

Clinical cardiac electrophysiologic evaluation of the positive inotropic agent, DPI 201–106

G. S. BUTROUS, N. M. G. DEBBAS, J. ERWIN, D. W. DAVIES, H. P. KELLER*, M. W. LUNNON†, A. W. NATHAN AND A. J. CAMM

Department of Cardiology, St Bartholomew's Hospital, London, U.K., *Biopharmaceutical Dept. Sandoz AG, Basle, Switzerland, and †Clinical Research Unit London, Sandoz Ltd., Feltham, U.K.

KEY WORDS: DPI, cardiac electrophysiology, QT interval.

DPI 201–106 is a new positive inotropic agent. The cardiac electrophysiology of 16 patients was studied before and during DPI 201–106 administration (loading dose of intravenous DPI 201–106, 1.8 mg kg⁻¹ h⁻¹ administered over 10 min, followed by a maintenance dose of 0.2 mg kg⁻¹ h⁻¹). DPI 201–106 had no effect on the sinus node. The AH interval during fixed-rate atrial pacing became prolonged during DPI 201–106 infusion. There was a significant prolongation of the QT interval [QT (corrected), 417 ± 22 to 502 ± 35 ms, P < 0.05; QT (atrial pacing at 600 ms), 374 ± 17 to 419 ± 23 ms, P < 0.05; QT (ventricular pacing at 600 ms), 409 ± 37 to 449 ± 30 ms, P < 0.05]. The ventricular effective refractory period significantly prolonged during DPI 201–106 administration (242 ± 21 to 287 ± 56 ms, P < 0.05), but the supernormal-period duration decreased. The atrial effective refractory period was shortened in four patients and prolonged in one (261 ± 67 to 240 ± 53 ms, NS). The corrected atrial repolarization time (PT_{ac}) shortened significantly during DPI 201–106 infusion (479 ± 26 to 445 ± 22 ms at 20 min of the maintenance dose, P < 0.05). Atrial fibrillation was initiated in five patients during DPI infusion, but no ventricular arrhythmia was provoked. These findings suggest that DPI 201–106 has novel differential electrophysiological effects on atria and ventricles.

Introduction

DPI 201–106 is a diphenylmethyl-piperazinyloindole derivative with cardiotonic effect which has been demonstrated *in vitro*^[1,2] and *in vivo*^[3] in various animals. Its potent inotropic action has also been shown in man^[4]. DPI 201–106 has a novel mechanism of action which is not related to cAMP, to beta-adrenergic or histaminergic receptor stimulation, or to the liberation of catecholamines or to a glycoside-like action^[2,5]. There is increasing evidence that this agent modulates Na⁺ channels and hence affects phase 0 and phase 2 of the cardiac cell action potential. Kohlhardt *et al.*^[6] found that DPI 201–106 prolonged the conductance of the Na⁺ channels, i.e. prolonging the open state. Tetrodotoxin abolishes the effect of DPI 201–106^[7], hence the inotropic effect of DPI 201–106 is due to its interaction with

the regulation of Na⁺ channels, probably by interfering with one of its inactivators^[6]. DPI 201–106 causes an increase in intracellular calcium, but does not enhance calcium entry through slow channels^[7]. The effect of DPI 201–106 on the Na⁺ channel may increase the intracellular Na⁺ load which interferes with the dynamics of the Na⁺/Ca²⁺ exchange^[8] and, thereby, increases the intracellular calcium load. This may consequently prolong phase 2 of the action potential (the plateau) and increase the availability of calcium for contractile activity. The prolongation of cardiac action potential is, therefore, associated with positive inotropic action^[2]. Action potential prolongation is reflected by the significant prolongation of the QT interval which has been noticed during intravenous administration of DPI 201–106^[3].

The proposed mechanism of action may, therefore, influence other electrophysiological parameters of cardiac tissue, as suggested by some animal experiments^[2]. The aim of this paper is to report the results of a clinical cardiac electrophysiological study of DPI 201–106.

Submitted for publication on 19 June 1987 and in revised form 26 October 1987.

Address for correspondence: Dr G. S. Butrous, Department of Cardiological Science, St George's Hospital and Medical School, Cranmer Terrace, London SW17 0RE, U.K.

Patients and methods

PATIENTS

Sixteen patients (six females), age range 18–76 years (mean 52 ± 15 years), were included in this study. Of 10 patients, the study was performed as a part of routine clinical cardiac electrophysiological evaluation for palpitations in eight, and syncope in two. The other six patients had 2:1 or complete heart block and had already been fitted with dual-chamber pacemakers. None of the patients were on amiodarone. Other antiarrhythmic medications were discontinued for at least 72 h prior to the study in all patients. The aims and procedure of the study were fully explained to each patient and written consent was obtained. The study was approved by the Ethics Committee of St Bartholomew's Hospital, London.

