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The effect of a new inotropic agent, DPI 201–106, on systolic time intervals and the electrocardiogram in healthy subjects

P. C. RÜEGG & E. NÜESCH
Clinical Research Department, Sandoz Ltd, Basel, Switzerland

1 DPI 201–106 (DPI) is a novel inotropic agent, with Na^+ channel agonistic action combined with a sensitization of contractile proteins to Ca^{++}. In a double-blind trial in healthy volunteers ($n = 20$) cardiovascular effects (blood pressure, heart rate, ECG) of single oral doses were studied. In addition systolic time intervals (STIs) were assessed in 10 of these subjects. DPI plasma concentrations were measured by h.p.l.c.
2 Preejection period was shortened by 14 ms ($P < 0.01$) and 30 ms ($P < 0.01$) 1 h after 30 and 60 mg, respectively, suggesting a dose-dependent inotropic effect. Heart rate was slightly reduced after both doses. Mean blood pressure remained unchanged.
3 Corrected QT interval duration (QTc) was prolonged by a mean of 7 ms (NS) and 22 ms ($P < 0.001$) 1 h after 30 and 60 mg, respectively. PQ and QRS intervals remained unaffected.
4 Peak plasma levels were attained at 1–2 h and the terminal elimination half-life was approximately 15 h.
5 It is concluded that DPI has positive inotropic and negative chronotropic properties which make it potentially useful for the treatment of heart failure.

Keywords DPI 201–106 inotropic agent systolic time intervals heart failure

Introduction

The current uncertainty about the inotropic efficacy of glycosides in patients with chronic cardiac failure as well as their narrow safety margin have prompted a search for more potent orally effective inotropic compounds.

DPI 201–106 (DPI) is 4-[3-(4-diphenylmethyl-piperazin-l-yl)-2-hydroxypropoxy]-1H-indol-2-carbonitrile and represents a novel type of cardiotonic agent. The mechanism of its positive inotropic effect appears to be a Na^+ channel agonistic action (Buggisch *et al.*, 1985) combined with a sensitization of contractile proteins to Ca^{++} (Scholtysik *et al.*, 1985). In addition, DPI shows Ca^{++} antagonistic (Hof & Hof, 1985) and local anaesthetic effects (Scholtysik & Williams, 1986) in pharmacological experiments. First experimental studies in patients with congestive heart failure have shown a favourable haemodynamic response and tolerability to single doses of DPI (Hogan *et al.*, 1986; Kostis *et al.*, 1986; Linderer *et al.*, 1987; Thormann *et al.*, 1986; Uretsky *et al.*, 1987), confirming results from animal experiments. The present study was undertaken to assess the cardiovascular effects and pharmacokinetics of single oral doses of DPI in healthy volunteers in order to characterize further its dose-effect relationship.

Methods

Population

Twenty healthy male volunteers gave written consent to participate in this study after they had

Correspondence: Dr P. C. Rüegg, Clinical Research Department, Sandoz Ltd, 4002 Basel, Switzerland

been informed of the nature and details of the protocol, which was approved by an Ethics Review Committee. Subjects ranged in age from 21 to 42 years (mean 30 years), and weighed between 56 and 81 kg (mean 69 kg). The subjects were in good health, as assessed by history, physical examination, ECG and laboratory tests Twelve out of the 20 subjects were cigarette smokers. In 17 subjects hydroxylator phenotype was determined (Mahgoub *et al.*, 1977) and one was found to be a poor metabolizer for debrisoquine.

Protocol

In a double-blind design, single oral doses of 30 mg and 60 mg DPI and placebo were administered in randomized order with an interval of at least 7 days between the doses. On the morning of the study days, at approximately 08.30 h, the study compound was administered on an empty stomach, as an aqueous drink solution (volume 100 ml). No other drugs were permitted during the study. Food and xanthine containing beverages were not allowed before the last systolic time interval measurement, i.e. until 5 h after dosing, and subjects had to refrain from smoking on the study days.

