post-ganglionic sympathetic-blocking drug. Debrisoquine is as effective as guanethidine as a hypotensive drug: it has fewer side-effects than the latter, while a shorter duration of action may be an advantage in certain circumstances.

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Clinical Evaluation of Oral Long-acting Isoprenaline in Treatment of Heart-block

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The need for a safe and effective treatment of heart-block has long been recognized. Of the many drugs used isoprenaline hydrochloride has, since its introduction by Nathanson and Miller (1952), been the most promising one, and the one most carefully studied.

Since the first reports of the use of a slow-release oral preparation (Saventrine) in the treatment of heart-block (Dack and Robbin, 1961; Corday *et al.*, 1962; Fleming and Mirams, 1963) we have been investigating this preparation on a clinical basis, and we now present the results of assessment of its use in a larger series of cases treated since June 1962. A similar study was reported by Bluestone and Harris (1965). The active principle, in the form of small granules, is first coated with varying numbers of layers of ethyl cellulose separated by talc. The coated granules are then incorporated into tablets, each containing 30 mg. of isoprenaline hydrochloride. Ethyl cellulose is insoluble in the fluid contents of the gastro-intestinal tract, but water-absorption causes the layers to expand and disintegrate. This process is independent of pH, gastro-intestinal mobility, and variation in intestinal enzymes. The active ingredient is released slowly, for intestinal absorption, over a period of eight hours after the administration of a single dose.

Isoprenaline hydrochloride (Isupren, isoproterenol U.S.P., isopropylnoradrenaline) is 1-(3,4-dihydroxyphenyl)-2-isopropylaminoethanol. It possesses an isopropyl group on the terminal nitrogen of the side-chain in place of the methyl group of adrenaline. It is a sympathomimetic amine, the stimulant action of which on the heart is its only sympathomimetic action which might be classified as excitatory. It is a vasodilator, a bronchial dilator, and it inhibits intestinal and uterine motility. It has been used by the subcutaneous, intravenous, sublingual, and rectal routes in the treatment of heart-block.

Intravenous injection of 0.02 mg. of isoprenaline in complete heart-block produces an increase of the ventricular rate for a few minutes, while the effect of subcutaneous injection lasts one to two hours, and with sublingual administration the action starts in 15 to 30 minutes and lasts for 45 to 120 minutes. The action of isoprenaline is similar to that of adrenaline (epinephrine) but is less likely to produce ectopic beats and is more sustained (Nathanson and Miller, 1952). Unlike adrenaline, it rarely moves the idioventricular pacemaker more distally (Chandler and Clapper, 1959). While adrenaline may precipitate ventricular tachycardia or fibrillation, isoprenaline

has a predominant effect upon the high idioventricular or supra-ventricular pacemaker and is less likely to do so (Adelman *et al.*, 1957). It increases cardiac output and lowers systemic vascular resistance, so that the mean systemic arterial pressure shows little change. The increase of cardiac output may be due to an increase of the heart rate or to stimulation of the strength of myocardial contraction, or to both factors (Stack *et al.*, 1958), and this appears to be the case both in the normal heart and in the presence of complete atrioventricular block. There is a greater effect on the sinoatrial pacemaker than on nodal or ventricular foci (McGaff *et al.*, 1959), so that the accelerating effect is greatest in the normal.

Material and Management

Twenty-one patients (14 males, 7 females) were selected for this treatment over three years and there have been 26 trials. The ages of the patients varied from 5 to 76 years. Two patients had ischaemic heart disease, three had primary myocardial disease, and one had calcific disease of the mitral and aortic valves. In two the heart-block was post-operative, following total correction of Fallot's tetralogy, and in 13 the cause was unknown. The presenting symptom in all cases was that of inefficient cerebral perfusion in the form either of Stokes-Adams attacks or of prolonged confusional states. Five patients had heart failure as well. In 18 cases the heart-block was complete and in three it was partial or varying in degree. Attacks of ventricular tachycardia were considered to contraindicate the use of this preparation, which otherwise was given a trial in every case. The initial dosage given was usually 30 mg. six-hourly (120 mg./day), and this was increased if necessary, usually every two to three days, to a maximum of 120 mg. four-hourly (720 mg./day). The pulse rate was recorded every hour, E.C.G.s were obtained at least once daily, and a careful watch was kept for side-effects. The goal, of course, was to produce a stable and sufficient idioventricular rate with the fewest possible side-effects. With patients who required artificial pacemaking from the start, we carried out the same regimen in the hope that we might be able to take them off the pacemaker later.

