Electrophysiological effects of L 9394 (benzoyl-indolizine) in man

A. WALEFFE, A. BORDALO¹, P. BRUNINX, H. J. J. WELLENS², AND H. E. KULBERTUS

From the Laboratory of Electrocardiology, Institute of Medicine, University of Liège, Belgium; and the Department of Cardiology, University of Limburg, Maastricht, The Netherlands

SUMMARY The electrophysiological effects of L 9394 (benzoyl-indolizine), a substance chemically related to amiodarone, but devoid of iodine atoms, were investigated by programmed electrical stimulation of the heart in 12 patients with various forms of tachycardia. Four subjects had electrocardiographic evidence of the WPW syndrome and episodes of circus movement tachycardia. Paroxysmal supraventricular tachycardia, confined to the atrioventricular (AV) node, was found in 3 patients. In 2 cases, where a short PR interval was present, the main complaint was the occurrence of paroxysmal atrial fibrillation. In the remaining 3 instances, the arrhythmia consisted of slow ventricular tachycardia (1 case), supraventricular tachycardia of the focal type (1 case), and episodes of primary ventricular fibrillation, not related to acute myocardial ischaemia (1 case).

L 9394 injected intravenously was seen to lengthen the transnodal conduction time as well as the effective and functional refractory periods of the node. Similar effects were found on the retrograde VA pathway. The drug had no action on the infra-Hisian conduction system, on the refractory periods of ventricular muscle, or on the refractory periods of accessory bypasses.

The drug was injected during an episode of tachycardia in 6 cases with reproducible supraventricular re-entrant tachycardia. Three had a tachycardia circuit confined to the node. In those instances, the drug had beneficial effects (slowing and interruption of tachycardia, decrease or abolition of echo zone; loss of ability to induce tachycardia). In the other 3 cases, an accessory pathway was incorporated in the circuit. L 9394 interrupted the tachycardia in 2 instances (by anterograde AV block), but failed to protect all 3 patients against reinitiation of tachycardia by premature stimuli.

It is concluded that L 9394 does not share all the pharmacological properties of amiodarone and will not replace it in all its indications.

Amiodarone has been reported to be an effective antiarrhythmic agent for different types of arrhythmia (Coulmel *et al.*, 1974; Rosenbaum *et al.*, 1974; Touboul *et al.*, 1975; Rosenbaum *et al.*, 1976; Wellens *et al.*, 1976; Waleffe *et al.*, 1978). Side-effects however have limited wide acceptance of the drug in clinical practice (Geerts, 1971; Verin *et al.*, 1971; Babel and Stangos, 1973; Pritchard *et al.*, 1975; Burger *et al.*, 1976). L 9394, a benzoyl-indolizine derivative, is a new substance which is chemically related to amiodarone (Fig. 1) (Charlier

et al., 1976, 1977). However, since L 9394 is not a carrier of iodine atoms, there are reasons to believe that the drug is likely to be devoid of at least some of the side-effects of amiodarone. We therefore decided to investigate the electrophysiological properties of L 9394 in man.

Subjects and methods

Twelve patients were studied. Data on age, sex, and type of arrhythmia are given in Table 1.

After obtaining informed consent, 4 catheters were introduced into the femoral vein using the Seldinger technique. One quadripolar catheter was positioned high on the lateral wall of the right atrium: the two distal electrodes were used for stimulation and the proximal electrodes for re-

¹Research Fellow of the Calouste Gulbenkian Foundation, Lisbon, Portugal.

²This work was performed while H. J. J. Wellens was Chaire Franqui Professor at the University of Liège.

The various measurements were made before and after the injection of 2 mg/kg of L 9394, administered intravenously over a 5-minute period. All measurements were repeated at the end of the injection (time zero) and again every fifteenth minute, during 1 hour.

All data obtained during the stimulation study were recorded on tape (HP 8868 A) and directly registered on an eight-channel Elema Mingograf recorder. Leads I, II, III, V1, V6, the intracavitary right atrial lead, the left atrial lead (when available), and the His bundle electrogram were simultaneously recorded. For recording the His bundle electrogram, a 854 Universal Amplifier with input adapter was used.