Measurements and computations

Blood pressure and heart rate were measured at hourly intervals before and for up to 12 h after drug administration, in the supine position, after 5 min lying. Twelve-lead electrocardiograms were taken 1 h before, and in hourly intervals for up to 12 h after dosing. ECG intervals (PQ, QRS, QT) were measured with a 'PROCOMILYZER' signal processor, Polimed AG, Switzerland. QTc intervals were calculated according to Bazett's formula by dividing the measured interval by the square root of the preceding RR interval (Bazett, 1920).

Systolic time intervals (STIs) were registered only in the first 10 subjects and measured by simultaneous registration of an ECG (modified extremity leads), a phonocardiogram and an external carotid arterial pulse tracing by means of an 'AVL Myocard Check', automated signal processor, AVL GmbH, Graz, Austria. Measurements were performed at rest in the supine position after 10 min lying 1 h before and for up to 5 h after dosing. At each time point, three measurements were performed, each measurement being the mean of 10 evaluable heart cycles. The following parameters were measured: duration of electromechanical systole (QS_2) and left ventricular ejection time (LVET). Preejection period (PEP) was calculated as the difference of QS_2 and LVET. QS_2 was corrected for heart rate, i.e. QS_2I, by using a regression coefficient of 1.13 as proposed by Johnson *et al.* (1981). PEP was not corrected for heart rate.

Venous blood samples were taken at intervals for up to 48 h after the dose. The analysis of the plasma samples was performed using h.p.l.c. with a detection limit of 0.5 ng ml^{-1} for the parent compound. The analyst was blinded in respect of the dose administered, but not of the sampling time. The pharmacokinetic data of each subject were evaluated separately for the two doses with nonlinear regression methods according to an explicit solution function of a two-compartment open model with first-order absorption (Wagner, 1975). For some of the subjects, mainly after the lower dose (30 mg), the plasma concentrations showed practically no α phase. They had to be evaluated with the solution function of a one-compartment open model. The parameters α and β (disposition rate constants), ka (absorption rate constant), Δt (time-lag) and V/F (volume of central compartment divided by fraction of oral dose absorbed) were estimated from the data by means of the SAAM 27 programme (Berman & Weiss, 1978). Each data set was weighted with a fractional standard deviation of one. The respective half-lives were calculated by dividing 0.693 (= ln 2) by the respective rate constants.

The parameters t_{max}, the time when maximal plasma concentrations $Cp(t_{max})$ occurred, and $Cp(t_{max})$ were compiled from the data. The AUC(0–48 h) was calculated from the data by means of the trapezoidal rule.

Results are reported as means ± s.d., if not otherwise indicated. All differences quoted are comparisons between active treatment and placebo. The null hypothesis of no drug effect was tested by means of an analysis of variance with repeated measures, and the drug effects were tested against placebo by means of Dunnett's test (Winer, 1971).

Results

All 20 subjects completed the trial as planned. DPI was well tolerated, without any subjective or objective side effects. Laboratory parameters, i.e. haematology, chemistry and urinalysis were uneventful.

Blood pressure and heart rate

The mean supine blood pressure at baseline was 115 ± 10 mm Hg systolic and 76 ± 7 mm Hg

diastolic, and heart rate was 59 ± 11 beats min^{-1}. The mean arterial pressure remained unaffected after the study compound. The mean systolic blood pressure increased slightly 1 h after both doses, by 6 ± 8 mm Hg (30 mg, $P < 0.01$ *vs* placebo) and 5 ± 8 mm Hg (60 mg, $P < 0.05$). At the same time the mean diastolic blood pressure remained unchanged (30 mg) or decreased by 5 ± 8 mm Hg (60 mg, $P < 0.01$).

The heart rate showed a dose-dependent reduction by 3 ± 4 ($P < 0.05$) and 5 ± 7 beats min^{-1} ($P < 0.01$) 1 h after 30 and 60 mg, respectively. The maximal negative chronotropic effect occurred between 1 and 2 h (see Figure 1).