Case Reports

Two cases, each illustrating a particular aspect or problem, are described below.

Case 13.—An 8-year-old boy, operated on for total correction of Fallot's tetralogy, developed complete heart-block on the operating-table. He had suffered from left hemiplegia and epileptic

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fits due to a cerebral abscess five months before the operation. His ventricular rate ranged between 40 and 48 per minute. At the age of 12 long-acting isoprenaline was given for five days, with a maximum dose of 120 mg./day. No effect on the pulse rate was noted and the drug was discontinued. A few months later he developed frequent syncopal attacks, during which the pulse rate fell to 28–31, with periods of pulselessness for 10–12 seconds. An induction pacemaker (Abrams, Birmingham, type) was implanted and he was discharged. In the following year he had to be admitted twice for thoracotomy to change a broken pacemaker wire. When the wire broke for the third time he was 14 years old and weighed 69 lb. (31.3 kg.). It was decided to give Saventrine a further trial in the hope of sparing the boy yet another thoracotomy. The drug was started as usual with 120 mg./day and gradually increased to 360 mg./day, on which dose he was discharged. Before treatment his ventricular rate was 34–40 and he was having Stokes-Adams attacks; on discharge the rate was 40–65 and he was well. Four months later he still had the same pulse rate, without black-outs. He was an accurate observer of his own pulse rate, and commented that the rate of 65 was always reached about two and a half hours after each dose of Saventrine.

Case 14.—A 71-year-old man had his first attack of unconsciousness two years before his admission to our unit. On admission his fourth pacemaker had failed and he had had three syncopal attacks. His pulse was irregular, of large volume, and rate 34. The E.C.G. showed an idioventricular rate of 28, and a pacemaker rate of 18, to which the ventricle responded if not refractory. The atrium was beating at a rate of 60. Long-acting isoprenaline was started with 120 mg./day and gradually increased to 540 mg./day. While on the latter dose, one hour after administration of 90 mg., he complained of "terrible" palpitation, and the E.C.G. showed an atrial rate of 100 with 3:1, 2:1, and occasional 1:1 ventricular response. The dosage was reduced to 360 mg./day, and then further to 240 mg. because of a similar disturbing attack. On this dose his ventricular rate was only 38, and after provision of the fifth artificial pacemaker long-acting isoprenaline was stopped.

Results

Of the 26 trials the results were classified as follows:

Good (sinus rhythm restored and maintained) ...	4
Satisfactory (stable increase of ventricular rate) ...	8
Unsatisfactory (no effect or unstable state produced) ...	14

Side-effects.—The commonest side-effect was the production of ventricular ectopic beats, which occurred in seven of our series. They were not thought to preclude the use of the drug unless they appeared with a small dose. Atrial flutter was present in one of our series. Tremulousness of the hands or of the whole body occurred in three. It did not necessitate discontinuation of the drug, and tended to improve with the passage of time. Five patients complained of palpitation—in four it was mild or transient, but in one (Case 14) the attacks were so disturbing that the drug had to be discontinued. Sweating or flushing was not noted, and our patients did not mention visual, gastro-intestinal, bladder, or sleep disturbance. In one patient (Case 7) a large dose (540 mg./day) was stopped abruptly just before an operation to change an internal pacemaker. He had a long period of asystole on the operating-table, and life had to be maintained by external cardiac massage while the new pacemaker was connected. Although this event might have been fortuitous, it is now advised that long-acting isoprenaline, especially if it has been given in large dosage for a long period, should be withdrawn gradually.

