Intravenous Drug Therapy of Stokes-Adams Disease

Effects of Sympathomimetic Amines on Ventricular Rhythmicity and Atrioventricular Conduction

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In the treatment of Stokes-Adams disease emergency resuscitation from cardiac arrest can be effected by external electric stimulation or countershock. For the acute problems of persistent ventricular standstill and frequently recurrent seizures, which often appear immediately after resuscitation, intrinsic ventricular pacemakers must be aroused, accelerated, and maintained. In the treatment of these problems the effects of drugs on ventricular rhythmicity and atrioventricular conduction were evaluated. We have found the slow intravenous administration of dilute solutions of sympathomimetic amines to be an effective and safe technique. Epinephrine and isoproterenol were the most useful agents and were comparable in efficacy and toxicity.

Epinephrine and many similar drugs are widely used in the treatment of serious cardiovascular disturbances. In this paper detailed information obtained in the treatment of patients with Stokes-Adams disease is presented concerning the cardiovascular actions of these drugs, especially their effects on ventricular rhythmicity. Thereby, it is hoped, the choice and use of a particular drug for a particular purpose will be improved.

Because the ventricles beat in response to the sinoatrial pacemaker during normal sinus rhythm, the effects of drugs on the slower ventricular pacemakers are masked, except when ventricular arrhythmias are excited. To observe the effects of drugs on ventricular activity in man independent of the sinoatrial pacemaker, Gilchrist and later Nathanson and Miller studied patients with complete heart block. Nathanson also produced transient sinoatrial arrest or atrioventricular block by pressure on the carotid sinus, and during these brief periods he studied the effects of drugs on ventricular rhythmicity. Although valuable, the data provided by these studies are insufficient for the optimal therapeutic use of sympathomimetic drugs.

Technic

During the treatment of 94 patients with Stokes-Adams disease with the new techniques of external electric stimulation and defibrillation of the heart, opportunities arose in 21 patients to study sympathomimetic drugs and 1 molar sodium lactate under the unique circumstance of complete absence of spontaneous ventricular activity. With electric currents applied externally to the chest wall, emergency resuscitation can be effected from Stokes-Adams attacks due either to ventricular standstill, tachycardia, or fibrillation. At times, after resuscitation, the heart fails to beat spontaneously when the external pacemaker is turned off. Continuous electric stimulation then is necessary as long as spontaneous ventricular beats remain absent.

In the treatment of this difficult problem, sympathomimetic agents and sodium lactate were administered by intravenous infusion to arouse spontaneous ventricular beats. The arousal of ventricular pacemakers provided an unusual and particularly valuable criterion for the evaluation of the effects of drugs on ventricular rhythmicity. Arousal, being an all-or-none phenomenon, was unequivocal and simpler to evaluate than acceleration and maintenance.

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*Cardiac Pacemaker and External Defibrillator manufactured by the Electrodyne Co., Norwood, Mass.
sympathomimetic drugs were also administered intravenously to a few patients with intrinsic ventricular pacemakers, by preventing their disappearance, or by improving atrioventricular conduction.

Blood pressures, electrocardiograms, and rates of drug administration were recorded as often as at 1-minute intervals during periods of change. The P-P and R-R intervals were measured as indices of the sinoatrial and idioventricular rates; variations in QRS configuration indicated changes in ventricular pacemakers, and the relations between P and QRS indicated the state of atrioventricular conduction. Representative values from quantitative data are shown in the figures.

Periods of electric stimulation are shown in the

Fig. 1. Electrocardiograms (lead aVF at half standardization) illustrating arousal of an intrinsic ventricular pacemaker by epinephrine in a patient (E.S.) with prolonged ventricular standstill. A. (10:36 a.m.) Electric stimuli (E) produced ventricular responses (V). When no stimuli were applied, there were no spontaneous ventricular beats. B. (11:01 a.m.) When stimulation was interrupted after the infusion of epinephrine for 5 minutes, intrinsic ventricular beats appeared. C. (11:05 a.m.) With continued infusion of epinephrine the sinoatrial and ventricular pacemakers accelerated; thereupon the infusion was stopped. D. (12:27 p.m.) When the idioventricular rate became very slow, syncope occurred and electric stimulation was resumed. E. (12:29 p.m.) Intrinsic ventricular beats failed to appear during a test interruption of stimulation lasting 16 seconds; 12 seconds of ventricular standstill between the 2 segments are not shown.