ECG evaluations

PQ and QRS intervals did not show any drug effect. However, the QTc (Bazett) interval was prolonged dose-dependently compared with placebo (see Figure 2). The mean maximal effect was seen between 1 and 3 h post dose, with a QTc prolongation by 8 ± 17 ms (30 mg, NS) and 22 ± 24 ms (60 mg, $P < 0.01$) at 1 h. After the higher dose, QTc was significantly prolonged for up to 5 h (15 ± 14 ms, $P < 0.01$). Besides these changes of the QTc duration, the ECGs showed dose-dependent reduction in the amplitude of the T-wave, and in two subjects after 60 mg a transient biphasic T-wave in the precordial leads was recorded.

Systolic time intervals

Systolic time intervals (STIs) were measured in 10 subjects; their mean values are given in Table 1

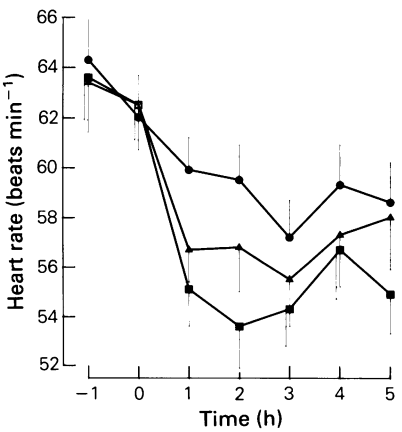

Figure 1 Standing heart rate in healthy volunteers before and after single oral doses of DPI 201-106 (30 (▲) and 60 mg (■)) and placebo (●) (mean ± s.e. mean, $n = 20$).

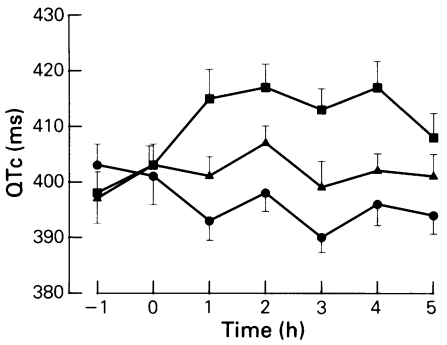

Figure 2 QTc (Bazett) interval (ms) in healthy volunteers before and after single oral doses of DPI 201–106 (30 (▲) and 60 mg (■)) and placebo (●) (mean ± s.e. mean, $n = 20$).

and Figure 3. DPI elicited a dose-dependent shortening of QS_2I and PEP as well as a reduction of PEP/LVET, suggesting positive inotropic and/or vasodilating properties. The maximal effect for all three parameters was observed at 1 h after dosing, with a mean shortening of QS_2I by 7 ± 8 ms (30 mg, NS) and 18 ± 17 ms (60 mg, $P < 0.05$). PEP was shortened by 14 ± 12 ms (30 mg, $P < 0.01$), and 30 ± 14 ms (60 mg, $P < 0.01$), and the PEP/LVET ratio was reduced by 0.06 ± 0.05 (30 mg, $P < 0.01$) and 0.11 ± 0.05 (60 mg, $P < 0.01$). These effects were detectable until 5 h after dosing. PEP and the PEP/LVET ratio proved to be more sensitive than QS_2I to distinguish the three treatments.

Pharmacokinetics

Mean plasma concentrations are given in Figure 4, and the derived parameters listed in Table 2. The maximal plasma concentrations were reached between 1 and 2 h after administration irrespective of the dose, with a t_{max} of 1.3 ± 0.8 and 1.4 ± 0.6 h after 30 and 60 mg, respectively. These concentrations were 20 ± 11 and 48 ± 23 ng ml^{-1}. The area under the concentration-time curves from 0 to 48 h (AUC(0–48 h)) were 124 ± 47 and 324 ± 82 ng ml^{-1} h, after 30 and 60 mg, respectively. Absorption occurred with half-lives of 0.29 ± 0.13 and 0.38 ± 0.39 h after 30 and 60 mg. Mean time-lags were between 0.20 and 0.25 h. The half-lives of the α-phase of the subjects who could be evaluated with a two-compartment model were 1.7 ± 1.0 h ($n = 14$) and 2.5 ± 0.9 h ($n = 19$) after 30 and 60 mg. The respective β half-lives were 13 ± 11 and 17 ± 7 h ($n = 20$). The comparison of the two doses, i.e. the 60 mg: 30 mg values showed a ratio of 2.4 ± 0.9 ($Cp(t_{max})$) and 2.7 ± 0.6 (AUC(0–48 h)). The subject who

