ATEBRIN IN PAROXYSMAL TACHYCARDIA AND PAROXYSMAL AURICULAR FIBRILLATION

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Received February 14, 1949

There is a wide range of remedies available for the treatment of the paroxysmal arrhythmias, which comprise auricular and ventricular paroxysmal tachycardia and paroxysmal flutter and fibrillation. Although vagal stimulation by pressure on the carotid sinus or eyeballs sometimes stops paroxysmal tachycardia, it is not effective in auricular fibrillation. Again, trials have been made of many drugs which include strophanthus, quinine, and quinidine (sulphate and chloride), both natural and synthetic, potassium acetate, α -fagarin, acetyl-beta-methyl-choline, magnesium sulphate, doryl, prostygmim, carbachol, ipecacuanha, apomorphine, and atropin.

In recent years, Gertler *et al.* (1946-47) have employed atebtrin in the treatment of paroxysmal arrhythmias with clinical and experimental results that have seemed encouraging but require confirmation. Our own experience, in this connection, is set forth hereafter.

PHARMACOLOGICAL CONSIDERATIONS

Gertler and Karp (1947) showed that atebtrin, derived from *acridin*, could paralyze the inhibitor vagal fibres of dogs' hearts, thereby proving a certain parallelism with quinidine in its pharmacological action, since both inhibit cholinesterase (Wealsch and Nachmanson, 1944) and intensely depress the heart's excitability, an action also demonstrated experimentally by Chin (1937) and Harvey (1939). A paralysing action on the motor end-plate has also been described by these workers. Molitor (1941) described various alterations of the cardiac rhythm, including heart-block and ventricular flutter and fibrillation, through toxic doses of atebtrin. In view of these similar pharmacological effects of atebtrin and quinidine, Gertler and Karp (1947) inferred that the former should restore the sinus rhythm in patients with auricular fibrillation, and they proved this action experimentally on dogs.

Moreover, it was shown that atebtrin was not toxic for the myocardium in anti-malarial therapeutic doses (Hecht, 1933; Gertler and Karp, 1947; Heimann and Shapiro, 1943; Smith and Stoeckle, 1946).

Gertler and Karp (1947) made preliminary trials by animal experiment and came to the conclusion that this medicine, given by intravenous infusion in doses of 2-17 mg. per kilo body weight, produced no cardio-toxic phenomena and was effective in stopping experimental fibrillation. Using atebtrin subsequently clinically, they confirmed these conclusions with the qualification that larger doses might produce ventricular arrhythmias or heart-block as described by Molitor (1941). Smith and Stoeckle (1946) had previously shown that a massive dose of atebtrin given intravenously had toxic effects on the heart-lung preparation in dogs. On the other hand, Gertler and Yohalem have explained this on the basis of atebtrin in massive concentration being strongly acid and producing

effects similar to those of any other acid solution injected in the same way (Gertler, Hoff and Humm, 1946; Gertler and Yohalem, 1947).

Gertler and Yohalem's first clinical paper proves the usefulness of atebrin in paroxysmal auricular fibrillation and supraventricular paroxysmal tachycardia in man, as a medicine comparable with quinidine; it also shows that the effect of intravenous injection of atebrin for auricular fibrillation in man is comparable to the results obtained by Gertler and Karp in experiments on animals. The similarity of action of atebrin and quinidine may be due to the characters of their chemical formulas. Recent investigations by Di-Palma and Lambert (1948) confirm the importance of the methoxy and dioxymethylenic groups in the action of anti-fibrillatory substances. These authors, studying the experimental fibrillation umbral in hearts under quinidine, cinchonine, α -fagarin, and N-methyl-dibenzil-amine found that, though one of these drugs—cinchonine—had no methoxy group, all of them possessed an evident anti-fibrillatory power. Cinchonine is almost as active as quinidine, and α -fagarin five times more so, but the authors fail to prove the anti-fibrillatory action of N-methyl-dibenzil-amine (a pressor substance of the sympatho-mimetic amine type) against the previous opinion of De Espanés *et al.* (1946). They only mentioned atebrin by the way, this drug also having a methoxy group in its formula. Agreeing with previous assertions of Dawes (1946), Di Palma and Lambert concluded that the methoxy group and the di-oxy-methylenic group are of the utmost importance in the structure of anti-fibrillatory drugs and expect research along these lines will produce the ideal anti-fibrillatory substance whose pharmacological effects may be produced through the metabolism of muscular contraction. Possibly the finding of atebrin is a step forward in this direction.