Sympathomimetic drugs and sodium lactate were given by intravenous infusion at carefully regulated rates and the state of intrinsic ventricular activity was observed electrocardiographically during test interruptions of stimulation, usually at 1- or 2-minute intervals. Freshly prepared solutions were usually administered at initial rates of 4 μg per minute (1 ml or 15 drops of a 1:250,000 solution). The rate of drug infusion was increased stepwise until intrinsic ventricular pacemakers appeared (fig. 1B) or until toxic effects were observed, such as premature beats, excessive ventricular acceleration, excessive elevation of the blood pressure, or excessive cerebral stimulation. Then, drug administration was maintained, slowed, or stopped and the cardiovascular effects were noted. If ventricular pacemakers disappeared or became too slow to maintain an adequate circulation, electric stimulation was resumed immediately. If intrinsic ventricular pacemakers again remained absent, further trials of the same drug or other drugs were carried out. In this way repeated quantitative comparisons were made within a short period of time from the same baseline of absent spontaneous ventricular activity.

The effects of 1-molar sodium lactate on ventricular rhythmicity were also studied. It was administered intravenously in amounts ranging from 70 to 200 ml at rates of 7 to 30 ml per minute—dosages suggested by Bellet and Wasserman.

RESULTS

The effect of various drugs on ventricular rhythmicity and atrioventricular conduction were studied in 21 patients with Stokes-Adams disease; a total of 83 drug trials was carried out. In 16 patients drugs were administered during 23 periods of absent intrinsic ventricular activity lasting from 2½ to 108 hours during which the external stimulator was the only ventricular pacemaker. In 9 patients drugs were administered on 12 occasions when an intrinsic ventricular pacemaker was already present. The periods of observation lasted 1 to 23 hours; from 1 to 7 drug trials were carried out in each. Epinephrine was tested 37 times; isoproterenol (isopropyl-
INTRAVENOUS DRUG THERAPY OF STOKES-ADAMS DISEASE

Fig. 2 Top. Quantitative data from epinephrine trial illustrated in figure 1. The gray background here and in subsequent figures indicates periods of external electric stimulation when there was no spontaneous ventricular activity.

Fig. 3 Bottom. Repeated arousal, acceleration, and maintenance of an idioventricular pacemaker by epinephrine. Arousal of an idioventricular pacemaker at 1:16 and 2:03 p.m. permitted stopping of external electric stimulation (gray background). With excessive acceleration at 1:18 p.m. to a cycle length of 1.16 seconds (53 beats per minute) the drug dose was reduced and the rate slowed. Omission of epinephrine at 1:28 and 2:28 p.m. was followed by excessive ventricular slowing, so that resumption of electric stimulation was necessary at 1:45 p.m. and readministration of epinephrine at 2:38 p.m. Thereafter the ventricular rate was maintained at its former level of 1.60 second; (38 beats per minute).
norepinephrine or Isuprel†) 29 times; levaterenol (norepinephrine) 10 times; phenylephrine (Neosynephrine) 1 time; and 1-molar sodium lactate 5 times.

Arousal, Acceleration, and Maintenance of Intrinsic Ventricular Pacemakers

Attempts were made to arouse intrinsic ventricular activity with sympathomimetic drugs 51 times. Epinephrine was effective in 18 of 24 trials in doses ranging from 5 to 44 μg per minute (average 20 μg per minute). In 5 instances the ineffective doses ranged from 10 to 19 μg per minute; larger amounts were not given because of excessive elevation of the blood pressure. In the sixth instance, in a patient dying of cerebral damage, 64 μg per minute were given without cardiac effect.

Isoproterenol was effective in 19 of 20 trials in doses ranging from 5 to 43 μg per minute (average 12 μg per minute). In the 1 ineffective trial no more than 13 μg per minute were given because of a fall in blood pressure. Although the average effective dose of isoproterenol was somewhat less than that of epinephrine, the difference was not statistically significant.

Levaterenol was given 7 times because of hypotension during absent intrinsic ventricular activity. The amounts given (3 to 32 μg per minute) had a striking vasopressor effect but did not arouse ventricular pacemakers; on 1 occasion transient atrioventricular conduction was recorded (see fig. 9).

Observations of the effects of these drugs in accelerating and maintaining ventricular pacemakers were made after ventricular activity had been aroused and also on 12 occasions when an idiioventricular pacemaker was already established. In these trials both epinephrine and isoproterenol were potent and effective. Quantitative documentation of these actions will not be presented because they are already well known1,2 and our data, obtained during primarily therapeutic administration, are limited and incomplete.

