EPHEDRINE SULPHATE AND BARIUM CHLORIDE IN THE PREVENTION OF STOKES-ADAMS SEIZURES

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The peculiar syncopal attacks which are named after Stokes and Adams have as their predominant feature either a complete and transient cessation of ventricular beating or else the temporary development of such an extremely slow ventricular rate than an adequate cerebral circulation is not maintained. Complete ventricular arrest is the commoner variety. Recovery of the heart beat may take place after a pause of some seconds', or even of five minutes', duration.¹¹ Extreme bradycardia is a less frequent cause of Stokes-Adams seizures. Should the ventricular rate fall to less than nine or ten beats per minute then a semi-conscious stuporose state is apt to arise. This persists until a greater rate of blood flow through the brain is brought about by an increase in the rate or power of the ventricles. On the other hand, a further reduction in rate, perhaps to six or seven beats per minute, is accompanied by loss of consciousness, cyanosis, muscular twitchings, and a deepening coma, which can only be relieved by a more efficient pumping action of the heart.

STOKES-ADAMS ATTACK: PREDISPOSING CONDITIONS

Stokes-Adams seizures develop in a variety of circumstances. In partial heart-block associated with a progressive defect in the conducting power of the bundle of His, seizures are apt to occur over the period when, starved of their full quota of impulses from the sino-auricular node, the ventricles are left to initiate their own independent rhythm. Vagal stimulation in the presence of a pre-existing partial block of toxic origin is a potent cause of ventricular standstill. In such cases I have seen typical Stokes-Adams seizures induced by digitalis, by vago-carotid pressure in the neck, and, in one instance, by sudden over-distension of the rectum during the hasty administration of an enema.

Repeated or single seizures may herald the onset of permanent complete block, and, the idioventricular rhythm becoming firmly established, the patient may live for years, never to experience another Stokes-Adams attack. But seizures at irregular and infrequent intervals, either in the course of chronic partial or in complete block, associated with permanent degenerative changes in the conducting tract, are less easy of explanation. Uncommonly, seizures appear in rapid succession for a number of days, cease of their own accord, only to return again in a few weeks or months for no very obvious reason. One patient under my observation had 352 fully developed Stokes-Adams attacks with loss of consciousness (exclusive of many minor attacks of giddiness and faintness) between April, 1930, and January, 1932. The seizures occurred in groups for a few days at a time: there were as many as 131 attacks over a period of four days. Ventricular fibrillation was demonstrated as the cause of the temporary arrest of the circulation in this patient. In intermittent complete heart-block, in which periods of total failure of the bundle of His alternate from time to time with shorter or longer intervals during which the auricular impulse is carried to the ventricle, repeated seizures of great severity are common, and may progress in spite of treatment to a status epilepticus, with a fatal termination.

That the underlying cardiac mechanism responsible for the temporary arrest of the circulation therefore varies in different cases, and probably also even in the same individual at different times, is a fact more fully appreciated in recent years. It would seem established that in the majority of Stokes-Adams attacks occurring in the course of chronic complete block the centre of impulse formation controlling the ventricular rhythm becomes suddenly depressed, and until it, or another centre, awakens, a critical state exists, during which the circulation is in abeyance. Whether the attack is precipitated by preponderating vagal influences, reduction in sympathetic tone, a block of the idioventricular impulse itself, the development of ventricular fibrillation, or by the presence of unknown chemical factors in the blood stream, is of less consequence than the fact that in complete heart-block the ventricular rhythm is, as a general rule, peculiarly sensitive to sympathetic stimulation.⁶

VALUE AND LIMITATIONS OF ADRENALINE

It has been shown that adrenaline is capable of arousing a dormant ventricular rhythm. When seizures are recurring frequently no drug has proved more effective in their prevention than adrenaline.^{14 17} It is not always successful, but until we have a greater knowledge of the different mechanisms responsible for the Stokes-Adams attack it will not be possible to discriminate accurately between those who will benefit from its use and those who will not. It should always be given a trial when seizures happen frequently. When attacks appear only at long intervals their prevention with adrenaline is less easy. Ineffective by the mouth, and relatively short in its action, adrenaline cannot well be employed for this purpose. Ephedrine and barium chloride, both of which are alleged to increase the rate of spontaneous ventricular beating, have been suggested for use in those cases of block in which seizures occasionally arise at infrequent intervals. Both may be taken orally over long periods of time, and neither produces much systemic disturbance.