Gertler and Karp point out that atebrin also has certain advantages over quinidine, of which most of the properties have been known since the work of Lewis (1925). Whereas clinical effects with quinidine are sometimes delayed five to ten hours (Wegria, 1942 and 1948), no doubt because of its staying in the cardiac muscle (Weissman, 1945), atebrin given intramuscularly in doses of 0.4 g. reaches a 60–220 mg. per litre of blood level within the first hour and, at the end of three hours, falls to 60–120 mg. (Shannon, 1944), and remains for a long time at 1 : 300,000 (Dikshit, 1939). Thus the maximum effects of atebrin are attained before three hours and can be maintained afterwards owing to its persistent retention in the organism; Molitor (1941) reported that one isolated dose took 7 or 8 days to disappear from the organs (the heart not being mentioned) and in some patients traces of it were found nine weeks later, owing to the cumulative tendency of the drug and its slow excretion (Dearborn *et al.*, 1943).

Although atebrin is not notably toxic for the myocardium it is not to be administered lightly. Its general toxic effects are well known (Temkin and Ramsey, 1944; Bispham, 1941).^{*} These will not be dealt with here. However, since the doses suggested by Gertler and Yohalem are well under the toxicity level, its use is permissible and advisable for clinical trial. Using doses therapeutically effective though under the anti-malarial dosage, we only seriously suspected toxic phenomena in one case, whereas therapeutically effective doses of quinidine are frequently toxic (Vega Diaz, 1949; Maranon and Vega Diaz, 1948; Wegria and Nickerson, 1942).

Gertler and Yohalem (1947) state that according to Nahum *et al.* (1946) and Jervell (1946), the circular movement causing auricular fibrillation is due to the existence of an exciting factor, E, on which a vagal stimulation is superimposed (as recently confirmed by Schlichter, 1948), and that this so-called exciting factor may exist in many morbid processes such as thyrotoxicosis, acute infections, and stretching of the auricular fibres during the great dilatations of cardiac insufficiency (Best and Taylor, 1944). These authors conclude that, in the restoration of sinus rhythm in cases of auricular fibrillation, the intensity of these two factors is important. Thus in grave hyperthyroidism as in acute infections and in cardiac insufficiency, the anti-fibrillatory effect might be very poor and it is in such cases that Atebrin may be less useful. Gertler and Yohalem presented a case of paroxysmal auricular fibrillation and one of supra-ventricular paroxysmal tachycardia and stated

^{*} See also Fourth General Report of the Malaria Committee of the League of Nations (1937). *Treatment of Malaria*, Bull. of Health Organ, League of Nations, 6, 895.

that, when publishing the paper in question, they had nine other cases in their experience at Mount Sinai Hospital. In the case of auricular fibrillation they injected intramuscularly a dose of 0.6 g. atebirin in 10 c.c. novocaine at 1 per cent, sinus rhythm reappearing in two and a half hours' time. In a second attack of auricular fibrillation the same dose was repeated at intervals of 12 hours and the rhythm became normal two hours after the second injection. In these circumstances the authors gave 0.1 g. orally three times a day during ten days and once a day during three more, without any reappearance of arrhythmias. Their second case, in a paroxysm of infra-nodal tachycardia (referred to as supra-ventricular), was treated with 0.1 g. intravenous atebirin, sinus rhythm being restored 45 seconds after injection.

CASE REPORTS

Using doses similar to those of Gertler and Yohalem, we have employed atebirin* in

- 4 cases of paroxysmal auricular fibrillation;
- 1 case of (infra-nodal) nodal paroxysmal tachycardia; and
- 1 case of variably occurring paroxysmal auricular flutter.

Case 1. A. C. R., aged 21. Isolated attacks of palpitation since the age of 15, lasting at first three to four hours, and only occurring under strain or emotion. Attacks occurring two or three times a year. Two months ago began to feel early-morning extrasystolic sensations and attacks of tachycardia were more frequent, being repeated up to four times daily and always beginning and ending suddenly. The last two attacks lasted 12 and 16 hours respectively and a sensation of precordial oppression came on four or five hours after start of each attack.

Clinical examination. Inspection and palpation of heart and major vessels revealed no abnormality. First sound at apex ill-defined.

Arterial pressure 122/65 mm. Heart radiologically normal.

Electrocardiograms: normal during phases of normal rhythm.