ADMINISTRATION OF DPI 201-106

DPI 201–106 was given intravenously according to the following method: a loading dose of $1.8 \text{ mg kg}^{-1} \text{ h}^{-1}$ was given intravenously over 10 min (except for the first five patients to whom $0.8\text{--}1.5 \text{ mg g}^{-1} \text{ h}^{-1}$ were given according to recommendation of the Ethics Committee). This was followed immediately by constant infusion of DPI 201–106 at a dose of $0.2 \text{ mg kg}^{-1} \text{ h}^{-1}$ for the entire duration of the study (maintenance dose).

PROTOCOLS

Three protocols were included in this study:

Measurement of intracardiac intervals and refractoriness

USCI electrode catheters were introduced via the femoral vein under local anaesthesia (approximately 10 ml of 1% lignocaine) and placed to record and stimulate the right atrium and right ventricular apex. A tripolar electrode was positioned adjacent to the His bundle. The intracardiac signals and four surface electrocardiographic leads (I, aVF, V1 and V6) were recorded simultaneously on a Siemens Elema Mingograph 1600 ink-jet recorder at a paper speed of 100 mm s^{-1} . Programmed stimulation at twice the diastolic threshold was performed using a Bloom stimulator.

Basic intervals were measured, during the loading and maintenance doses in sinus rhythm and during constant rate atrial and ventricular pacing (600, 500 and 400 ms) to ± 5 ms accuracy. These intervals included the following: (a) RR interval, measured between two consecutive high right atrial electrograms; (b) AH interval, between the first rapid deflection of the low right atrial electrogram and the

start of the His bundle deflection; (c) HV interval measured from the onset of the His bundle electrogram to the earliest ventricular activation on the surface electrocardiogram; (d) QRS duration, measured between the earliest and last deflection on the surface electrocardiogram; and (e) QT interval, from the earliest deflection of the QRS in the surface electrocardiogram to the end of the T wave^[9]. The measured QT intervals during sinus rhythm were corrected for rate using Bazett's formula^[10]:

$$QT_c = QT_m / \sqrt{(RR)}$$

where QT_c is the corrected QT interval, QT_m is the measured QT interval, and RR is the RR interval.

The QT intervals were also measured during fixed-rate atrial pacing (QT_a) and fixed rate ventricular pacing (QT_v).

Refractory periods were assessed by pacing (at twice the diastolic threshold) the high right atrium (or right ventricular apex) at a constant rate for eight beats followed by an extra atrial (or ventricular) paced beat at a decreasing coupling interval. The following parameters were assessed^[11]: (a) the functional atrioventricular nodal refractory period, which was defined as the shortest distance between the last His bundle deflection of the atrial driven cycle and the His deflection following the extra-stimulus; (b) the effective atrioventricular nodal refractory period which was defined as the longest interval between the last atrial deflection of the driven cycle length and the atrial deflection of any extra-stimulus beat which failed to result in a His bundle depolarization; (c) the atrial refractory period, was the longest interval between the last atrial driven stimulus and any atrial extra-stimulus which did not result in atrial depolarization; (d) the effective ventriculo-atrial refractory period was assessed by ventricular programmed stimulation — it was the longest interval between the last ventricular deflection of the driven cycle length and the ventricular deflection of any extra-stimulus beat which failed to result in retrograde conduction to the atria; and (e) The effective ventricular refractory period which was defined as the longest interval between the last ventricular driven stimulus and any extra-stimulus spike that resulted in no ventricular depolarization.

Anterograde atrioventricular and retrograde ventriculo-atrial Wenckebach cycle lengths were determined by gradually increasing atrial or ventricular pacing rates, respectively until a beat failed to conduct anterogradely or retrogradely.

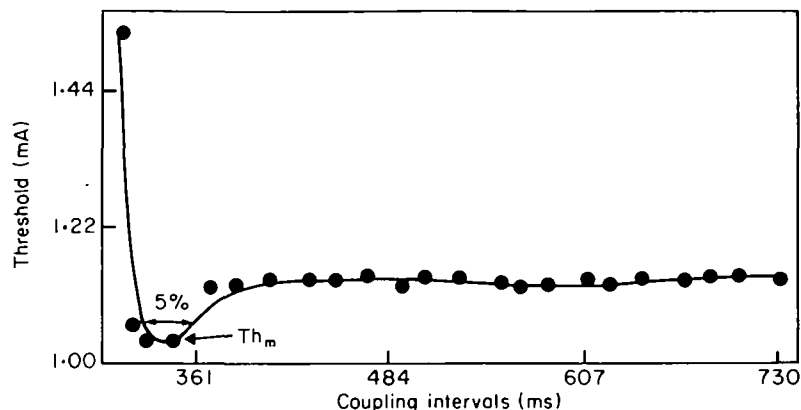


Figure 1 The cathodal strength interval curve, showing the measurements of the supernormal period in this study. The level of the 5% supernormal-period duration is also shown. Th_m , minimal threshold during supernormal period.