Figure 1 shows electrocardiograms and

*Supplied through the courtesy of Winthrop Laboratories.

Figure 2 presents quantitative data illustrating the arousal and acceleration of an intrinsic ventricular pacemaker by epinephrine. At 10:55 a.m., after 10 hours during which ventricular beats occurred only with external stimulation (fig. 1A), epinephrine was given intravenously at a rate of 8 μg per minute. Within 5 minutes, after the total infusion of 40 μg of epinephrine, the P-P interval shortened and an idiioventricular pacemaker appeared with an R-R interval of 1.87 seconds (32 beats per minute) (fig. 1B); thereupon the electric pacemaker was stopped. The idiioventricular pacemaker accelerated rapidly to a cycle length of 1.32 seconds (45 beats per minute) (fig. 1C) and the epinephrine was stopped at 11:05 a.m. The idiioventricular pacemaker began to slow and its rate declined steadily to an R-R interval of 2.82 seconds (21 beats per minute) at 12:27 p.m. when syncope occurred. At this moment electric stimulation was resumed (fig. 1D) with an immediate rise of blood pressure and return of consciousness. Two minutes later a test interruption of stimulation (fig. 1E) showed that intrinsic ventricular activity was again absent.

Figure 3 shows in another patient the repeated arousal, acceleration, and maintenance of an idiioventricular pacemaker by epinephrine. The drug was given after 90 hours during which ventricular beats occurred solely in response to external electric stimuli. Dependence of the ventricular rhythm upon the drug was demonstrated repeatedly by the disappearance or abrupt slowing of the ventricular pacemaker whenever epinephrine was omitted. Finally, 21 hours after the beginning of epinephrine administration, the ventricular rhythm persisted at a satisfactory rate when the drug was stopped.

The effect of levaterenol was then tested upon this stable ventricular pacemaker. As expected, the blood pressure rose and there was a concomitant reflex slowing of the sinoatrial rate; the independent ventricular pacemaker, however, accelerated sharply. When the R-R interval had shortened to 1.38 seconds (43 beats per minute), a new ventricular pace-
Fig. 4 Top. Comparison of epinephrine and isoproterenol (I.P.N.) in arousing ventricular activity. The initial trial of epinephrine, which was started at 11:51 a.m., was stopped at 12:35 p.m. because of a marked pressor response without arousal of intrinsic ventricular activity. Isoproterenol at 12:42, 1:10, and 1:40 p.m., and epinephrine at 2:40 p.m. promptly aroused idioventricular pacemakers. Each time omission of the drug was followed by disappearance of spontaneous ventricular activity, which necessitated resumption of external electric stimulation.

Fig. 5 Bottom. Variability of ventricular rhythmicity after 2 isoproterenol (I.P.N.)-induced arousals. Isoproterenol administration started at 8:10 p.m. aroused an initially fast ventricular pacemaker, cycle length 1.14 seconds (54 beats per minute). The rate slowed promptly with cycle lengths varying between 2.10 and 2.40 seconds (29 and 25 beats per minute), and occasional conducted beats occurred until 8:32 p.m. External electric stimulation was resumed at 9:16 p.m. because of the slowing ventricular rate, whereupon spontaneous activity ceased. At 9:32 p.m. a smaller dose of isoproterenol aroused the pacemaker again. This time, however, it stabilized promptly at a cycle length of 1.60 seconds (38 beats per minute).
maker appeared, which continued to accelerate to a cycle length of 1.23 seconds (49 beats per minute). Then levaterenol was stopped and this potentially toxic sequence was reversed promptly.

The efficacy of epinephrine and isoproterenol in arousing intrinsic ventricular activity was compared by administering them in varying order and in close sequence to 9 patients. No superiority of one drug over the other was demonstrated.

In figure 4 the effects of epinephrine and isoproterenol in arousing a ventricular pacemaker were compared after 12 hours of continuous external electric stimulation. Five observations were carried out within a 3-hour period from an apparently similar baseline of absent intrinsic ventricular activity. An initial attempt to arouse a ventricular pacemaker with epinephrine failed but 3 subsequent trials of isoproterenol and a final trial of epinephrine aroused transient ventricular activity. Comparison of the effects of isoproterenol with the initial epinephrine trial suggests a marked difference between the 2 drugs. However, the final epinephrine observation indicates a similar effectiveness of these agents.