Discussion

When heart-block threatens life, and an increase of the idioventricular rate is urgently needed, isoprenaline is best given by the intravenous route. The recommended dose is 10–30 drops a minute of 1% isoprenaline solution, the rate of administration being guided by the ventricular rate and by the appearance of ectopic beats. When facilities exist, however, the introduction of an electrode catheter to the right ventricle, to establish arti-

ficial pacemaking, is preferred, for it provides immediate and reliable relief in a critical situation.

Chandler and Clapper (1959) kept six out of seven patients free from Stokes-Adams attacks for an average of 113 days by sublingual isoprenaline, with a dose of 10–20 mg. every two to three hours. For prolonged treatment, however, oral administration of long-acting isoprenaline is more convenient.

In our experience small doses usually had little effect. Thus we had only three satisfactory results with 180 mg./day. The response to the preparation is somewhat unpredictable, and there is great variability in different subjects. Furthermore, with the same patient and the same dose the effect may vary from time to time. This was well illustrated in two of our cases (Nos. 17 and 18). We do not know the mechanism of this variability, and studies of blood levels and urinary excretion will be needed to elucidate this.

Although release of the active principle from the long-acting isoprenaline tablets is meant to be uniform, a definite relation between the time of the dose and its effect was repeatedly observed. Thus the maximum increase in ventricular rate and the tremulousness, when present, usually occurred together one to two hours after the dose.

Dack and Robbin (1961) pointed out that several types of beneficial effects are noted with oral sustained-action isoprenaline: (1) sinus rhythm may be restored; (2) in patients with two idioventricular pacemakers the faster one may be maintained and the slower suppressed; (3) the idioventricular pacemaker may not shift but its rate becomes faster; and (4) no distinct effect on ventricular rate may be noted, but the rhythm remains stable and ventricular asystole does not occur.

There is no doubt that sinus rhythm can be restored even after years of atrioventricular block (Case 14). It happened in six of our patients and was maintained in four of them. In all of these four cases heart-block was of recent onset (three months or less), and in two of them the block was incomplete from the start. These four patients received steroids as well as long-acting isoprenaline, but in one of them (Case 4) the block returned after discontinuation of isoprenaline and while on the same dose of steroids, and in two (Cases 19 and 20) the block was abolished by increasing isoprenaline while reducing steroids.

The two patients in whom sinus rhythm returned but was not maintained require a special note. Isoprenaline increases the atrial as well as the idioventricular rate, and if the dose required to restore sinus rhythm is large the sinus tachycardia produced may be more disturbing to the patient than a quiet slow rate. The disturbance is especially great, of course, if the degree of block is unstable. We therefore believe that the use of isoprenaline is likely to be disappointing in cases of unstable heart-block, unless they are controlled by a small dose which does not produce very marked sinus tachycardia.

Although the rhythm disturbance in Stokes-Adams attacks is usually ventricular asystole or a very slow idioventricular rate, it is sometimes ventricular tachycardia or even paroxysmal ventricular fibrillation. It is important, therefore, to monitor all patients who get these attacks in order to observe the mechanism in the particular case and to avoid the use of isoprenaline where this is ventricular tachycardia or fibrillation.

In 46% of the trials in this series the need for artificial pacemaking was averted. We conclude that it should be tried in all cases except those where Stokes-Adams attacks are due to ventricular tachycardia or fibrillation. The presence of ventricular ectopic beats before treatment does not contraindicate such a trial, but very close observation is required in such cases during the trial period. Multifocal ventricular activation may be a sign of poor coronary perfusion, the result of low cardiac output associated with the slow rate.

The drug should be given a full trial in the manner described before being discarded as unsatisfactory. This means a prolonged period of close observation in hospital, with oscilloscopic

monitoring of the E.C.G., at least initially, an hourly pulse chart, and frequent E.C.G.s, while the dose is adjusted. The drug should be abandoned if it has insufficient effect to relieve Stoke-Adams attacks or failure, if it gives rise to unpleasant side-effects, or if the rate or rhythm is so unstable as to be intolerably disturbing or dangerous.

