on the heart and not mediated through reflexes from the central nervous system. However, Hockman, Mauck, and Chu (1967) have suggested a possible central nervous system action of the drug. Ectopic ventricular rhythms elicited by electrical stimulation of diencephalic and mesencephalic loci in dogs and cats were not only abolished after intravenous administration of small doses of phenytoin but their subsequent induction, by stimulation for a period from 30 minutes to 7 hours, was also prevented.

Its rapid action, lack of serious side-effects, and, in particular, its value in digitalis arrhythmias make phenytoin a safe and reliable antiarrhythmic drug.

SUMMARY

Phenytoin was used to treat serious cardiac arrhythmias following open heart surgery in 14 patients. It was rapidly and highly effective in abolishing supraventricular and ventricular arrhythmias in all but one patient. Rapidity of action and relative paucity of side-effects make the drug an effective antiarrhythmic agent.

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