The variability of drug effect on the heart is strikingly illustrated again in figure 5. In 2 closely spaced trials isoproterenol readily aroused a ventricular pacemaker; other cardiac effects of the 2 doses, however, differed strikingly, even though they were given to the same patient so closely together and from the same baseline of absent intrinsic ventricular activity. In the first trial the basic ventricular pacemaker slowed progressively and was interrupted by occasional conducted beats and frequent beats from other slow ventricular foci; in the second trial the ventricular pacemaker stabilized promptly and persisted at a much faster rate than before with only a few multifocal beats. This change in response emphasizes the caution necessary in quantitating and in comparing the cardiac effects of drugs.

On 1 occasion phenylephrine was compared with epinephrine and isoproterenol (fig. 6). In a dose that produced a marked rise in blood pressure, phenylephrine did not accelerate the ventricle. In contrast, epinephrine and isoproterenol produced marked ventricular acceleration and change in focus with variable blood pressure responses.

Cardiac Toxicity

Phenomena suggesting potential cardiac toxicity were observed with each sympathomim-
INTRAVENOUS DRUG THERAPY OF STOKES-ADAMS DISEASE

Fig. 7. Comparison of therapeutic effect (arousal of ventricular pacemaker) versus toxic effects (excessive acceleration and multifocal ventricular activity) of epinephrine and isoproterenol (I.P.N.). Isoproterenol at 12:27 and 1:00 p.m. aroused ventricular activity that was transient and was marked by excessive acceleration to a cycle length of 0.84 second (71 beats per minute) and multifocal ventricular beats. Epinephrine, on the other hand, at 11:48 a.m. and 2:00 p.m., aroused slower, and more persistent ventricular rhythms without multifocal beats.

motic drug tested. These effects, which were considered to be possible forerunners of ventricular tachycardia or fibrillation, were acceleration of idioventricular pacemakers above 50 beats per minute (R-R = 1.2 seconds) and the appearance of premature beats after an interval of less than 1.2 seconds. The limit of acceleration was placed at this rate of 50 beats per minute, which we consider safe and sufficient for almost all therapeutic purposes and which is well below the level of acceleration found by Schwartz et al. to precede ventricular fibrillation. Multifocal ventricular activity at a rate slower than 50 beats per minute (R-R more than 1.2 seconds), whether it occurred as single beats or as shifts among dominant pacemakers, is often seen spontaneously in complete heart block and therefore was not considered ominous. Of particular concern were rapid ventricular rhythms from new or multiple foci and premature beats that were very frequent or that came from multiple foci. Premature beats that fall on the preceding T waves have also been described as being particularly ominous, but we observed none.

Potential cardiac toxicity was observed with epinephrine and isoproterenol in 10 patients: excessive ventricular acceleration (over 50 beats per minute) 6 times and premature beats 5 times with isoproterenol; excessive acceleration twice and premature beats 4 times with epinephrine. Whenever these signs of potential toxicity were observed, administration of drugs was slowed or stopped, whereupon the untoward manifestations disappeared promptly. Serious clinical toxicity of ventricular tachycardia of more than a few beats' duration or ventricular fibrillation never occurred in the course of this drug therapy. One paroxysm of atrial tachycardia due to epinephrine was observed. It lasted only a few seconds, stopping after omission of the drug, and was of no clinical significance.

Usually, excessive acceleration or premature beats occurred when the drug dose was continued or increased after a therapeutic effect had been obtained. Sometimes, however,
the toxic effect could not be dissociated from the therapeutic one. As shown in figure 7, for example, isoproterenol twice aroused an intrinsic ventricular pacemaker but multifocal ventricular activity and tachycardia occurred at the same time. On the second trial the dose of isoproterenol that produced the tachycardia was inadequate to maintain ventricular activity and the ensuing standstill required electric stimulation (fig. 8). In contrast, epinephrine in 2 trials shortly before and after the isoproterenol, aroused and maintained an intrinsic ventricular pacemaker without the production of multifocal beats.

Increase in Atrioventricular Conduction

Another cardiac effect of sympathomimetic amines is to increase atrioventricular conduction. This may occur as an isolated effect (fig. 9) or together with other cardiac responses to the drugs (figs. 5 and 10). This phenomenon was observed 17 times in 6 patients: 4 times with epinephrine, 12 times with isoproterenol, and once with levaterenol. All 6 patients showed occasional spontaneous atrioventricular conduction of some degree; nevertheless it was clearly established that the drugs also increased conduction. The doses of the drugs that produced this effect were in the same range as the doses that aroused ventricular pacemakers: 5 to 15 μg. per minute of epinephrine and 4 to 22 μg. per minute of isoproterenol. Varying degrees of conduction were observed, from occasional beats to normal 1 : 1 atrioventricular conduction. Atrioventricular conduction was transient, lasting from a few seconds (fig. 9) to 45 minutes (fig. 10); this phenomenon, therefore, was of little clinical value although of considerable theoretical interest.