During one attack infra-nodal paroxysmal tachycardia (Fig. 1) appeared and was stopped by pressure on the carotid sinus. On another occasion when vagal stimulation proved inefficacious, three doses of 0.1 g. of atebirin were given intravenously at two-hourly intervals and exactly twenty seconds after the last injection the attack stopped. It was recorded electrocardiographically in transit to sinus rhythm. Later examination of this patient revealed the presence of hyperthyroidism.

Case 2. O. G., aged 23. Always tended to have palpitations. Two years ago, in acute bout of alcoholic intoxication, had paroxysmal tachycardia lasting half an hour which was stopped with ouabaine. Before attacks, had extrasystoles; during the attacks, cold sweat and collapse, with livid appearance. Attacks began and ended suddenly.

Personal history. Rheumatic fever at 16. Afterwards some flitting rheumatic pains.

Clinical examination. The only outstanding feature was a systolic murmur in the aortic area during expiration and slight increase of the second sound at the same area. Blood pressure 120/70. Radioscopy showed a slight hypertrophy of left ventricle.

Electrocardiogram. In a curve recorded two hours before one of the attacks (Fig. 2) auricular extrasystoles were found and a slurring in the ascending limb of the R wave in lead I and in the descending limb of this wave in lead III. During the attack nodal paroxysmal tachycardia was demonstrated. A dose of 0.4 g. of atebirin was injected intramuscularly, and the attack ceased after five minutes. In previous attacks digitalis had failed and quinidine had caused deep disturbances of the ventricular complex when the dose reached 1.2 g. so that it had to be discontinued.

* In all our cases we have used Bayer's atebirin, in 0.1 g. and 0.3 g. capsules. When we want to give 0.4 g. we put the solution of one 0.3 g. and one 0.1 g. capsule in the same syringe; we have dissolved atebirin in 1 per cent novocaine solution for intramuscular injection and in distilled water for intravenous use.

FIG. 1.—Case 1. (A) Attack of infra-nodal tachycardia. (B) 20 seconds after a third dose of 0.1 g. atebtrin, intravenously.

Case 3. M. L., aged 59. Rheumatic fever in childhood, without relapses. For many years attacks of paroxysmal tachycardia, rather infrequent. Flatulence of large bowel with intermittent diarrhoea.

Clinical examination. Plethora. Soft presystolic murmur at apex. Marked meteorism. Arterial pressure 140/75 mm. Basal metabolic rate +40 per cent.

Radioscopy. Large globular heart, of slightly mitral shape; in right anterior oblique, slight deviation of the œsophagus by moderate dilatation of the left auricle.

Electrocardiogram. Between attacks: full-sized P waves; curves otherwise normal. In attacks: paroxysmal flutter-fibrillation (Fig. 3). 8 ml. cedilanid injected and 4 ml. twelve hours afterwards. Twelve hours later, the rhythm not having become normal, 0.6 g. atebtrin was injected intramuscularly in 10 ml. 1 per cent novocaine solution; the attack was thus brought to an end after lasting seventeen hours. In both electrocardiograms the slanting S-T segments characteristic of digitalis effect were observed.

Case 4. J. R. de A. Productive tuberculosis of the right lung with marked fibrotic retraction of this hemithorax. One year before first examination there was a severe bout of arrhythmia, diagnosed as extrasystolic, which lasted six hours. A few days later there was a further attack, this time of paroxysmal arrhythmia, lasting several days and cut short with digitalis. Since then, attacks have always occurred following irregularity of the pulse and have been repeated every two or three months. The last one started one month before our examination and is still persisting. Slight cardio-respiratory insufficiency phenomena.

Clinical examination. Constitutionally normal; heart sounds intense; lessening of breath sounds in left hemithorax. Complete arrhythmia with high heart rate. Blood pressure 115/75. No passive congestion. B.M.R. +33 per cent.

FIG. 2.—Case 2. (A) Electrocardiogram taken two hours before the attack recorded at (B). (B) Supraventricular tachycardia. (C) Normal rhythm ten minutes after an intramuscular injection of 0.4 g. atabrin.

Electrocardiograms. In the first curve, auricular fibrillation of right ventricular type (Fig. 4). Treated with quinidine sulphate; the rhythm became normal when 1.6 g. had been given. Relapsed 76 hours later; then treated with 0.1 g. intravenous atabrin, sinus rhythm being restored within three minutes.

Case 5. C. G. C., aged 28. Rheumatic fever when 10 years old. Residual slight effort syndrome. For the last five months paroxysmal tachycardia of increasing duration; from a few minutes at first to sixteen hours in the attack before last. They are bouts of auricular fibrillation with high ventricular rates. So far they have responded to quinidine sulphate.