THE ACTION OF EPHEDRINE AND BARIUM

It would appear that, while ephedrine in large doses may act as a depressant to the mammalian heart, yet the cardiac stimulant effects of smaller quantities are quite well marked in the case of the human heart.² Its effects in therapeutic doses are less intense than those of adrenaline, but they persist for a longer time. Their similarity in action is indicated by the fact that, while adrenaline stimulates the myoneural junction of the sympathetic system, ephedrine acts upon the nerve endings of the sympathetic fibres.¹ The ventricles receive a rich sympathetic supply; and, though no experimental observations are available regarding the action of ephedrine on the blocked heart of animals, from analogy with the action of adrenaline, and from the few isolated instances in which the drug has been used in clinical examples of heart-block, it is not surprising to find that an acceleration of the ventricular rate was induced. Miller,¹² the first to test the action of ephedrine in complete heart-block, found that in his patient the auricles increased in rate from 110 to 125 and the ventricles from 33 to 55 per minute after a subcutaneous dose of 100 milligrams. Hollingsworth⁹ found that in a case of complete heart-block daily doses of 50 mg. by mouth were sufficient to abolish repeated Stokes-Adams seizures. Within forty-eight hours of withdrawing the drug the attacks recurred. Stecher^{21 22} reported a similar case. Parade and Voit¹³ found thyroxine, caffeine, and digitalis ineffective in preventing seizures, but when taking a synthetic preparation of racemic ephedrine by mouth their patient obtained practically complete relief for a period of two years. The drug was then discontinued,

attacks soon reappeared, and death in a seizure followed before adrenaline could be administered. Wood²⁵ presents very convincing evidence of the value of ephedrine. In his patient 24 mg. twice daily were sufficient to control typical Stokes-Adams seizures over many months. Roberts and Taber¹⁹ found that 25 mg. of ephedrine twice daily controlled attacks in their patient. Death supervened in a seizure twenty-four hours after a further reduction in the daily dose.

As regards the value of barium chloride in the prevention of attacks, the reports in the literature are often at variance, and are decidedly less convincing than the results obtained with ephedrine. The experimental work of Rothberger and Winterberg²⁰ and van Egmond,⁵ which indicated that the excitability of the ventricular muscle was increased by barium chloride, suggested to Levine¹⁰ its clinical application as a possible remedy for the prevention of Stokes-Adams seizures. Cohn and Levine,³ in reporting three cases of the Stokes-Adams syndrome, formed a favourable impression of the value of barium chloride; but it is admittedly difficult to distinguish between a spontaneous alleviation of symptoms and a definite effect produced by the drug. Reviewing the work of Levine,¹⁰ Levine and Matton,¹¹ Herrmann and Ashman,⁸ Parsons-Smith,¹³ Strauss and Meyer,²³ and Price and Nisse,¹⁸ the conclusion is reached that, in general, barium chloride does appear to have some effect in reducing the frequency of seizures. On the other hand, Wilson and Herrmann²¹ have reported that in a case of complete block, complicated by repeated convulsive syncopal attacks, barium chloride administered in doses of 1/2 grain thrice daily for thirty-eight days was without benefit. Stokes-Adams attacks recurred repeatedly despite its use. The more recent clinical accounts of Drake⁴ and Heard,⁷ and the absolutely negative results obtained by Parsonnett and Hyman¹⁶ in eight cases of complete heart-block, clearly cast a doubt on the efficacy of this drug, and fail to substantiate the more optimistic reports of some years ago.

CLINICAL TESTS

As a means of estimating the worth of these drugs two methods were employed. It seemed desirable to discover if, when they were given by mouth, any significant change took place in the rate of the independent ventricular rhythm. Cases of complete heart-block, free from seizures for months or years, were selected for the test. After an ample control period of ten days or more, during which no drugs were administered, the patient being strictly confined to bed, ephedrine or barium chloride was prescribed for a week or a fortnight, and the effect on the heart rate recorded by frequent pulse counts at two- or four-hourly intervals, and by daily electrocardiograms. Six casts of complete heart-block were tested in this way.