Figure 9 shows transient, partial atrioventricular conduction due to administration of levaterenol during a prolonged period of external electric stimulation. The only other cardiovascular effect of the drug was a slight elevation of the blood pressure. Idioventricular activity was not aroused; when conduction failed there was ventricular standstill with syncope requiring immediate resumption of external stimulation.

Figure 10 shows the appearance of atrioventricular conduction together with the acceleration and maintenance of an idioventricular pacemaker with the administration of isoproterenol. Other cardiovascular effects were sinoatrial acceleration and fall in blood pressure. With the first 2 trials, 2 : 1 atrioventricular conduction occurred. During the
Intravenous Drug Therapy of Stokes-Adams Disease

Fig. 9. Restoration of partial atrioventricular conduction for 45 seconds by levarterenol (nor-epineph.). With a sinoatrial cycle of 0.70 second, the ventricular cycles were 1.40 seconds (2:1), 2.10 seconds (3:1), and 2.80 seconds (4:1).

Third drug trial, when the rate of administration was fastest, a step-by-step sequence was observed from complete block to 1:1 atrioventricular response. The repeated appearance of atrioventricular conduction with each trial of isoproterenol established the conclusion that the drug caused this change.

Effects of Sodium Lactate on Ventricular Rhythm

In view of the reported therapeutic value of intravenous molar sodium lactate in Stokes-Adams disease, we also tested its action in arousing or accelerating an idioventricular pacemaker in 5 patients.

In 1 patient who had been without intrinsic ventricular activity for 26 hours, 200 ml. of molar sodium lactate were administered in 6 minutes without effect. After half an hour, trial of sympathomimetic amines was started; epinephrine and isoproterenol, in sequence, both aroused ventricular activity.

In 3 patients there was slight acceleration of an established idioventricular pacemaker; after 100 ml. in 11 minutes, the R-R interval shortened from 3.56 to 2.76 seconds (17 to 22 beats per minute); after 150 ml. in 20 minutes, it changed from 1.40 to 1.28 seconds (43 to 47 beats per minute); and after 90 ml. given in divided doses in 1 hour, it shortened from 1.89 to 1.69 seconds (32 to 36 beats per minute). In 2 of these patients variable atrioventricular conduction was seen spontaneously or following administration of epinephrine; contrary to observations by others, atrioventricular conduction did not increase after sodium lactate in these patients. The fifth patient (fig. 11), who received 70 ml. in 12 minutes, showed a slight but definite slowing of the ventricular rate; sodium lactate then was stopped because of the appearance of frequent premature ventricular beats and bigeminy. In striking contrast was the marked acceleration observed in this patient after epinephrine and isoproterenol. A very few premature ventricular beats were also seen
at the height of the epinephrine acceleration, but none occurred with the isoproterenol.

Our large experience with sympathomimetic amines indicating their safety and efficacy, the relatively slight ventricular acceleration with sodium lactate, and the reported toxicity of this drug\(^7\)\(^1\) have deterred us from testing this agent further. Therefore we have not systematically compared molar sodium lactate with sympathomimetic agents in arousing intrinsic beats in patients with persistent ventricular standstill.

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**Fig. 10** Top. Repeated acceleration of idioventricular pacemaker and restoration of atrioventricular conduction (2:1 and 1:1) by isoproterenol (I.P.N.). Isoproterenol administered at 11:45 a.m., 12:55, and 4:15 p.m. accelerated the idioventricular rate (●) and also produced atrioventricular conduction (X).

**Fig. 11** Bottom. Comparison of epinephrine, isoproterenol (I.P.N.), and sodium lactate in accelerating an idioventricular pacemaker and in exciting premature ventricular beats. Epinephrine, administered at 10:53 a.m., accelerated the ventricular rate, excited occasional premature ventricular beats, and elevated the blood pressure. Isoproterenol, administered at 11:22 a.m., accelerated the ventricular rate even more without producing premature beats or raising the blood pressure. In contrast, sodium lactate, administered at 12:12 p.m., slowed the ventricular rate slightly and produced frequent premature ventricular beats and bigeminy.
INTRANOVENOUS DRUG THERAPY OF STOKES-ADAMS DISEASE