The effective refractory period of the AV node was defined as the longest A₁-A₂ interval failing to conduct through the AV node. The functional refractory period (FRP) of the AV node was considered as the shortest H₁-H₂ interval that could be obtained. Since it was not always possible to determine when the AV node became refractory during ventricular pacing (because of absence of a retrograde H potential and/or because of a gap phenomenon in VA conduction), no values will be given for the effective refractory period of the different parts of the VA conduction system. Statistical analysis was performed using the paired *t* test. Plasma levels of L 9394 were determined by using a chromatographic method (J. Broekhuysen, 1977, personal communication).

Results

The results are summarised in Table 2.

AV CONDUCTION

As indicated in the Table, the AH interval lengthened after the L 9394 injection in all but 1 of the 10 patients in whom it could be measured. Mean increase in AH interval was 32 ms (range 0 to 130 ms) (*P* < 0.05). In case 9, a sudden and distinct lengthening of the AH interval (jump from 120 to 240 ms) was transiently observed 30 minutes after the administration of L 9394.

Because some patients had the WPW syndrome, the refractory periods of the AV node could not be measured in all studies. The effective refractory period measured in 11 patients increased by an average of more than 113.6 ms (*P* < 0.001). The functional refractory period increased by an average of more than 89.4 ms (*P* < 0.001).

A pattern suggestive of a dual AV nodal pathway was present before L 9394 administration in 2 patients (cases 1 and 9). L 9394 did not alter the broken aspect of the AV conduction curve in case 9, the electrophysiological properties of both pathways being similarly affected by the drug. But in case 1, a smooth curve was observed during the initial 20 minutes after drug injection. In 2 patients (cases 3 and 5), the injection of L 9394 revealed a dual AV nodal pathway curve that had not been depicted before drug administration. In case 5, this dual pathway curve appeared 20 minutes after injection and persisted until the end of the investigation. In case 2, a patient with AV nodal re-entrant tachycardia, a smooth AV conduction curve was consistently obtained both before and after the administration of L 9394.

In patients without pre-excitation no change was observed in the HV interval.

(ms)		VA conduction system ERP (ms)			ERP _{RV} (ms)			ERP _{AP} (ms) AV direction			VA direction		
Before	After	Before	After	Δ	Before	After	Δ	Before	After	Δ	Before	After	Δ
420	80	240	410	170	220	230	10						
> 360	> 10	≤220	300	> 80	200	210	10						
> 410	> 90	≤230	≤230	? 0	220	220	0						
450	50	≤275	≤270	?	265	255	- 10						
430	105	?	?	?	215	225	10	440	?	?	< 225	< 240	?
?	?	?	?	?	240	230	- 10	280	280	0	280	290	10
?	?	?	?	?	230	220	- 10	< 270	< 290	?	< 240	260	> 20
?	?	< 260	< 260	?	240	240	0	290	310	20	340	350	10
540	100	< 230	410	> 180	210	210	0						
460	100												
		270	410	140	200	210	10						
530	170	290	block	∞	280	290	10						
440	100												
		360	500	140	330	220	- 110						
> 89.4		> 142			- 7.5						> 13.3		
< 0.001		< 0.01			NS			NS			NS		

Table 3 Effects of L 9394 on tachycardia

Case no.	CL	Tachycardia type	Initiation		Tachycardia zone (ms)		RR interval during tachycardia (ms)	
			Before	After	Before	After	Before	After
1	500	AVN RT	1 APB	—	250-230	—	360	—
2	500	AF	1 APB	—	210-180	—	400	—
	300	AVN RT	Rapid atrial pacing	—	—	—	330	—
	300		Rapid ventricular pacing	—	—	—	330	—
3	SR	AVN RT	2 APB 3 APB	—	—	—	310	—
5	270		rapid atrial pacing	—	—	—	—	—
	470	CMT (WPW)	2 APB	1 APB	320-265 } 390-300 }	290-380	450	—
	470		3 VPB	1 VPB				
6	290	CMT (WPW)	rapid atrial pacing	—	—	—	—	—
	500		1 APB	—	280-255	—	300	390
7	500	CMT (WPW)	—	1 VPB	—	290	—	—
	600		1 VPB	1 VPB	310-300	350	320-360	450

CL, cycle length; AVN RT, AV nodal re-entrant tachycardia; AF, atrial flutter; CMT, circus movement tachycardia; APB, atrial premature beat; VPB, ventricular premature beat; SR, sinus rhythm.