Sinus node function was assessed by pacing the high right atrium with pacing cycle lengths of 600, 500 and 400 ms, each for 1 min. The longest pause from the last paced atrial depolarization to the first sinus return cycle was considered to be the maximum sinus node recovery time. The maximum corrected sinus node recovery time was defined as the longest interval derived by subtracting the prepacing sinus cycle length from the sinus node recovery time^[12].

Assessment of ventricular supernormal period

In six patients, cathodal ventricular strength interval curves were assessed before and during the maintenance dose of DPI 201-106. The distal pole of the electrode was used for cathodal stimulation and the indifferent electrode was placed on the skin. The high right atrium was paced at a constant rate of 600 ms for eight beats followed by one ventricular extra-stimulus. The threshold of the ventricular extra-stimulus was assessed with 0.01 mA accuracy using Bloom stimulator at each coupling interval. The coupling interval of the ventricular extra-stimulus was decreased until the ventricular pacing threshold was > 10 mA.

The supernormal period was measured as that part of the strength interval curve where there was a 5% or more decrease in the threshold below the diastolic threshold. The period of supernormality in the cardiac cycle was expressed in relation to the QT interval (taking Q as 0% and the end of the T wave as 100%). The minimum threshold during the supernormal period (SNP- Th_m) was assessed relative to the diastolic threshold (Fig. 1).

Assessment of atrial repolarization

Six patients with 2:1 or complete heart block and who had been fitted with dual chamber pacemakers were included in this study to assess the atrial repolarization time (PT_a). Standard bipolar unpaced surface ECG leads I, II and III were recorded at high fidelity (0.6-30 Hz) and high gain ($\times 1000 - \times 10000$) on 0.5 inch magnetic tape before and during administration of DPI 201-106. The recording signals were then transferred onto the computer memory via a 12-bit analogue/digital converter. The signals were filtered using specially adapted software^[13]. The duration of the P and the T waves of the atrium (T_a) were measured from the displayed complexes using a high-resolution cross-hair cursor on a Tectronix 4010 VDU before and during the loading dose (5 min and 10 min) and during the maintenance dose (10, 20 and 30 min). The atrial repolarization duration (PT_a) was corrected according to the following equation^[13]:

$$PT_{ac} = PT_a + 0.29(1000 - RR)$$

where PT_{ac} is the corrected atrial repolarization time, PT_a is the measured atrial repolarization time, and RR is the sinus cycle length.

ASSESSMENT OF PLASMA LEVEL

Blood samples (10 ml) were taken immediately after the loading dose and at 5-10, 15-20 and 25-35 min intervals during the maintenance dose. Unchanged DPI 201-106 was extracted from alkalinized plasma into a methyltertbutyl ether/isopropranol n-hexane mixture and back extracted

into dilute phosphoric acid. A 500 µl aliquot was injected directly into a 100 × 2.1 mm spheri-5 RP-8 column and isocratically eluted with 0.005 M phosphoric acid/acetonitrile 35:65 (pH 2.5). Detection was in the UV range at 228 nm (Smith HT, unpubl.).

The assay confidence limits ($P=0.95$) over the whole study concentration range were approximately $\pm 20\%$ of the expected concentrations as estimated from calibration and control samples which had been included in the analysis. Most of the samples were analyzed twice showing a mean inter-assay coefficient of variation of less than 10%. All sample concentrations were above the limit of detection (10 ng ml^{-1}) .

ANALYSIS OF THE DATA

Mean \pm SD values were used to express the dispersion of the data. For statistical inference, Student's *t*-test or Wilcoxon's sign ranked test were used as appropriate. Significance was defined as $P < 0.05$.

Results

PLASMA LEVEL OF DPI 201-106

The plasma levels of DPI 201-106 in this study are shown in Table 1. The plasma concentration was steady during the maintenance infusion.

