

CLINICAL TRIAL OF ORCIPRENALINE IN BRADYARRHYTHMIAS

By Chin Hock, Lim, Charles C. S. Toh and Oon Teik, Khoo

SYNOPSIS

The intravenous and oral forms of orciprenaline was used in the treatment of patients with severe sinus bradycardia, high grade atrio-ventricular block or the sick sinus syndrome. Intravenous orciprenaline can be used to tide patients over a period of severe bradyarrhythmia, or prior to cardiac pacing. One patient developed ventricular tachycardia following an intravenous bolus of orciprenaline. Oral orciprenaline was used in 23 patients with severe bradyarrhythmia. Two patients responded poorly to it. Saventrine was given sequentially in nine patients. The merits and side effects of both drugs are discussed.

INTRODUCTION

In 1952, Nathanson and Miller introduced isoprenaline for the treatment of heart block and it still has an important role in the treatment of bradyarrhythmias. Nis Innissen and Thompson (1965) felt that the use of a sustained release form of isoprenaline could reduce the need for pacemakers. Intravenous isoprenaline and orciprenaline may be used to treat patients with Stokes Adams (S.A.) attacks resulting from very slow ventricular rates in acute myocardial infarction, either alone or prior to cardiac pacing. In poorer countries where it is cheaper to use oral drugs than to implant pacemaker generators, and for some patients, who for some reason refuse operation, isoprenaline has a special place.

Many papers have been published on the use of sustained release form of isoprenaline in the treatment of heart block (Bluestone and Harris, 1965; Miram and Fleming, 1963), but few papers have been published on the use of orciprenaline in this condition (Redwood, 1968). The purpose of this paper is to evaluate the

efficiency of orciprenaline and to compare it with Saventrine in the treatment of complete heart block and other forms of bradyarrhythmias.

PHARMACOLOGY

Orciprenaline (Alupent*) is a derivative of isoprenaline but it has predominant beta-two stimulative effects and is commonly used as a bronchodilator (Bogdan, 1969). However, it has chronotropic and inotropic effects. It stimulates the sino-atrial and atrioventricular nodes and accelerates atrioventricular conduction. In this regard, its potency is 1/10 to 1/40 of isoprenaline (Shanks, 1967). The peak effect of orciprenaline after oral ingestion occurs at 55 minutes compared with 40 minutes for isoprenaline (Freske and Thorspecken, 1961).

MATERIALS AND METHODS

I. Intravenous bolus of orciprenaline

Eleven patients with complete heart block were given an intravenous bolus of 250 to 1,000 micrograms of orciprenaline. These patients were monitored continuously, blood pressures and electrocardiograms were recorded every two minutes for 10 minutes and half-hourly thereafter. Two patients with minor arrhythmias were similarly treated.

II. Intravenous infusion of orciprenaline

Eleven patients (including 8 of the above patients) with complete heart block occurring on the first day of the onset of acute myocardial infarction were maintained on intravenous infusion of 7 to 14 micrograms per minute of

Department of Medicine, (Medical Unit II), University of Singapore, Sepoy Lines, Singapore 3.

CHIN HOCK, LIM, A.M., M.B., B.S., M.Med., M.R.A.C.P.,
Senior Lecturer.

CHARLES C. S. TOH, A.M., M.B., B.S., F.R.C.P.,
F.R.A.C.P., F.A.C.C., Associate
Professor.

OON TEIK, KHOO, A.M., M.D., L.M.S., F.R.C.P.E.,
F.R.A.C.P., F.R.C.P.G., Professor
of Medicine.

Address for Reprints:

Dr. Lim Chin Hock,
Department of Medicine, (Medical Unit II),
University of Singapore,
Sepoy Lines, Singapore 3.

(* Manufactured by C.H. Boehringer Sohn).

orciprenaline. The cardiac rhythm and rate were recorded continuously; the electrocardiogram and blood pressures were recorded initially at half-hourly intervals and later at two-hourly intervals. The observations were continued until sinus rhythm recurred or when the rate and rhythm were stable and satisfactory. One patient with complete heart block due to scleroderma was similarly treated.

III. Oral therapy

Oral orciprenaline was administered with a starting dose of 40 mgm. six-hourly, increasing according to the response.

- (a) There were five patients with complete heart block, treatment starting, approximately 48 hours after the onset of acute myocardial infarction
- (b) (i) Four patients had complete heart block from ischaemic heart disease.
(ii) Five patients had idiopathic complete heart block.
(iii) Three patients had complete heart block of miscellaneous aetiology.
- (c) Five patients were suffering from the sick sinus syndrome.