Summary

The usefulness and the limitations of an oral long-acting isoprenaline preparation (Saventrine) in the treatment of heart-block have been assessed from the results of 26 trials on 21 patients since 1962.

In 46% of the trials the need for artificial pacemaking was averted or overcome.

It is suggested that this preparation should be tried in every case where artificial pacemaking is to be considered or has failed, except in patients who have shown ventricular tachycardia or ventricular fibrillation.

The need for close observation during the trial stage is stressed and the dosage scheme used is outlined.

Side-effects, which were few in this series, are described. Sudden withdrawal of a large dose must be avoided.

ADDENDUM.—Since this report was completed, experience with Saventrine in a further 10 patients with complete heart-block has not diminished the validity of these findings and conclusions, except that in two cases severe diarrhoea prevented effective use of the drug. It occurred on a dose of 300 mg. daily in one case and 450 mg. daily in the other.

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Renal Failure Associated with Low-molecular-weight Dextran Infusion*

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Low-molecular-weight dextran has gained a place in medical practice since the early reports of Gelin (1961) and Gelin and Ingleman (1961), and was reviewed by Moore (1963), who maintained that there were three broad indications for its use in surgical practice: (1) trauma with shock, where low tissue blood-flow was responsible for at least part of the ensuing physiological disturbances; (2) extracorporeal circulation; and (3) localized ischaemia or the threat of localized ischaemia.

There seems no doubt that low-molecular-weight dextran is a potent rheological agent, capable of improving the flow in small vessels; its usefulness has been reported in Gram-negative septicaemia, vascular grafting, coronary occlusion, and Raynaud's phenomenon. Its antithrombotic properties have been studied and applied clinically by Winfrey *et al.* (1963).

Its use in the management of ulceration of the skin after arterial occlusion was reported by Bienenstock and Harding (1964). This application of low-molecular-weight dextran has been less closely studied, and may well have more risk because long courses, extending over some days, are involved. The regimen proposed by Bienenstock and Harding was to give a loading dose of 500 ml. in two hours and a maintenance dose "by slow continuous intravenous infusion for three days." Thereafter 500 ml. was given over six hours every three days until healing occurred.

The renal effects of low-molecular-weight dextran have attracted interest. Acute infusions produce an increase of urine flow in normal individuals. Gelin (1961) maintained that the diuresis was due to improved kidney perfusion. This claim has been questioned by Matheson *et al.* (1964).

Eliasson (1963) warned that the use of dextran in dehydrated patients could be dangerous because the dextran concentration in the tubular urine could become so high that the urine was rendered highly viscous. Hint (1963), commenting on a paper by Artz (1963) on the use of low-molecular-weight dextran in burns, warned that this highly viscous urine might actually threaten anuria, and stressed that patients receiving the substance must also be given adequate amounts of fluid. Eliasson, however, asserted that low-molecular-weight dextran had not been shown to cause any functional disturbances of the kidney.

We report three cases of acute renal failure, one of them fatal, following the use of low-molecular-weight dextran in prolonged courses. All three patients were adequately hydrated throughout, and in none of them was there evidence of any severe underlying renal disease. Renal biopsy in all cases showed grossly swollen tubular cells obliterating the tubular lumen. No glomerular, arterial, or interstitial pathology was found. Staining for dextran revealed a gross accumulation of that substance in the tubular cells. There were no intraluminal dextran casts. Because we felt that intermittent dosage was not entirely logical, we chose to use slow continuous infusions of 10% low-molecular-weight dextran in dextrose, averaging 1,000 ml. each day.

Case 1

A man aged 77 was admitted to hospital with an acute popliteal-artery obstruction. He was well hydrated, his blood-pressure was 270/110 mm. Hg, and the apex beat was in the sixth left intercostal space in the anterior axillary line. Blood urea, serum electrolytes, and microscopical examination of a centrifuged urine were normal. He was started on continuous intravenous heparin (30,000 units/day) and low-molecular-weight dextran solution. An infusion of

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