DISCUSSION

These observations show clearly the effectiveness and safety of epi-nephrine and isoproterenol administered intravenously in dilute solutions for the arousal, acceleration, and maintenance of intrinsic ventricular activity. For arousal, the effective intravenous dose was often only a small fraction of the usual subcutaneous dose: for example, only 40 μg. (8 μg. per minute for 5 minutes) of epinephrine (fig. 2) compared to 200 to 500 μg. The rapid appearance and disappearance of the effects of the drug contribute to safety by permitting moment-to-moment control. By the same token constant supervision is required; such close attention is feasible for emergencies but is impractical for long-term administration. For prolonged acceleration and maintenance, epinephrine, isoproterenol, and ephedrine may be given by other routes.

These rapid and clear-cut responses permit reliable measurements of the effects of these drugs and some comparisons of their actions. The striking differences in effects of the same agent in closely spaced trials in the same patient (figs. 4 and 5) indicate a change in cardiac responsiveness, even though the baseline for each trial was apparently the same in that there was no spontaneous ventricular activity. This change makes the comparison of different agents particularly difficult. Such difficulties would be multiplied by attempts at comparisons at widely spaced intervals or in different patients. The factors that produce such changes in cardiac responsiveness are unknown. Analogous, inexplicable sudden changes in ventricular rhythmicity account for the striking unpredictability that is so prominent a clinical feature of Stokes-Adams attacks and that complicates the evaluation of drug therapy.

If cardiac responsiveness remains unchanged, as demonstrated by uniform effects of the same drug at the beginning and end of a test period, fairly valid comparisons can be made, however, from a baseline of either absent ventricular activity or of a stable idioventricular rate. For example, in figure 7, the production of ectopic activity by isoproterenol sandwiched between fairly uniform responses to epinephrine without ectopic activity permits the conclusion that isoproterenol was more toxic in this patient at this time. The somewhat different observation in another patient, shown in figure 11, suggests the opposite conclusion that epinephrine was more toxic than isoproterenol. Variations of this kind from patient to patient emphasize the danger of generalizations about comparative toxicity on the basis of limited data.

In choosing between epinephrine and isoproterenol for patients with Stokes-Adams disease, one must consider the effectiveness of each drug in arousing, accelerating, and maintaining a ventricular pacemaker versus the risk of exciting ectopic ventricular activity. It has recently been stated that isoproterenol is superior to epinephrine because its effective dose is smaller and because it does not lead to ventricular tachycardia or fibrillation. The latter conclusion is based in one instance on a comparison in 1 patient of the effects of a single dose of each drug administered a day apart; the other instance described the clinical course of 2 patients, one of whom received epinephrine and subsequently isoproterenol, and the other of whom was treated only with isoproterenol. These observations exemplify the difficulties of comparison we have just enumerated and do not justify the conclusion reached by the authors.

From our studies a figure cannot be given for the minimal effective dose and for the therapeutic/toxic ratio of each drug. The dose of each drug necessary to arouse a ventricular pacemaker varied widely from patient to patient and at different times in the same patient. Data on toxicity were necessarily limited to fortuitous observations in these clinical studies. In this regard we are carrying out detailed quantitative studies of sympathomimetic drugs in dogs with surgically produced, permanent complete heart block.

Nevertheless, our many observations of these 2 drugs permit the general conclusion that there is no striking difference in their cardiac effects. Both agents were very effective in arousing, accelerating, and maintain-
ing a ventricular pacemaker in doses that were not significantly different. In any case, differences in doses are not an important basis of comparison; considerations of safety are of much greater clinical significance. Both drugs produced minor toxicity, in the form of excessive acceleration and premature ventricular beats, which disappeared promptly when drug administration was stopped. These untoward manifestations were infrequent and occurred about equally with both drugs.

Clear differences between the 2 drugs lie in their effects on the blood pressure and on the sinoatrial rate. Epinephrine usually had a marked pressor effect, whereas isoproterenol had no effect or lowered the blood pressure. Isoproterenol usually accelerated the sinoatrial rate markedly, whereas the effect of epinephrine was comparatively slight (figs. 6 and 11). In patients with atrioventricular conduction this action of isoproterenol may result in a rapid ventricular rate with untoward clinical manifestations. In figure 10, for example, at 4:38 p.m. the ventricular rate rose to 150 beats per minute (R-R = 0.40 second) as a result of sinoatrial acceleration and 1:1 atrioventricular conduction, both due to isoproterenol. Considerations of these actions often determined our initial choice. If the first drug was ineffective or toxic, we frequently tried the other agent, often with success.