Clinical examination. Short presystolic murmur at apex and ill-defined second sound at the pulmonary area. Harsh systolic murmur at the aortic area. Blood pressure 110/60 mm.

Radioscopy. Appearance of mitral and aortic disease without much cardiac dilatation, but with left ventricle hypertrophy.

Electrocardiograms. Curve between attacks of normal ventricular type without intracardiac conduction anomalies and with bicuspid P waves.

After one attack had lasted six hours, 0.1 g. atabrin was administered intravenously. Three hours later, the attack persisting, the dose was repeated; a further dose three hours later still was

FIG. 3.—Case 3. (A) Paroxysmal flutter-fibrillation. (B) After digitalis treatment and intramuscular injection of 0.6 g. atebirin. Observe anomalies in S-T spaces, of digitalis type. See text.

given, but without success. Three days after the last dose of atebirin quinidine sulphate was administered and the attack stopped half an hour after the second dose of 0.4 g.

Case 6. F. P., aged 60. Treated jointly with Dr. L. Alzua of San Sebastian. The patient was plethoric. He had had hypertension for many years, with generalized arteriosclerosis. For some years past, there had been phases of paroxysmal auricular flutter lasting several days with rhythm alternating from 3 : 1 to 4 : 1, nearly always of the pure flutter type. Digitalis medication had failed totally, even though the saturation stage had been reached (8 c.c. cedilanid in one dose and 4 c.c. twelve hours later). In this patient a first dose of 0.4 g. intramuscular atebirin (administered thus for lack of intravenous capsules) resulted in a transient restoration of normal rhythm, the ventricular rate dropping to about 60 per minute. No electrocardiogram could be taken at the time. One hour later he relapsed into a state somewhat different from his former one, a flutter-fibrillation remaining with periods of impure flutter. A second dose of atebirin again altered the rhythm, which was maintained at 120 a minute during more than 24 hours; but it was found that

FIG. 4.—Case 4. (A) Paroxysmal auricular fibrillation with ventricular complexes of right type. Relapse of an attack previously stopped with quinidine sulphate. (B) Normal rhythm three minutes after an intravenous injection of 0.1 g. atebirin. There are post-therapeutic anomalies of the S-T spaces of the precordial leads, which may be due either to the quinidine or the Atebrin. (C) Normal rhythm maintained 48 hours after the previous record.

this apparently normal rhythm was, in fact, a pure flutter with 2 : 1 block and severe subjective troubles.

Not much can be inferred from this case, since we suspect that the flutter concealed a stable auriculo-ventricular block, with high ventricular rate associated with left ventricular insufficiency due to coronary sclerosis. The relevant figures are therefore omitted, but will be published with a later paper.

DISCUSSION

We have obtained good results in four of the six cases of acute tachycardial arrhythmia treated with atebirin. In the other two we failed, and in one of these there were possible complicating phenomena. These two cases, however, lead us to refrain from premature conclusions.

Of the patients relieved, two had paroxysmal tachycardia and the other two auricular fibrillation. We cannot, therefore, make any generalization as to the pharmacological effect of this drug in paroxysmal arrhythmia.

Of the cases of paroxysmal tachycardia, one which was clinically normal showed phases of transient increase of metabolism, suggesting that hyperthyroidism might be of pathogenic significance. In the other case, with slight rheumatic aortic stenosis, the attacks of auricular fibrillation coincided with phases of alcoholic intoxication; and in spite of the almost certain liver disorder due to alcoholism the drug acted rapidly. One of the known toxic effects of this drug is that on the liver cell, but the fact that the attacks were stopped even by rather large doses encouraged further use of this drug. In this case, digitalis had failed on two previous occasions and quinidine had once produced toxic electrocardiographic manifestations that made it advisable to stop this medication.

One of the cases of paroxysmal auricular fibrillation had a rheumatic mitral lesion, while in the

other case the heart was sound but with a marked cardio-respiratory syndrome due to pulmonary fibrosis. Both had a high B.M.R. which, in one (Case 3), was clearly due to hyperthyroidism. The other case was questionable because of the respiratory syndrome.

Nothing conclusive can be inferred from these four cases beyond a consideration as to the role of hypermetabolism. The excellent results obtained in these four cases from the use of atebtrin do not seem to confirm the theory of Gertler and Yohalem as to the ineffectiveness of this drug in syndromes like hyperthyroidism in which the vagal influence is reduced. The only case of paroxysmal auricular fibrillation which did not yield to atebtrin was, in fact, free from this disorder of metabolism.