VA CONDUCTION

In 3 patients (cases 5, 6, 7), the presence of an accessory pathway (with an effective refractory period in VA direction shorter than that of the ventriculoatrial conducting system) did not permit accurate evaluation of changes in VA conduction

characteristics through the His AV nodal axis.

In 3 patients (cases 3, 4, 8), VA conduction persisted after drug administration up to the functional refractory period of the ventricle.

In 1 patient, after L 9394, a complete VA block occurred (case 11). Finally, in the remaining 5

Fig. 2(a)

Fig. 2 Case 1. Eight leads are simultaneously recorded: I, III, V1, V6, HRA (high right atrial lead), CS1 and CS2 (two coronary sinus leads), and the HBE (His bundle electrogram).

In (a) before drug administration, at a A_1A_2 interval of 240 ms, a long AH interval is observed ($H_1H_2 = 530$ ms) and an episode of AV nodal re-entrant tachycardia (with transient 2:1 AV block) is initiated.

In (b) and (c) after administration of L 9394, a jump in the curve plotting the H_1H_2 intervals against the A_1A_2 intervals is still observed (H_1H_2 equals 410 ms for an A_1A_2 of 350 ms, and 550 ms for an A_1A_2 of 340 ms). In spite of this, no echo beat or tachycardia is elicited, the fast conducting pathway being now blocked in the retrograde direction.

Fig. 2(b)

Fig. 2(c)

Fig. 3(a)

Fig. 3(b)

Fig. 3 Case 2. (a) Before drug administration, atrial pacing at a cycle length of 300 ms results in a Wenckebach type of response and its interruption is followed by the initiation of an episode of tachycardia (AV nodal re-entrant tachycardia). (b) After administration of L 9394, the Wenckebach type of block is more obvious during atrial pacing. After interruption of pacing, one AV nodal re-entry cycle is completed, but this is not followed by tachycardia, the slow conducting pathway being now blocked in the anterograde direction.

subjects (cases 1, 2, 9, 10, 12), the effective refractory period of the VA conduction system lengthened by an average of at least 142 ms.

EFFECTIVE REFRACTORY PERIOD OF RA AND RV

In all but 2 cases, the ERP of the right atrium slightly lengthened. The changes were statistically significant ($P < 0.001$) but, in absolute values, they appeared trivial. The ERP of the right ventricle failed to show any consistent alteration.

ERP OF ACCESSORY PATHWAY

An accessory pathway was present in 4 cases (2 right-sided; 2 left-sided). The drug was found to have no effect on its effective refractory period either in anterograde or retrograde direction.

MECHANISM OF TACHYCARDIA

In the 3 patients with AV nodal re-entrant tachycardia (cases 1 to 3), and in 3 of the 4 subjects with WPW (cases 5 to 7), episodes of tachycardia could be initiated by electrical stimulation (Table 3).

In case 1 (Fig. 2), before the administration of the drug, a single atrial extrastimulus (S_2) delivered between 250 and 230 ms after the preceding stimulus (S_1) initiated an AV nodal re-entrant tachycardia with a cycle length of 360 ms. In addition, S_2 stimuli, delivered from 210 ms to 180 ms after S_1 , started episodes of atrial flutter with a ventricular cycle length of 400 ms. After L 9394 administration, the jump in the curve plotting the H_1H_2 against the A_1A_2 intervals transiently disappeared; it was again observed after a 20-minute period; extrastimuli however could induce only one or two re-entrant echo beats, but no sustained tachycardia. Atrial flutter could not be elicited.