Table 1 Plasma level of DPI 201-106 (in ng ml^{-1})

	Loading	Maintenance		
		10 min	20 min	30 min
Low*	271 \pm 174	86 \pm 20	105 \pm 28	88 \pm 20
High*	371.8 \pm 264	125 \pm 45	137 \pm 67	128 \pm 48

*'Low' denotes those patients who had a lower loading dose ($0.8\text{--}1.5 \text{ mg kg}^{-1} \text{ h}^{-1}$) in compliance with the Ethics Committee recommendation; 'high' denotes a loading dose of $1.8 \text{ mg kg}^{-1} \text{ h}^{-1}$.

EFFECT ON BLOOD PRESSURE

There was an increase in the supine systolic blood pressures during the loading dose of DPI 201-106 (systolic 127 ± 24 to $146 \pm 16.3 \text{ mmHg}$, $P < 0.01$). Diastolic blood pressures did not show significant changes (74.4 ± 11 to $88 \pm 9 \text{ mmHg}$, NS).

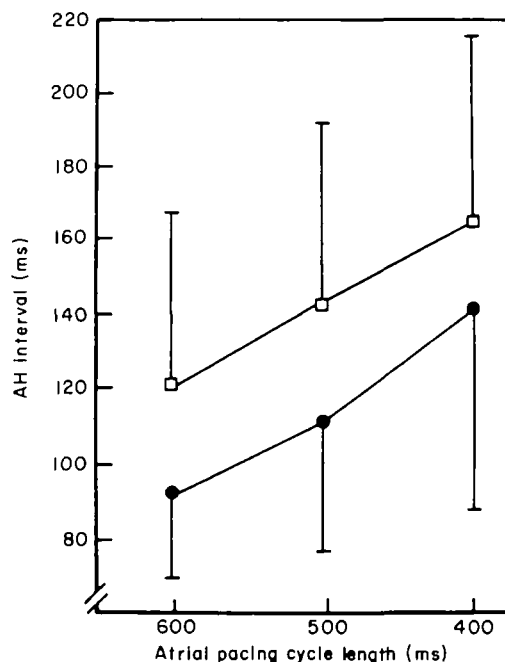


Figure 2 Changes in the AH interval during different atrial pacing rates before (●) and during (□) the maintenance dose of DPI 201-106. These changes were statistically significant ($P < 0.05$). The values are represented as mean \pm SD.

EFFECT ON SINUS NODE FUNCTION

There was a slight, but statistically insignificant, increase in the RR intervals after the loading dose of DPI 201-106 (795 ± 166 to $850 \pm 211 \text{ ms}$). The maximum sinus node recovery time changed from $1106 \pm 281 \text{ ms}$ to $948 \pm 242 \text{ ms}$ (NS), and the corrected sinus node recovery time decreased from 301 ± 123 to $231 \pm 156 \text{ ms}$ (NS).

EFFECT ON THE ATRIOVENTRICULAR NODE

There were no changes in the AH intervals in sinus rhythm during the loading or maintenance dose of DPI 201-106 ($72.5 \pm 14 \text{ ms}$). On the other hand, the AH intervals at constant rate atrial pacing showed a significant prolongation ($P < 0.05$) during the maintenance dose of DPI 201-106 compared with the control (Fig. 2).

There was a slight increase in the functional atrioventricular nodal refractory period during the maintenance dose in four out of six patients in whom these measurements were possible (413 ± 78 to $437 \pm 79 \text{ ms}$, NS). It was difficult to assess the change in atrioventricular nodal effective refractory periods because in four patients these refractory periods were limited by atrial refractoriness.

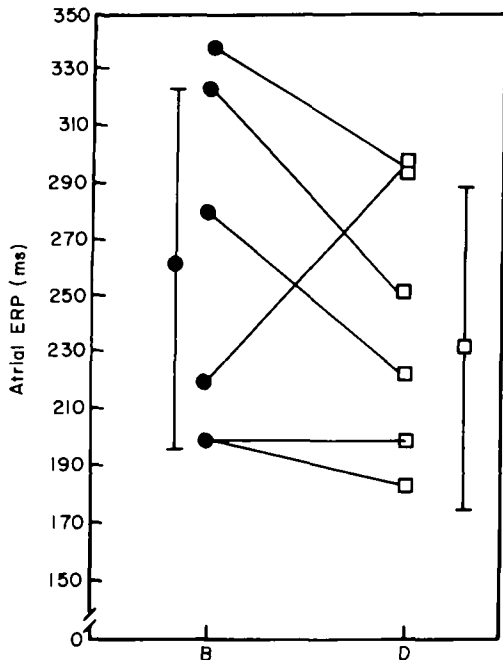


Figure 3 Changes in the atrial effective refractory period before (B) and during (D) and maintenance dose of DPI 201-106. These changes were statistically insignificant. The values are represented as mean \pm SD.