As a further measure of the efficacy of ephedrine it has been administered at intervals to two patients for over a year, both of whom suffered from complete heart-block and had been accustomed to fairly frequent seizures. Actually, this method would seem to be the more desirable test of the two, but when attacks of any kind appear only at rare and infrequent intervals the effect of treatment directed at their prevention is difficult to assess. It is not uncommon to find that even frequently repeated Stokes-Adams seizures may cease spontaneously for no very obvious reason. *Vis medicatrix naturae* must always complicate therapeutic deductions.

EFFECT OF EPHEDRINE AND BARIUM ON VENTRICULAR RATE

In four of the six patients ephedrine taken orally brought about and maintained a definite acceleration of the ventricular rate. In the two remaining individuals (Cases 2 and 4) the test was indecisive. Case 2 was that

of an elderly man with a relatively high ventricular rate (46 per minute) in an advanced degree of congestive heart failure. Adrenaline has but little accelerating effect on the ventricles at such a rate,⁶ and it may be for similar reasons that ephedrine (in 1-grain doses, thrice daily for six days) was apparently ineffective in this man. In Case 4 the test was vitiated by the patient's insisting on leaving his bed during the period when the drug was being given. It was therefore not possible to discriminate between the effects of increased bodily activity and any sympathetic stimulation induced by ephedrine. Both these cases may therefore be dismissed and regarded as negative results.

Barium chloride was taken by mouth for several days by the four patients (Cases 1, 5, 10, and 14) whose ventricles were accelerated by ephedrine. Although proved to be susceptible to sympathetic stimulation, no demonstrable effect was produced on the ventricular rate by barium chloride in these four individuals. The response of these cases may now be examined in a little more detail.

Case 1

The patient is an active woman, who had a number of Stokes-Adams seizures between 1923 and 1926. Alive and well at the present time, she has been under observation since 1928, and has had no further attacks. The effect of 1/2 grain doses of ephedrine, twice daily, over a period of eleven days was tested in November, 1928. It increased the ventricular rate by an average of 4 beats per minute throughout the period of its administration, the maximum rate in the control period being 28 per minute. For two days she received 40 mg. of barium chloride at six-hour intervals, and then 60 mg. for the succeeding nine days. No change in the pulse rate, blood pressure, or form of the electrocardiogram was observed.

Case 5

The patient, a man, has been under observation as a case of complete heart-block since August, 1931. One Stokes-Adams seizure occurred in December, 1930. There have been no further attacks, and he keeps well and reasonably fit for work. Ephedrine was given in increasing amounts over a period of eleven days, commencing with 1/2 grain twice a day and rising to 1 grain four times a day (see Fig. 1). The ventri-

FIG. 1.—Shows the effect of the oral administration of ephedrine on the pulse rate in Case 5. The daily maximum and minimum of two-hourly pulse counts are recorded.

cular rate increased from a maximum of 38 in the control period to 46 during the time the drug was taken. Thereafter the rate gradually declined during the succeeding days. At a later period he received 240 mg. of barium chloride for three days, followed by double this amount for a further period of three days. No effect on the rates of auricles or ventricles was recorded. Extrasystoles were not detected.

Case 10

The patient was an elderly woman, who had one severe Stokes-Adams seizure on the day of her admission to hospital. She died two months later of hypostatic pneumonia without experiencing another attack, although she had had at least 352 typical attacks in the previous twenty months. The pulse rate ranged from 28 to 32 during the control period. Ephedrine in 1/2 grain doses, four times in the twenty-four hours, produced no appreciable effect, but on doubling the dose the rate varied from 32 to 36 during the four days on which this amount was taken. The rate returned to its pre-existing level within thirty-six hours. Barium chloride was tried in larger doses than in the previous cases. For three days

fell from 250 mm. Hg during complete block to 210 during the three to one rhythm. Ephedrine was abruptly discontinued on the night of May 31st.

A remarkable series of symptoms arose within twelve hours of discontinuing the treatment with ephedrine. In the early hours of the following day (June 1st) she complained of headache and pains in the back, and suffered from two fainting turns of no more than a few seconds' duration. During the forenoon the heart rate gradually declined. At 11 a.m. the ventricles were beating at a rate of 16 per minute, and she complained of increasing weakness. At 11.55 a.m. the rate was 11 per minute. At 12.15 p.m. it had declined to 9 beats per minute (Fig. 4). She was pale, with slow, sighing respira-

FIG. 2.—Displays an electrocardiogram of a mild Stokes-Adams attack recorded in Case 14 on July 2nd, 1931. The period of ventricular arrest measures 9.8 seconds, and is preceded by two to one block and followed by three to one. Ephedrine was effective in abolishing these seizures.

she received 60 mg. thrice daily, increased to 90 mg. for a similar period, and finally 120 mg. thrice daily for six days. No appreciable alteration in the rate of the pulse was observed, though occasional extrasystoles were recorded.