In case 2, AV nodal re-entrant tachycardia could be started only by rapid atrial or ventricular pacing (Fig. 3). After L 9394, no tachycardia could be induced.

In case 3, supraventricular tachycardia could be initiated by 2 or 3 atrial extrastimuli or by rapid atrial pacing. After drug administration, the ability to induce tachycardia was lost in spite of the unmasking effect of a previously concealed dual AV nodal pathway.

In case 5 (Fig. 4), a left-sided accessory pathway was associated with a dual AV nodal pathway curve unmasked by L 9394 injection. Episodes of tachycardia with two different cardiac rates (suggesting circuits with AV conduction over either the fast, or the slow AV nodal pathway, and VA conduction over the accessory pathway) could be initiated before drug administration by giving a salvo of at least 3 ventricular extrastimuli, more rarely by 2 atrial premature beats, or by rapid atrial pacing

at a rate producing a Wenckebach phenomenon. After the drug, a jump in the AV conduction curve became clearly apparent. Initiation and termination of tachycardia were facilitated. Circus movement tachycardia, using the accessory pathway retrogradely, could be started by either a single ventricular or atrial premature beat with relatively large tachycardia zones (at that time the fast AV nodal pathway had become refractory), by rapid atrial pacing at rates producing a second degree AV block, and by ventricular pacing. The tachycardia could easily be terminated by 2 ventricular premature beats and, with greater difficulty, by a single ventricular extrastimulus, or by 3 atrial premature beats. The tachycardia cycle length was significantly prolonged after L 9394 (410 ms as compared with 290 or 380 before the injection), this lengthening being in part the result of the exclusive use of the slow AV nodal pathway for anterograde conduction.

In 6 patients with reproducible paroxysmal re-entrant tachycardias, L 9394 was administered during an episode of tachycardia. The injection resulted in termination of the rhythm disorder in all patients with the intranodal type of tachycardia and in 2 of the 3 cases with the WPW syndrome (cases 5 and 7). The heart rate during tachycardia decreased in each subject; this was related to slowing of conduction along the AV node and not to prolongation of the VA conduction time.

OTHER INDICES

Sinus node function tests were not performed during this investigation because of a lack of time during the procedure.

In 2 of the cases, the threshold for atrial stimulation was noted to increase after L 9394 administration. In case 9, for example, the threshold at the end of injection rose to 20 mA. This value was 5 times greater than the control value. It fell to 7 mA 22 minutes later and to 5 mA after 30 minutes. In case 2, the threshold was measured at 7 mA at the end of the injection and at 4 mA 30 minutes later.

In the remaining subjects, no attempt was made to measure systematically the threshold for atrial stimulation. Since stimulation was done at twice the threshold value, any increase of less than 100 per cent would have passed unnoticed.

Arterial blood pressure was monitored throughout the study, in 4 cases by continuous intra-arterial pressure recording, and in the remaining instances by repeated measurements by sphygmomanometer. No significant change was observed.

The plasma level of L 9394 was $3.0 \text{ ng/ml} \pm 2.0$ at the end of injection and 0.47 ± 0.21 15 minutes

later. After the end of injection, the plasma levels showed an exponential decrease. No correlation was observed between the pharmacological effects and the plasma levels of the drug during this initial distribution period (Wellens and Durrer, 1974).

Discussion

The results of our investigation show that L 9394 is a substance which acts mainly on the AV node. It lengthens the transnodal conduction time as well as the effective and functional refractory periods of the node. As opposed to amiodarone (Touboul *et al.*, 1975; Wellens *et al.*, 1976; Waleffe *et al.*, 1978), it has no effect on anterograde conduction over the intraventricular conduction system, on ventricular muscle, and accessory pathways.

The observed changes are of the same order of magnitude as those which have been reported previously with ouabain (Wellens *et al.*, 1975; Wu *et al.*, 1975), propranolol (Wu *et al.*, 1974), and verapamil (Wellens *et al.*, 1977).