In one of the remaining two patients no changes occurred, but in the other an increase was seen. It was also difficult to assess the effective refractory period of ventriculo-atrial conduction because in two patients it was limited by the ventricular refractory period and in an additional two patients poor or no retrograde conduction could be seen. In only one patient was there a noticeable increase in the

ventriculo-atrial refractory period at the atrio-ventricular nodal level (480 to 600 ms).

The anterograde Wenckebach cycle length showed no significant change (377 ± 98 to 383 ± 163 ms), neither did the retrograde Wenckebach cycle length (508 ± 170 ms to 548 ± 147 ms).

EFFECT ON ATRIAL ELECTROPHYSIOLOGY

Refractory period

In four out of six patients who underwent electrophysiological studies, the atrial refractory period decreased during the maintenance dose of DPI 201-106. One patient had a marked increase in the atrial refractory period. The mean value, however, showed no statistical difference (261 ± 67 to 240 ± 53 ms) (Fig. 3).

Atrial PT duration

In six patients who had complete heart block the corrected atrial repolarization time (PT_{ac}) interval showed a significant decrease during the maintenance dose particularly after 20 and 30 min ($P < 0.05$). These changes were mainly due to changes in the atrial T-wave duration, as P-wave duration showed no significant changes (Table 2). In these patients the corresponding QT_c interval showed a noticeable prolongation (see below).

EFFECT ON VENTRICULAR ELECTROPHYSIOLOGY

HV interval and QRS duration

The HV interval and QRS duration remained unchanged during both the loading and maintenance infusion of DPI 201-106 at 45 ± 8 ms and 91 ± 12 ms, respectively.

Table 2 Changes (ms) in the surface electrocardiograms of patients with complete heart block before and during DPI 201-106 administration*

Parameter	Control	Loading		Maintenance		
		5 min	10 min	10 min	20 min	30 min
PP	780 \pm 111	846 \pm 126	842 \pm 143	838 \pm 152	915 \pm 130	874 \pm 140
P wave	111 \pm 8	112 \pm 11	112 \pm 6	114 \pm 5	116 \pm 5	116 \pm 7
PT_p	415 \pm 25	416 \pm 24	408 \pm 19	410 \pm 14	416 \pm 14	411 \pm 12
PT_{ac}	479 \pm 26	460 \pm 31	454 \pm 33	457 \pm 32	445 \pm 22	447 \pm 31
RR	1214 \pm 144	1210 \pm 143	1208 \pm 139	1203 \pm 156	1263 \pm 57	1246 \pm 67
QT_c	493 \pm 49	565 \pm 45	574 \pm 45	549 \pm 51	572 \pm 49	567 \pm 56
N	6	6	6	5	4	3

*For abbreviations see text.

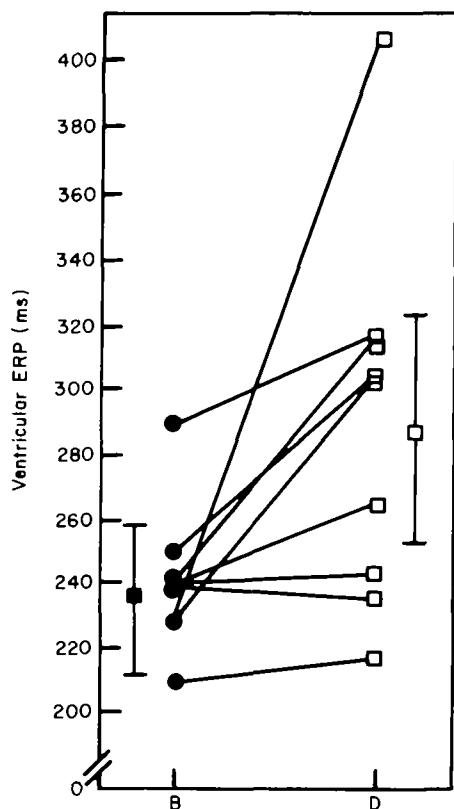


Figure 4 Changes in the ventricular effective refractory period before (B) and during (D) the maintenance dose of DPI 201-106a. These changes were statistically significant ($P < 0.05$). The values are represented as mean \pm SD.

Ventricular effect refractory period

There was a significant increase in the ventricular effective refractory period in six out of nine patients studied during the maintenance infusion of DPI 201-106 as estimated by extra-stimulus technique (242 ± 21 ms to 287 ± 56 ms, $P < 0.05$). This increase was also seen in all six patients in whom the cathodal strength interval curve was assessed (300 ± 25 ms to 333 ± 31 ms $P < 0.01$) (Fig. 4).