A TOXIC EFFECT ATTRIBUTED TO EPHEDRINE

Case 14

The patient was an obese woman, aged 61, who in 1930 suffered from dyspnoea and was found to have a persisting two to one block (P-R interval 0.18 second). In June, 1931, she began to have repeated syncopal attacks due to ventricular arrest (Fig. 2), the block being either two to one (P-R interval 0.185 second) or three to one (P-R interval 0.165 second). By April, 1932, electrocardiograms demonstrated a complete dissociation of auricles (rate 70) and ventricles (rate 28), and syncopal attacks were infrequent. In May, 1932, her response to ephedrine was tested. At this time she complained of repeated frontal headaches, general weakness,

FIG. 3.—Shows the effect of ephedrine on the pulse rate in Case 14 in May, 1932. The ventricular rate increased from 30 to 36, and four days after commencing the drug a three to one block replaced the complete block formerly present. The ventricular rate fell to 7.5 per minute on suddenly discontinuing the drug's administration.

tions, unable to make the least bodily exertion, and was semi-conscious, but sufficiently well to ask for nourishment. At 12.35 p.m. she complained of nausea, and immediately afterwards lost consciousness in a typical Stokes-Adams seizure. She was quite unconscious for one and a half minutes, during which time the ventricles continued to beat at a rate of 7.5 per minute. Recovery was gradually accomplished by a spontaneous increase in ventricular rate, first to 10 and then to 15 beats per minute. Between 1 and 2 p.m. she had three further seizures, each of which resembled the first in that the ventricles continued to beat throughout the attack at a rate of approximately 7 or 8 per minute. A subcutaneous injection of 0.5 c.cm. adrenaline abolished the attacks by increasing the ventricular rate to 23 per minute and inducing four to one block. A further course of ephedrine restored three to one rhythm. She gained rapidly in health and was discharged from hospital, taking 1 grain of ephedrine thrice daily.

FIG. 4.—Shows an electrocardiogram recorded in Case 14 on June 1st, 1932, sixteen hours after discontinuing the administration of 3 grains of ephedrine per day. The ventricular rate is 8.5 beats per minute. The auricular rate is 82.4.

and great exhaustion on the least bodily exertion. She was, in consequence, confined to bed for three months. For one week she received daily 120 mg. of barium chloride, and for a second similar period double this amount. No change was observed in the rate of the ventricles or in the electrocardiograms. Extrasystoles did not occur. Ephedrine in 1/2 grain doses, four times a day, was commenced on May 26th. It produced an increase in the ventricular rate from 30 to 36, as demonstrated in Fig. 3; but four days after commencing the drug a regular three to one block, with a P-R interval of 0.395 second, replaced the complete dissociation formerly present. The systolic blood pressure

These alarming symptoms, which immediately followed the abrupt withdrawal of ephedrine (and were later abolished by its continued administration) suggests that over-stimulation was a cause for the exhaustion of the few remaining conducting strands in the bundle of His, and also of the rhythmic centre controlling the independent ventricular beat. When the drug was discontinued conduction failed, and the transition from high-grade partial to complete block was rendered dangerous by a progressive slowing in the idioventricular rate. As a general principle it would appear desirable to use the minimum

quantity of ephedrine capable of increasing the ventricular rate, as larger doses may, at least in certain cases, cause over-stimulation and later exhaustion of the idio-ventricular centre.

EPHEDRINE IN TWO CASES OF STOKES-ADAMS SYNDROME

Of fourteen patients with complete heart-block under observation only two were accustomed to have seizures at sufficiently frequent intervals to warrant a fair test of the efficacy of ephedrine in their prevention.

Case 4

A patient (Case 4, referred to above) came under observation in April, 1932, suffering from complete heart-block with a history of repeated Stokes-Adams seizures at intervals of from three to six weeks for three years. Ephedrine in 1/2 grain oral doses thrice daily was commenced on July 2nd, 1932, and continued until October 31st, 1933. Not one seizure was experienced during these sixteen months. The drug was discontinued on November 1st, 1933, and he remained well and free from attacks for seven weeks, when a single seizure again took place. He recommenced taking the drug the following day, and from December 22nd, 1933, until February 5th, 1934, when last seen, he has had no further attacks.