Those patients developing complete heart block after acute myocardial infarction were monitored continuously, and electrocardiograms and blood pressures were recorded two-hourly until sinus rhythm returned or transvenous cardiac pacing was started (1 patient). The other patients were seen regularly as out-patients, initially at weekly intervals and later at monthly intervals. Oral orciprenaline was given for a month followed by oral Saventrine (9 patients). At each visit, the apex beat, a lead II E.C.G. strip and blood pressures were recorded. The pulse rate was recorded after 10 deep knee bends. Those patients who were literate were told to record their pulse rates an hour before and an hour after taking the oral drug.

The response to treatment in those patients with stable bradyarrhythmias is classified as follows:

1. Good response—when there is greater than 30% increase in heart rate or restoration of normal conduction.
2. Satisfactory response—stable increase in heart rate (20–29%) without side-effects.
3. Unsatisfactory response—less than 20% increase in heart rate or the development of serious arrhythmias.

RESULTS (Table I)

I. Effects of a single intravenous injection

Seven of the eight patients with complete heart block following acute myocardial infarction had good response while one showed only a satisfactory response. The percentage increase in heart rate in this group of patients ranged from 7 to 82% and the average increase was 38%. The average dose required was 250 micrograms to produce a good response and its effect would last approximately 20 minutes.

One patient with sinus bradycardia with an initial rate of 58/min. showed a satisfactory response but a second patient with junctional bradycardia developed ventricular tachycardia after 500 micrograms of orciprenaline. This was terminated by a thump on the chest. A patient with complete heart block due to acute non-specific myocarditis presented with Stokes Adams attacks. The ventricular rate rose from 30 to 130 per minute after 500 micrograms of orciprenaline (Fig. 1). She was subsequently paced.

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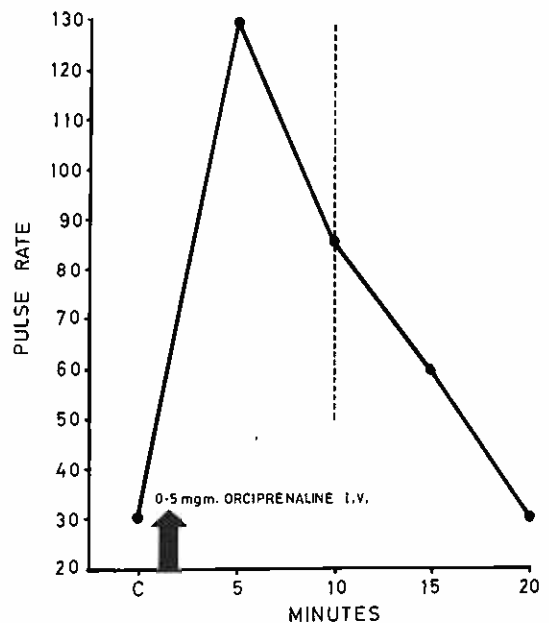


Fig. 1. An intravenous bolus of 0.5 mgm. (500 ug.) of orciprenaline produced a dramatic increase in ventricular rate. The peak effect was seen after 5 minutes.

TABLE I
RESPONSE TO VARIOUS FORMS OF ORCIPRENALINE THERAPY

Route of Administration	Aetiology	No. of Patients	Arrhythmias	Response			Resting Pulse Rate		% Increase in Pulse Rate		Serious Complications	Pacing	Died
				Good	Satisfactory	Poor	Range	Average	Range	Average			
A. I.V. Bolus	AMI	8	CHB	7	1	—	33—64	48	7—82%	38%	—	1	—
	IHD	1	SB	1	—	—	—	58	—	44%	—	—	—
		1	JB	—	—	1	—	40	—	300%	VT	—	—
B. I.V. Infusion	Acute Myocarditis	1	CHB	1	—	—	—	30	—	333%	—	1	—
	AMI	11	CHB	9	1	1	33—68	53	0—79%	44%	—	1	—
	Scleroderma	1	CHB	1	—	—	—	30	—	33%	—	—	—
C. Oral	AMI	5	CHB	5	—	—	40—54	48	34—60%	40%	—	4	1
	IHD	4	CHB	4	—	—	38—58	46	36—50%	42%	—	2	1
	Idiopathic	5	CHB	5	—	—	42—60	48	38—55%	45%	—	1	—
	Miscellaneous	3	CHB	1	1	1	32—45	40	0—55%	42%	SA attack in 2	2	—
	Idiopathic	5	SSS	5	—	—	20—40	36	70—350%	90%	—	—	—

KEY

CHB = Complete heart block.

SB = Sinus bradycardia.

JB = Junctional bradycardia.

AMI = Acute myocardial infarction.

IHD = Ischaemic heart disease.

SSS = Sick sinus syndrome.

VT = Ventricular tachycardia.