Levarterenol, another widely used sympathomimetic amine, had cardiovascular effects quantitatively different from those of epinephrine and isoproterenol. Its major action was a striking vasopressor one. Although we did not observe it to restore intrinsic ventricular activity, it did accelerate a ventricular pacemaker that was already present and it did excite multifocal ventricular beats. These effects on cardiac rhythmicity are of clinical importance as toxic manifestations when the drug is used as a vasopressor agent in the treatment of shock. In 1 observation (fig. 6) phenylephrine in a vasopressor dose had no effect on the idioventricular pacemaker. Further observations of this type may uncover the vasopressor agent that carries minimal risk of exciting ventricular tachycardia or fibrillation.

Our experience with molar sodium lactate is too limited for adequate evaluation of this drug in Stokes-Adams disease. It accelerated the ventricle only slightly in comparison with epinephrine and isoproterenol, yet it produced ectopic ventricular activity. These observations suggest a relatively low efficacy in arousal and acceleration of ventricular rhythm and a relatively small therapeutic/toxic ratio.

In addition to stimulating ventricular rhythmicity, epinephrine, isoproterenol, and levarterenol increased atrioventricular conduction. This effect on conduction was transient and therefore was not clinically significant. This observation has been reported by others in man and is related to the experimental demonstration that epinephrine shortens the refractory period and increases the speed of atrioventricular conduction. All the patients in whom we saw this effect of drugs, at other times had spontaneous variations in atrioventricular conduction of the type that has been termed paroxysmal or intermittent heart block. These changes in conduction in patients with complete heart block are of great theoretical interest: they indicate a functional component as well as an organic basis for heart block and suggest the possibility that a clinically useful drug may be found to increase and maintain atrioventricular conduction.

Intravenous Administration of Sympathomimetic Drugs in the Treatment of Stokes-Adams Disease

The technique of external electric stimulation and defibrillation permit the emergency resuscitation of patients from Stokes-Adams attacks. There are 2 other problems, however, in the management of this disease: persistent absence of intrinsic ventricular activity and frequent recurrence of attacks. The intravenous administration of epinephrine or isoproterenol is often indicated to arouse, accelerate, or maintain intrinsic ventricular pacemakers. When the idioventricular pacemaker slows markedly or stops frequently, the drugs may stabilize the ventricular rate at an ade-
quate level and stop the seizures, making electric stimulation unnecessary.

After the resuscitation of a patient with Stokes-Adams disease from ventricular standstill with the external electric pacemaker, stimulation should be stopped promptly to see whether intrinsic ventricular activity has returned. If a satisfactory and stable ventricular pacemaker (at least 25 beats per minute) is not present, external electric stimulation must be continued. Since prolonged stimulation in the conscious patient is usually painful, it is often desirable to arouse intrinsic ventricular activity without delay. Therefore, if intrinsic ventricular activity remains absent for 1 hour or more, epinephrine or isoproterenol should be administered intravenously according to the technic and with the precautions we have described. The ventricular pacemaker aroused by drugs may be unstable and may require prolonged continuous regulation of the drug infusion. In this situation, it is often preferable to stop drug administration, to return to the dependable electric pacemaker for as long as desired, and then to try drugs again.

Considerations of the different effects of these 2 drugs on the blood pressure and on the sinoatrial rate often determine the initial choice. In patients with high blood pressure isoproterenol is preferable, since it has no vasopressor action; when the pressure is normal or low, epinephrine is the drug of choice. In patients who have recently had atrioventricular conduction epinephrine should be used, since it is a much less potent accelerator of the sinoatrial pacemaker than is isoproterenol and there is, accordingly, less risk of a rapid ventricular rate should atrioventricular conduction return. Familiarity with a drug and its ready availability may also influence the initial selection.

Intravenous administration of the drug should be started at a rate of 4 μg. per minute (15 drops or 1 ml. of a solution containing 4 mg. of the drug in 1 L. of 5 per cent dextrose in water), and its effects should be observed electrocardiographically during frequent short interruptions of electric stimulation. Every few minutes the rate of infusion should be increased by increments of 4 to 8 μg. per minute until a ventricular pacemaker is aroused or until cardiac or systemic toxicity is produced in the form of frequent or multifocal premature ventricular beats, ventricular acceleration faster than 50 beats per minute, excessive rise or fall of the blood pressure, or excessive stimulation of the central nervous system. If the first drug fails to arouse a satisfactory ventricular pacemaker or if it produces toxicity, its administration should be stopped and the other drug should be tried subsequently.