Case 14

Another patient (Case 14) was admitted to hospital on June 25th, 1931, and that evening there were several "fainting attacks" in succession. Single attacks occurred on June 26th, 29th, and 30th. On July 1st there were about half a dozen attacks, and on the next day about twenty seizures were observed in the course of an hour or two. Fig. 2 demonstrates a period of ventricular asystole lasting 9.8 seconds, preceded by two to one block and succeeded by three to one. Adrenaline, 0.5 c.cm. subcutaneously at 2 p.m., was followed by freedom from attacks until 5 p.m., when two similar fainting turns were experienced. Ephedrine was begun in 1/2 grain doses by mouth four times a day at 6 p.m. that evening. No seizures were observed or complained of on July 3rd, 4th, or 5th. Ephedrine was discontinued at 8 p.m. on the 5th, and at 6 a.m. on the following day there were three minor attacks. The drug was recommenced on the evening of July 6th, and continued until her discharge from hospital on July 18th, 1931. On the 8th and 9th two short attacks were complained of, at about 8 a.m. on each occasion. By rearranging the times of administration of the drug no further attacks arose.

It seems reasonable to conclude that ephedrine played a part in the prevention of seizures in this woman, probably by facilitating conduction (though the block remained two to one) and increasing the excitability of the ventricular muscle. She voluntarily gave up taking the drug about January, 1932, and between then and April, 1932, when she was again admitted to the ward, she had several seizures. The block being complete, her response to ephedrine was tested in May, 1932, as described previously, when toxic effects supervened on its sudden withdrawal. She was discharged from hospital on June 15th, 1932, and from that date until the end of July, 1933, she took 1 grain thrice daily. She had no attacks during this time. During August, 1933, she was persuaded gradually to give up its use. After discontinuing it she had three seizures in four weeks. From September 1st, 1933, until January 30th, 1934, taking 1/2 grain thrice daily, she has had no further attacks, and refuses to make any further reduction in the dose. Electrocardiograms show that the block is complete, and the usual ventricular rate 30 per minute.

Both these cases point strongly to the efficacy of ephedrine as a means of preventing Stokes-Adams seizures. During its administration syncopal attacks ceased. When its use was abandoned seizures returned. No ill effects were observed when it was being taken; on the contrary, both individuals have now a much greater response to effort than formerly, and each, unknown to the other, attributes improvement in health and well-being to the drug. In Case 4, after eighteen months' treatment, the patient is now able to enjoy a walk of four to five miles over the rough country of the Pentland Hills. In

Case 14 the patient can do housework, which she was formerly forced to decline.

Barium chloride has not been tested under similar conditions, as from the earlier observations it was evident that, in spite of larger doses than those recommended, it did not appreciably alter the rate of the ventricles. It may be that it acts by increasing their irritability without a decisive change in rate, and that in certain cases barium might enhance the response to ephedrine. Employed alone, it can hardly be expected to compete with ephedrine, as a remedy for the prevention of occasional seizures. It is perhaps too much to hope that ephedrine will prove effective in all cases of the Stokes-Adams syndrome. If attacks recur despite adequate dosage, then it would seem reasonable to combine it with barium chloride.

SUMMARY AND CONCLUSIONS

In six cases of complete heart-block ephedrine taken orally increased the rate of ventricular beating in four. In two patients the test was indecisive.

Barium chloride produced no demonstrable effect on the ventricular rate in the four cases responding to ephedrine. It did no harm in doses larger than those originally recommended.

In two cases of complete heart-block, complicated by occasional Stokes-Adams seizures, ephedrine taken for two and a half and one and a half years respectively proved entirely successful in the prevention of syncopal attacks. When the drug was discontinued typical seizures returned.

It is recommended that the dose of ephedrine should be the minimum quantity consistent with an acceleration of the resting ventricular rate. Larger doses may cause over-stimulation. If the drug be then suddenly omitted, profound slowing of the ventricular rate, with repeated Stokes-Adams attacks, may occur, as a result, presumably, of exhaustion of the idioventricular centre. A dose of 1/2 grain by mouth at eight-hour intervals may be sufficient.

In the absence of positive findings it is difficult to credit barium chloride with the power of preventing Stokes-Adams seizures.

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