In contrast to verapamil (Wellens *et al.*, 1977), L 9394 had some effect on the retrograde VA pathway in several patients. This may of course reflect an action on the AV node but functional changes within the His-Purkinje system used retrogradely cannot be ruled out.

Our observations indicate that L 9394 is a potentially interesting drug for the treatment of tachycardias confined to the AV node. In the 3 patients whom we studied, the episodes of tachycardia were ended by the intravenous injection of the drug. In addition, L 9394 decreased or totally eliminated the echo zones and made the patients

lose their ability to develop sustained paroxysmal supraventricular tachycardia during programmed electrical stimulation.

The effects in patients with circus movement tachycardia associated with pre-excitation are less clear. In the 3 patients studied, the drug produced slowing of transmission through the anterograde AV nodal part of the tachycardia circuit which resulted in a significant slowing of the cardiac rate during circus movement tachycardia. L 9394 interrupted tachycardia in 2 instances, but failed to protect all 3 patients against reinitiation of tachycardia by premature stimuli. These observations resemble those made in patients with concealed bypasses after administration of ouabain (Wellens *et al.*, 1975; Wu *et al.*, 1975), propranolol (Wu *et al.*, 1974), and verapamil (Wellens *et al.*, 1977). As pointed out by others (Wellens *et al.*, 1975; Wu *et al.*, 1975), by producing selective slowing of conduction within the AV node, these drugs, like L 9394, may actually favour the initiation and perpetuation of circus movement tachycardia in the presence of a ventriculoatrial accessory pathway. Delaying conduction through the node increases the chance for a premature impulse to reach the ventricular end of the bypass when it is excitable and thus promotes VA conduction over this pathway and initiation as well as perpetuation of tachycardia. This was clearly shown in case 5 of this series in whom an accessory bypass as well as a dual nodal pathway were simultaneously present. Prolongation of the conduction time especially along the slow nodal pathway made it much easier to induce the tachycardia after drug administration.

Drug induced changes of the pattern of atrio-ventricular conduction have previously been re-

Fig. 4(a)

Fig. 4(b)

Fig. 4(c)

Fig. 4 Case 5. (a) The curve plotting the H_1H_2 against the A_1A_2 intervals is smooth in the control state, but shows after administration of L 9394 a typical jump at 320 ms. Tracings were obtained before (b) and after (c) administration of the drug. Before L9394 (b) single ectopic beats elicited at A_1A_2 intervals of 330 and 320 ms failed to initiate tachycardia. After L9394 (c) the ectopic beat elicited at an A_1A_2 interval of 320 ms produced a sudden increase of the AH time and initiated an episode of tachycardia with a longer cycle length (410 ms) than in the basic conditions (290 to 380 ms). LRA: low right atrial lead.

ported (Wu *et al.*, 1974; Wellens *et al.*, 1975, 1977). Two different situations were encountered in this series. In 2 patients, a dual AV nodal pathway was shown only after administration of L 9394. In one other case, a dual pathway curve was identified before drug administration, but changed into a smooth curve afterwards. The possible explanations for such a phenomenon have been discussed previously (Wellens *et al.*, 1975).

In summary, it is apparent that L 9394 does not share all the pharmacological properties of amiodarone and in spite of its possibly better tolerance, it will not completely replace amiodarone. As it has little effect on the atrial and ventricular muscles and on the accessory pathways it is unlikely that L 9394 will be as effective as amiodarone on a large spectrum of arrhythmias. We want to stress however that our data were obtained after intravenous administration of L 9394. Little is known of the pharmacokinetics of this substance in the human. In addition, previous experience has indicated that the effect of intravenous amiodarone is different from that obtained after long-term oral administration (Berkman *et al.*, 1975). In view of this, chronic studies (Wu *et al.*, 1977) on the effect of L 9394 administered orally are needed before any definite conclusion can be drawn regarding the clinical usefulness of this drug.

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Requests for reprints to Professor Henri Kulbertus, Division of Cardiology, Institute of Medicine, University of Liège School of Medicine, 66 Blvd de la Constitution, B-4020 Liège, Belgium.