QT interval

Corrected QT intervals showed a significant increase after the loading dose of DPI 201-106 (417 ± 22 ms to 502 ± 35 ms, $P < 0.05$) (Fig. 5). This increase was also evident during the constant rate atrial or ventricular pacing (Fig. 6).

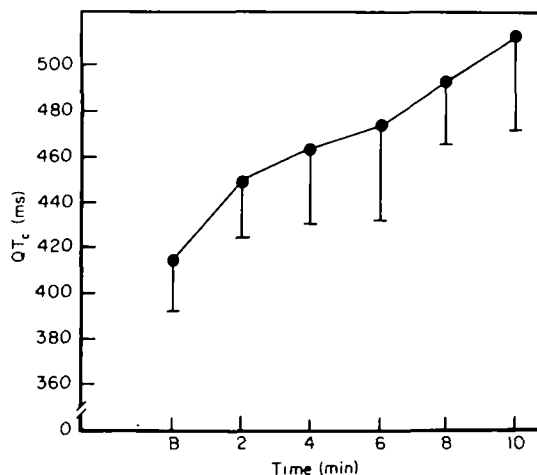


Figure 5 Changes in QT_c during the loading dose of DPI 201-106. These changes were statistically significant ($P < 0.05$). B, before drug administration. The values are represented as mean \pm SD.

Effect on ventricular supernormal period

DPI 201-106 had no effect on the ventricular diastolic cathodal threshold. The supernormal period could be demonstrated in five of six patients during DPI 201-106 infusion. The minimum threshold during the supernormal period (SNP-Tm) significantly increased ($P < 0.05$) (Table 3); but the supernormal-period duration decreased ($P < 0.05$, Table 3) during DPI 201-106 infusion. The relation of the supernormal to the atrially paced QT interval showed that, during DPI 201-106 infusion, there was a significant shift in the position ($P < 0.05$, Table 3) away from the peak of the T wave. The upper limit shifted from $133 \pm 8\%$ to $121 \pm 19\%$, but these were not significant (Table 3).

EFFECT ON CARDIAC ARRHYTHMIAS

There was no ventricular proarrhythmic effect of DPI 201-106. In one patient with ventricular tachycardia, the tachycardia was still provokable during the infusion. In five patients, however, DPI 201-106 appeared to facilitate the provocation of atrial fibrillation. In three of these patients the atrial fibrillation was provoked by atrial extra-stimulus near the atrial refractory period. Two of these had a history of paroxysmal atrial fibrillation. In two patients, atrial fibrillation was spontaneous and lasted for 2-4 h: one had a history of paroxysmal atrial fibrillation and the other a congenital atrio-ventricular block.

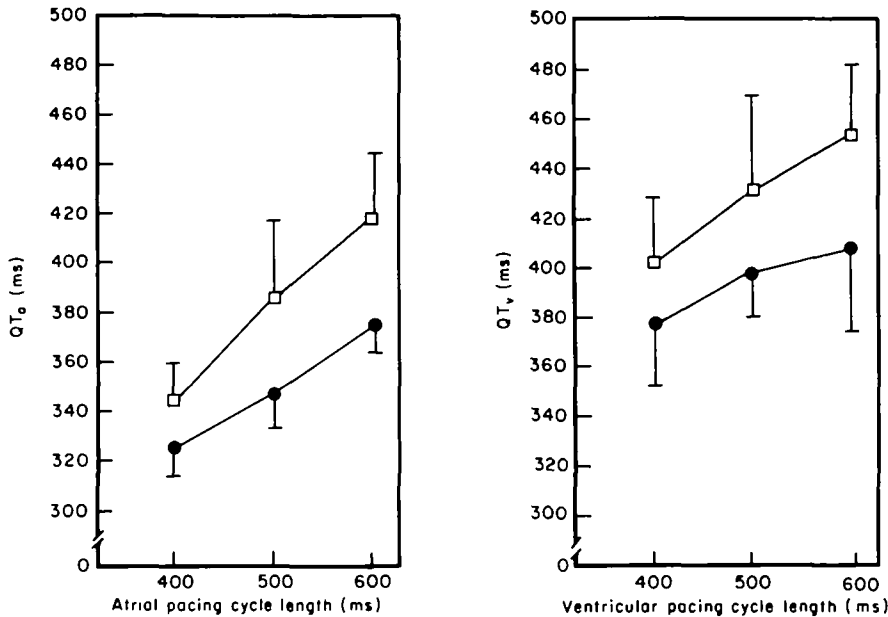


Figure 6 Changes in the atrially paced QT interval (QT_a) and ventricularly paced QT interval (QT_v) before (●) and during (□) the maintenance dose of DPI 201-106. The differences were significant ($P < 0.05$). The values are represented as mean \pm SD.