Table 1 Mean duration of electromechanical systole (QS_2I), preejection period (PEP) and PEP/left ventricular ejection time ratio (PEP/LVET) before and after single oral doses of 30 and 60 mg DPI 201–106 (n = 10)

Parameter	*Dose DPI (mg)*	*Baseline mean ± s.d.*	*Difference vs placebo*[1] *0 h*	*1 h*[2]	*3 h*	*5 h*
QS_2I (ms)	30	496 ± 12	−8	−7	−2	−4
	60	498 ± 14	−6	−18**	−5	+1
PEP (ms)	30	112 ± 14	−7	−14**	−7	−8*
	60	115 ± 13	−3	−30**	−17**	−7
PEP/LVET	30	0.35 ± 0.05	−0.02	−0.06**	−0.03	−0.03*
	60	0.36 ± 0.04	0	−0.11**	−0.07**	−0.03*

[1] Dunnet's test active *vs* placebo
*$P < 0.05$, **$P < 0.01$
[2] Time after drug administration (h)

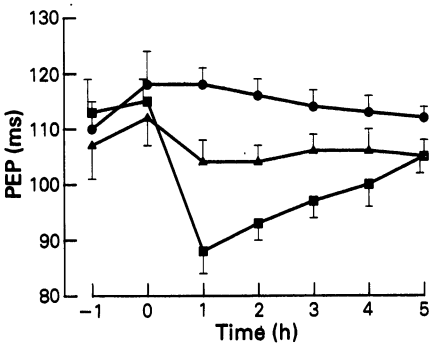

Figure 3 Preejection period (PEP) (ms) in healthy volunteers before and after single oral doses of DPI 201–106 (30 (▲) and 60 mg (■)) and placebo (●) (mean ± s.e. mean, n = 10).

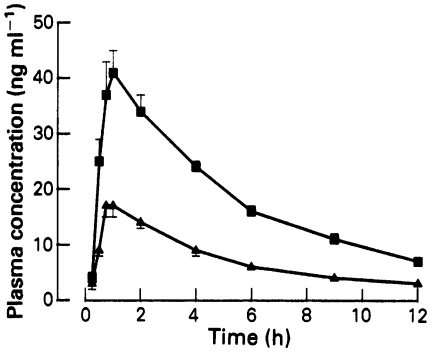

Figure 4 Plasma concentrations of unchanged compound in healthy volunteers after single oral doses of DPI 201–106 (30 (▲) and 60 mg (■)) (mean ± s.e. mean, n = 20).

had been shown to be a poor debrisoquine metabolizer during the screening was not distinguishable from the other subjects in terms of the kinetic profile.

Discussion

Systolic time intervals (STIs) are a well established means of non-invasively investigating cardiac

Table 2 Principal pharmacokinetic parameters of parent compound after single oral doses of 30 and 60 mg DPI 201-106 in healthy volunteers (n = 20, mean ± s.d.)

Parameter[1]	*30 mg*	*60 mg*
$t_{½}(\alpha_1)$ (h)	1.73 ± 1.02	2.50 ± 0.90
$t_{½}(\beta_2)$ (h)	13.3 ± 10.8	16.9 ± 7.5
$t(ka)$ (h)	0.29 ± 0.13	0.38 ± 0.39
Δt (h)	0.25 ± 0.13	0.24 ± 0.10
V/F (l)	2031 ± 1609	1382 ± 748
AUC(0–48 h) (ng ml^{-1} h)	124 ± 47	324 ± 82
Cp (t_{max}) (ng ml^{-1})	19.9 ± 10.5	47.9 ± 22.9
t_{max} (h)	1.25 ± 0.76	1.38 ± 0.64

[1] for abbreviations see text.

performance. They have a role in clinical pharmacology where they find particular application in the detection of inotropic activity. However, the interpretation of results frequently is limited by the fact that in addition to contractility changes these parameters are markedly influenced by other variables such as heart rate, preload and afterload (Gibson *et al.*, 1978).