Atebrin thus appears to be a useful drug for acute tachycardial arrhythmias, above all for those with a raised metabolic rate, whether or not this is due to hyperthyroidism (Vega Diaz, 1949; Maranon and Vega Diaz, 1948). This point is important since it is known that in hyperthyroidism anti-tachycardial drugs often fail, or must be given in maximum doses, or produce toxic phenomena (Maranon and Vega Diaz, 1948). In Case 3, relief was only obtained with atebtrin, although there were clinical and electrocardiographic signs of digitalis saturation. It may be that the digitalis restored normal rhythm (the dose having been large enough to warrant this supposition), or the effect may have been due to the complementary action of the two drugs. This summation phenomenon is widely known and used in cardiological clinics,* but it frequently gives rise to similar doubts. The attacks may also have ended autochthonously. Nevertheless, the fact remains that in this case the paroxysm only stopped when atebtrin was administered.

The two cases of failure deserve separate mention.

Regarding Case 5, atebtrin was not efficacious although quinidine was. Previous attacks had been arrested by quinidine and it had to be employed again after several hours of unavailing use of atebtrin.

Our sixth case, of paroxysmal auricular flutter with 3 : 1 and 4 : 1 auriculo-ventricular block, had great left ventricular stress of the common left bundle-block type, with clinical evidence of atheroma. Atebrin seemed to restore normal rhythm at a rate of 60 a minute without the transition being recorded electrocardiographically. One hour later impure flutter had set in. A second dose of atebtrin produced tachycardia at the rate of 120 a minute—2 : 1 flutter with troublesome subjective phenomena. This case is one of atebtrin failure in flutter, but at least it shows that the drug has an effect on cardiac rhythm.

SUMMARY

Six cases are presented of paroxysmal tachycardial arrhythmia treated with atebtrin. In four of them (two of paroxysmal tachycardia and two of paroxysmal auricular fibrillation) the bouts were stopped in a striking manner. In the other two the drug proved ineffective, although one of these cases (paroxysmal auricular flutter) was difficult of interpretation. It is considered that atebtrin is a useful medicament, especially in patients with a high B.M.R. or slight hyperthyroidism. It may be less dangerous than quinidine, although possibly of less potency and less efficacious when repeated.†

From these few observations no conclusive inferences can be drawn, but it does seem that atebtrin possesses an anti-tachycardial and anti-fibrillatory action. Because of the quickness of its action and its sustained effect through its permanency in the body, atebtrin may well be the remedy of choice in some cases, especially when the B.M.R. is somewhat high, since quinidine is much more rapidly eliminated and may be more toxic. With quinidine there is only a small margin between therapeutic and toxic doses, and these are sometimes the same; moreover, when it is toxic it sets up serious cardiac complications almost from the start, even with doses that are not large.

* To give only one example, it is unanimously recognized that carotid pressure after a dose of digitalis is efficacious to stop a paroxysm of tachycardia in which such treatment had previously failed.

† Since writing this paper we have been able to try atebtrin in a further case of paroxysmal auricular fibrillation, without producing any effect whatever after three intravenous doses of 0.1 g. This makes us even more reticent than we were, notwithstanding the initial successes.

Atebrin, which is not toxic for the myocardium in therapeutic doses, gives a wide margin between therapeutic and toxic doses. Its effects are slow and general rather than cardiac, and this reduces the chances of emergencies, notwithstanding the retention of the drug in the system. This very retention, moreover, enables us to trust in the continuity of the effects even when it is not repeatedly administered; this cannot be said for the other anti-fibrillatory or anti-tachycardial drugs. This fact makes us consider that atebrin may, therefore, be useful in maintenance doses as a prophylactic medicament.

Further experience of success or failure must be awaited before a judgement can be formed as to the usefulness of this medication for acute tachycardia, its indications and its dosage.

NOTE: Since this paper was sent in a new publication by Gertler and Yohalem has appeared (*Amer. Heart J.*, 37, 79, 1949), in which they again insist on the scantier success of atebrin in auricular fibrillation of hyperthyroid origin. Although working in a hospital department mainly engaged in endocrinology we have not been able to amplify our experience as regards atebrin in the last few months. We fully concur with all these authors' other data. In another paper of ours (Maranon and Vega Diaz, 1948) we have drawn attention to the possibility of some cases of hypermetabolism not being directly hyperthyroid, the thyroid intervening only as an interposed agent of hypothalamic regulation.

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