Table 3 Cathodal supernormal period*

Parameter	Control	During DPI
Diastolic threshold (mA)	0.49 \pm 0.30	0.46 \pm 0.27
SNP-Tm (%)	16 \pm 10	9 \pm 9
5% duration (ms)	155 \pm 76	79 \pm 42
5% position (%)	85 \pm 11-133 \pm 8	97 \pm 14-121 \pm 19

*For abbreviations and details see text.

Discussion

DPI 201-106 demonstrates a novel spectrum of electrophysiological effects which may reflect on its mechanism of action. The most remarkable effects were on ventricular electrophysiological parameters. The marked prolongation of the QT interval and the increase in ventricular refractory period, as documented in this and other studies^[2], may be explained by the prolongation of action-potential duration produced by DPI 201-106^[2], possibly due to the agonistic effect of DPI 201-106 on the Na⁺ channel as explained above. The effect of DPI 201-106 on the supernormal period is of particular interest. There are, to our knowledge, no studies on

the effect of DPI 201-106 on the cellular action potential supernormal period. The clinically assessed supernormal period of the ventricle is thought to be dependent on the dispersion of the action-potential duration^[14]. The decrease in the duration of the supernormal period during DPI 201-106 infusion in this study may be due to prolongation of the cellular action potentials leading to a decrease in their dispersion. The fact that supernormal periods were shifted towards the end of the T waves supports this explanation.

The effect of DPI 201-106 on atrial electrophysiology is of particular interest. Contrary to the effect on the ventricles, there was a decrease in the atrial effective refractory period in four out of six patients studied. This observation was consolidated by the observation that the corrected atrial repolarization time (PT_{ac}) was also shortened. The measurement of PT_{ac} in patients with heart block has been described previously^[13] and, in general, the PT_{ac} behaves in a similar way to the ventricular QT_c interval. DPI 201-106 prolongs the action potential duration in the isolated rabbit atria^[2]. It is, therefore, difficult to attribute the findings of this study to a direct effect of DPI 201-106. A reflex mechanism may be an alternative explanation. Cholinergic

fibres selectively innervate atrial tissue^[15]. An increase in the vagal tone by baroreceptor stimulation may decrease the effective atrial refractory period^[16]. The increase in systolic blood pressure during DPI 201–106 infusion may trigger baroreceptor activity and, thereby, increase vagal activity. The high incidence of induced atrial fibrillation in this study may also be explained by a possible increase in vagal tone^[17]. Some support for this view come from Walker *et al.*^[18] who noticed that DPI 201–106 significantly prolonged the sinus cycle length, sinus node recovery time, atrio-ventricular nodal functional refractory period, right ventricular functional refractory period and the QT interval. These findings could not be reproduced in cardiac transplanted dogs.

DPI 201–106 does not show a significant effect on the sinus node. The slight slowing of the sinus rate did reach statistical significance. This finding is not consistent with the hypothesis of increased vagal tone. If this hypothesis is correct, then DPI 201–106 must decrease the sensitivity of the sinus node to vagal effects. The atrio-ventricular nodal conduction during sinus rhythm did not alter during DPI 201–106 infusion; however, there was a slight, but significant, prolongation during fixed-rate atrial pacing. The atrio-ventricular nodal functional refractory period also increased slightly. These findings are consistent with the hypothesis of increased vagal activity. The agonistic effect of DPI 201–106 on the Na⁺ channel and its consequent influence on the action potential duration may not be applied to atrio-ventricular nodal tissues because they depend mainly on the Ca²⁺ channel. Recently, it was found that DPI 201–106 has a calcium antagonistic effect with prolonged treatment^[19]. It is therefore not clear whether the electrophysiological effects seen in this study will be applicable to long-term treatment.

It should be mentioned that two different loading doses were used in this study. This was at the request of the Ethics Committee of St Bartholomew's Hospital. The recommendation was that the first four patients should receive a lower loading dose before proceeding to the loading dose of 1.8 mg kg⁻¹ h⁻¹ as originally intended. However, the same effects were observed in the first four patients as in the rest of the patients. Because of the number of the patients, the pattern of the study and the doses used, it was not possible to assess dose response. Recently, it has been suggested that DPI 201–106 has some antiarrhythmic effects^[20]. This study was not designed to assess this possibility. On

the other hand, DPI 201–106 facilitated the initiation of atrial fibrillation in five patients. In one patient with ventricular tachycardia, DPI 201–106 did not change the electrophysiological pattern of that arrhythmia.