II. Effects of continuous intravenous infusion

Nine of the eleven patients with acute myocardial infarction and complete heart block showed good response. One was satisfactory and the other showed no response. Only one patient failed to revert to sinus rhythm and he had a permanent pacemaker generator implanted. The patient with complete heart block due to scleroderma, developed frequent and multifocal ventricular premature beats while on an intravenous infusion of isoprenaline at 3 micrograms per minute. He remained in stable complete heart block with a ventricular rate of 50 per minute while on a continuous intravenous infusion of orciprenaline at 7 micrograms/min.

III. Effects of oral administration

(a) Ischaemic heart disease:

Nine patients with complete heart block were treated with oral orciprenaline. Five had acute inferior infarction and four had chronic ischaemic heart disease. Of those with acute myocardial infarction, four were temporarily paced. Three of these were treated with oral orciprenaline when the catheter electrode was withdrawn and complete heart block recurred. Two patients with acute inferior infarction and complete heart block were not paced initially because of their advanced age, but were maintained initially on intravenous and subsequently on oral orciprenaline. This was stopped in 5 patients as 3 reverted spontaneously to sinus rhythm, 1 had a permanent pacemaker implanted and 1 died at home. One patient responded poorly to orciprenaline. (He developed ventricular tachycardia).

(b) Idiopathic group:

All five patients were treated with oral orciprenaline and three were sequentially treated with Saventrine. Four patients who had at least had 1 Stokes Adams attack prior to treatment, and observed over a period of 18 months, showed satisfactory response. None had Stokes Adams attacks during treatment and all of them experienced symptomatic improvement.

(c) Miscellaneous group:

The patient with scleroderma and complete heart block did not respond to oral orciprenaline and suffered from recurrent Stokes Adams attacks (Fig. 2). He refused a pacemaker for religious reasons. Another patient who had complete heart block due to congestive cardiomyopathy responded satisfactorily initially, but

was subsequently paced because of recurrent S.A. attacks.

(d) Sick Sinus Syndrome:

All 5 patients in this group showed good response. Four of them were subsequently treated with oral Saventrine, but one was unable to tolerate it, because of severe palpitations. (Figs. 3 and 4).

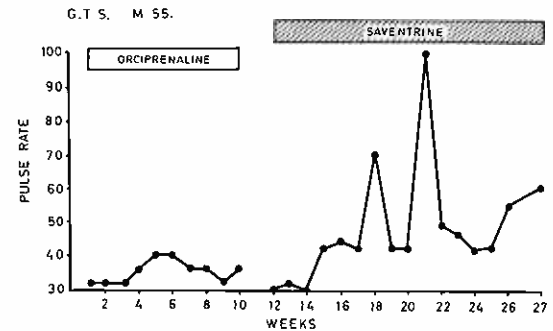


Fig. 2. This patient responded poorly to oral orciprenaline but had a satisfactory ventricular rate with Saventrine.

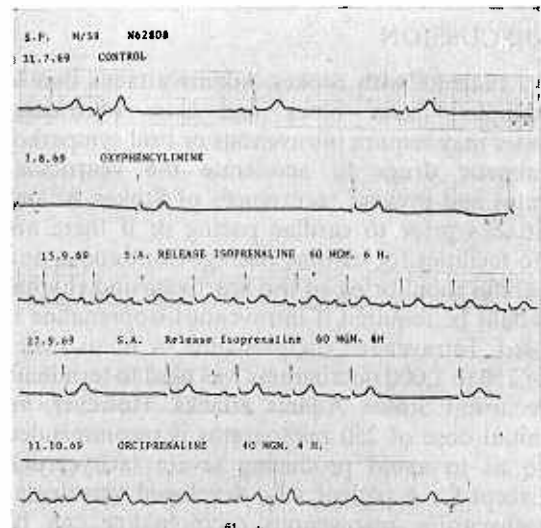


Fig. 3. A patient with the sick sinus syndrome who showed good response to oral therapy.

Side Effects

All the 23 patients treated with oral orciprenaline reported the presence of palpitations when specifically questioned. Only two were troubled by them. Three complained of muscular tremors when the dose of orciprenaline was 80 mgm. four hourly. This symptom improved when the dose was reduced. There were no gastrointestinal complaints.

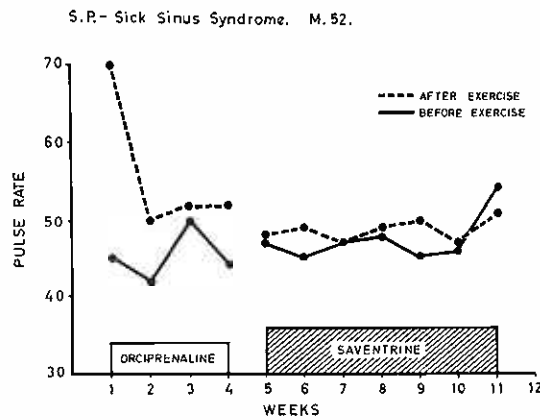


Fig. 4. The ventricular response to oral orciprenaline was almost similar to Saventrine.