When a ventricular pacemaker is aroused, the rate of drug administration should be adjusted until the idioventricular rate is between 35 and 45 beats per minute. When the ventricular rate has stabilized in this range, the rate of drug administration should be gradually slowed and then stopped if the ventricular rate is maintained.

Frequent Stokes-Adams attacks due to recurrent slowing or disappearance of the ventricular pacemaker constitute a second indication for the intravenous administration of epinephrine or isoproterenol. In this situation also, either drug may stabilize the ventricular rate between 35 and 45 beats per minute and prevent further attacks.

At this point, when a satisfactory ventricular rate has been achieved, other therapy, such as oral ephedrine or sublingual isoproterenol, may be instituted for the long-term management of Stokes-Adams disease. We have observed that seizures are unlikely to recur after 1 month has passed without an attack. During this period it is important to observe the patient closely and to have an external electric pacemaker in emergency readiness.

**Summary**

The effects of intravenously administered epinephrine, isoproterenol, levarterenol, phenylephrine, and sodium lactate on ventricular rhythmicity and atrioventricular conduction have been studied in 83 drug trials in 21 patients with Stokes-Adams disease.

Epinephrine and isoproterenol in dilute
solutions were equally effective in arousing ventricular pacemakers in patients without intrinsic ventricular activity while they were being kept alive by prolonged external electric cardiac stimulation. Both drugs were also effective in accelerating and maintaining ventricular activity. Minor cardiac toxicity (excessive ventricular acceleration above 50 beats per minute or premature ventricular beats), occurring equally with both drugs, was an indication to slow or stop drug administration; major cardiac toxicity (persistent ventricular tachycardia or fibrillation) did not occur. In addition, both epinephrine and isoproterenol occasionally produced transient increase in atrioventricular conduction.

Levarterenol, in addition to its marked vasopressor action, also affected ventricular rhythmicity and atrioventricular conduction whereas phenylephrine had only a vasopressor effect. Differences of this nature may prove important in the selection of a sympathomimetic amine for a particular cardiovascular effect.

Limited observations of sodium lactate showed it to be less effective than epinephrine and isoproterenol in arousing and accelerating ventricular pacemakers.

**SUMMARIO IN INTERLINGUA**

Le effectos de administracione intravenose de epinephrina, de isoproterenol, de levarterenol, de phenylephrina, e de lactato de natrium super le rhythmicitate ventricular e super le conduction atrioventricular esseva studiate in 83 essayos in 21 patientes con morbo de Stokes-Adam.

Epinephrina e isoproterenol in diluite solutions non differeva in lor efficacia in stimular pacemakers ventricular in patientes sin intrinsec activitate ventricular qui esseva tenite in vita per medio de prolongate externe electrostimulation del corde. Le duo drogas habeva etiam le efecto de accelerar e mantenere le activitate ventricular. Minor grados de toxicitate cardiac (excessos de acceleration ventricular supra 50 pulsos per minuta o prematur pulsos ventricular) occurreva con le un e con le altere del duo drogas e esseva prendite como indication pro relentar o arrestar le administration. Formas major de toxicitate cardiac (persistente tachycardia o fibrillation ventricular) non occurreva. In plus, tanto epinephrina como etiam isoproterenol produceva in certe casos augmentos transciente de conduction atrioventricular.

Levarterenol, a parte su marcate action vasopressori, etiam afficceva le rhythmicitate ventricular e le conduction atrioventricular, durante que phenylephrina habeva solmente un efecto vasopressori. Diferencias de iste genere va frequentemente provar se importante in le selection de un amina sympathomimetic pro evocar un specific efecto cardiovascular.

Minus extense observationes de lactato de natrium mostrava que illo es inferior a epinephrina e isoproterenol como stimulator e accelerator de pacemakers ventricular.

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The searching into the works of Nature, while it delights and inlarges the mind, and strikes us with the strongest assurance of the wisdom and power of the divine Architect, in framing for us so beautiful and well regulated a world, it does at the same time convince us of his constant benevolence and goodness towards us.—Statistical Essays. REVEREND STEPHEN HALE. From the Dedication to His Royal Highness, George, Prince of Wales. Volume I, The Second Edition, London, 1731.
Intravenous Drug Therapy of Stokes-Adams Disease: Effects of Sympathomimetic Amines on Ventricular Rhythmicity and Atrioventricular Conduction

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