In conclusion, DPI 201–106 has an interesting and novel spectrum of electrophysiological effects which may be important during the routine clinical use of this agent.

References

- [1] Herzig JW, Quast U. Increase in Ca⁺⁺ sensitivity of myocardial contractile structure by DPI 201–106 (Abstr). *J Mol Cell Cardiol* 1984; 16 (Suppl 3): 6.
- [2] Scholtysik G, Salzmann R, Berthold R, Herzig JW, Quast U, Markstein R. DPI 201–106, a novel cardio-active agent. Combination of cAMP-independent positive inotropic, negative chronotropic, action potential prolonging and coronary dilatory properties. *Nauny-Schmiedeberg's Arch Pharmacol* 1985; 329: 316–25.
- [3] Gloor HO, Kappenberger LJ. DPI 201–106: a positive inotropic agent with prolongation of the QT-interval (Abstr) *Circulation* 1985; 72 (Suppl III): 235.
- [4] Thormann J, Kramer W, Kindler M, Neuss H, Schlepper M. Comparative efficacy of the new cardiotonic agent DPI 201–106 versus dopamine in dilated cardiomyopathy: analysis by serial pressure and volume relations and 'one-line' MVO₂ assessment. *J Cardiovas Pharmacol* 1986; 8: 749–57.
- [5] Petein M, From AHL, Francis GS, Pierpont GL. DPI 201–106: a new non-adrenergic inotropic agent with possible beta adrenergic blocking activity (Abstr). *Circulation* 1985; 72 (Suppl III): 304.
- [6] Kohlhardt M, Frobe U, Herzig JW. Modification of single cardiac Na⁺ channels by DPI 201–106. *J Membr Biol* 1985; 89: 163–72.
- [7] Buggisch D, Isenberg G, Ravens U, Scholtysik G. The role of sodium channels in the effects of the cardiotonic compound DPI 201–106 on the contractility and membrane potentials in isolated mammalian heart preparations. *Eur J Pharmacol* 1985; 118: 303–11.
- [8] Capman RA. Control of cardiac contractility at the cellular level. *Am J Physiol* 1983; 245: H535–52.
- [9] Lepeschkin E, Surawicz B. The measurement of the QT interval of the electrocardiogram. *Circulation* 1952; 6: 378–88.
- [10] Bazett HD. An analysis of the time-relations of electrocardiograms. *Heart* 1920; 7: 353–70.
- [11] Josephson ME, Seides SE. *Clinical cardiac electrophysiology*. Philadelphia: Lea and Febiger, 1979; 23–59.
- [12] Narula OS, Samet P. Sinus node recovery in man. *Fed Proc* 1971; 30: 554.
- [13] Debbas NMG, Nathan AW, Cochrane T, Levy AM, Camm AJ. Characterization of atrial repolarization from the surface ECG-effect of antiarrhythmic drugs and atrial pacing (Abstr). *PACE* 1984; 7: 458.
- [14] Butrous GS, Davies W, Debbas N, Nathan AW, Camm AJ. Assessment of ventricular supernormal period in man: is it a useful new clinical parameter? (Abstr). *Eur Heart J* 1985; 6 (Suppl 1): 974.

- [15] Randell WC, Armour JA. Gross and microscopic anatomy of the cardiac innervation. In: Randell WC, ed. *Neuronal regulation of the heart*. Oxford: Oxford University Press, 1977: 13-41.
- [16] Prystowsky EW, Naccarelli GV, Jackman WM, Rinkenberger RL, Hegar JJ, Zipes DP. Enhanced parasympathetic tone shortens atrial refractoriness in man. *Am J Cardiol* 1983; 51: 96-100.
- [17] Coumel Ph, Leclercq J, Attuel P, Lavalley J, Flammang D. Autonomic influences in the genesis of atrial arrhythmias: atrial flutter and fibrillation of vagal origin. In: Narula OS, ed. *Cardiac arrhythmias*. Maryland, U.S.A.: The Williams and Wilkins Co. 1979: 243-55.
- [18] Walker MJ, Tuna IC, Gornick CC, Almquist A, Benditt DG. Magnitude and temporal sequence of cardiac electrophysiologic effects of DPI 201-106: a new inotropic agent (Abstr). *Circulation* 1986; 74: II-267.
- [19] Hof RP, Hof A. Mechanism of the vasodilator effects of the cardiotonic agent DPI 201-106. *J Cardiovasc Pharmacol* 1985; 7: 1188-92.
- [20] Scholtysik G, Williams F. Antiarrhythmic effects of DPI 201-106 (Abstr). *Br J Pharmacol* 1986; 87: 75P.