Saventrine produced more severe palpitations, and one patient could not tolerate the palpitations brought on by a single tablet of Saventrine. Headaches and flushing following Saventrine was present in one patient. However, Saventrine was found to produce an equally good ventricular response.

DISCUSSION

Patients with Stokes Adams attacks due to complete heart block and slow ventricular rates may require intravenous or oral sympathomimetic drugs to accelerate the ventricular rates and prevent recurrences of Stokes Adams attacks prior to cardiac pacing or if there are no facilities for cardiac pacing. Continuous and careful monitoring of the heart rate and rhythm would be required if intravenous isoprenaline is used. Intravenous orciprenaline in bolus doses of 250 to 1,000 micrograms was used to terminate recurrent Stokes Adams attacks. However, an initial dose of 250 micrograms is recommended so as to avoid producing severe tachycardia. Except for 1 patient who developed ventricular tachycardia, intravenous orciprenaline can be safely given to patients with bradyarrhythmias following acute myocardial infarction. An intravenous dose of 5 to 10 micrograms per minute could be used to maintain a satisfactory heart rate in patients with bradyarrhythmias. The effects of an intravenous bolus dose of 250 micrograms was observed to last approximately 20 minutes and it is suggested that bolus doses be repeated, if necessary after an interval of 15 to 20 minutes.

Oral drug therapy has been described to be of little value in patients with complete heart

block. Friedberg (1969) believed that if these patients remained asymptomatic while on them, they would have behaved similarly without them. Bluestone (1965), Nis Inissen (1965) have however found sustained release isoprenaline of value in patients with complete heart block and its use might reduce the need for pacemakers. We have found that 13 out of 14 patients with high grade A.V. block or marked sinus bradycardia showed good response to oral orciprenaline. Rasmussen (1971) paced 17 out of 23 patients with sino-atrial block, on the premise that this was a life threatening arrhythmia, which would not respond to drugs except atropine, and that Stokes Adams attacks may occur after long periods with an apparently benign course. Our patients with the sick sinus syndrome responded well to oral orciprenaline therapy.

Oral orciprenaline may have stronger chronotropic than inotropic effects, and this may explain why it produces less unpleasant side effects, such as palpitations, headache or hot flushes. Sustained release isoprenaline has a longer duration of action (6 hours) compared to oral orciprenaline (4 hours) which has to be taken more frequently to maintain a prolonged, uniform chronotropic effect. Orciprenaline does not appear to be superior to sustained release isoprenaline and the choice of either of these drugs would depend on cost and availability.

Since 1971, pacemakers are more readily available locally, consequently drugs are only used prior to pacing. Oral sympathomimetic treatment for chronic bradyarrhythmias has to be stopped should unpleasant side effects, serious arrhythmias, or Stokes Adams attacks occur and electrical pacing is instituted. Electrical pacing, whether temporary or permanent, is the treatment of choice in those patients with severe symptomatic bradyarrhythmias, or complicated by cardiac failure, or low cardiac output.

ACKNOWLEDGEMENT

We wish to thank C.H. Boehringer Sohn for their generous supply of drugs and their assistance in carrying out this trial.

REFERENCES

1. Bluestone, R. and Harris, A.: "Treatment of heart block with long acting isoprenaline." *Lancet*, 1, 1299, 1965.
2. Bogdan, A.: "Effect of orciprenaline on school absenteeism in asthma." *Archives of Disease in Childhood*, 44, 743, 1969.

3. Ferrer, M.I.: "The sick sinus syndrome in atrial disease." *Journal of the American Medical Association*, 206, 645, 1968.
 4. Fleming, H.A. and Mirams, J.A.: "A clinical trial of sustained action preparation of isoprenaline in the treatment of heart block." *Lancet*, 2, 214, 1963.
 5. Freidberg, C.K.: "Diseases of the Heart," 3rd Edition, 604, 1969.
 6. Freske, G. and Thorspecken, R.: *German Medical Monthly*, 6, 277, 1961.
 7. Nathanson, M.H. and Millar, H.: "The action of Norepinephrine, Epinephrine and Isopropyl Norepinephrine on the rhythmic function of the heart." *Circulation*, 6, 238, 1952.
 8. Newcombe, C.P., Desouza, D. and Towers, J.R.H.: "Atrial flutter with complete heart block." *British Heart Journal*, 22, 691, 1960.
 9. Nis Inissen and Thomsen, A.: "Oral treatment of atrioventricular block and other bradycardias with sustained action isoprenaline." *British Heart Journal*, 27, 926, 1965.
 10. Rasmussen, K.: "Chronic sino-atrial heart block." *American Heart Journal*, 81, 38, 1971.
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