Using the regression equations of Weissler *et al.* (1968) to correct STIs for heart rate variability may lead to overestimation of the inotropic action of compounds with negative chronotropic properties. As DPI is known to reduce heart rate, we therefore used the regression equation proposed by Johnson *et al.* (1981) to calculate the indexed duration of the electromechanical systole (QS_2I), with a slope of 1.13 instead of 2.1. Furthermore, for the same reason we did not correct the preejection period time (PEP) for heart rate variability.

As can be seen from the data, all STI parameters, which are known to correlate with cardiac inotropy (Johnson *et al.*, 1981), i.e. QS_2I, PEP as well as the PEP/LVET ratio, clearly showed a significant effect suggesting a positive inotropic action. The observation that 60 mg DPI has about twice the effect of 30 mg indicates a steep dose-effect curve in the dose range tested. An analysis of the individual plasma level-effect relationship at 2 h after dosing shows that 8/10 subjects responded with an increased contractility after 30 mg, and again 8/10 showed a further increase with 60 mg, as assessed by PEP. In all but one of the nine subjects who had a doubling of DPI plasma levels, the contractility increased (see Figure 5).

DPI is known to elicit peripheral vasodilation in several species, such as dogs (From *et al.*, 1984; Petein *et al.*, 1985), cats (Hof & Hof, 1985) and rats (Salzmann, personal communication). The observed changes in STIs might therefore be a composite of positive inotropic and afterload reducing actions, since both actions induce similar changes in the STI parameters (Hassan & Turner, 1983). Our data shows a dose-dependent increase in systolic blood pressure associated with a fall in diastolic blood pressure, particularly after 60 mg. This suggests left ventricular afterload reduction consequent of systemic vasodilation (fall in diastolic blood pressure); and the increase in systolic blood pressure may reflect the augmentation of cardiac contractility. Some of the inotropic activity observed with DPI could therefore be indirect, via a reflex increase in sympathetic activity. A fall in mean arterial pressure was prevented by the concomitant rise in contractility.

A comparison of the results of this study with

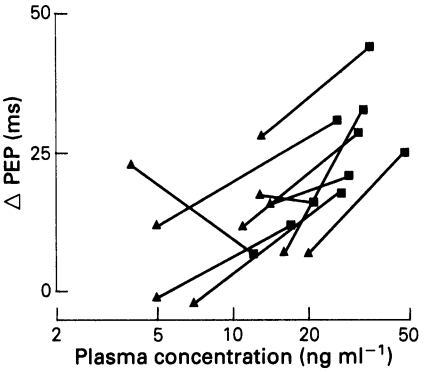

Figure 5 Individual plasma concentration-effect relationship in healthy volunteers ($n = 10$), 2 h after single oral doses of 30 ((▲) and 60 mg (■) DPI 201–106. ΔPEP = shortening (ms) of preejection period during active treatment as compared with placebo. Cp = DPI 201–106 plasma concentrations (ng ml^{-1}). Connected points belong to the same subject.

those of pharmacological *in vitro* investigations is difficult, since the concentration of unbound DPI is not known in man or in animal experiments. Nevertheless, it seems that the extent of the inotropic action as well as that of the effect of the repolarization occurs at similar concentrations in man and *in vitro*. As shown above, healthy volunteers with mean peak plasma levels of 48 ng ml^{-1} (= 0.1 μmol l^{-1}) after 60 mg showed clear circulatory effects along with a mean QTc prolongation of 6% *vs* placebo. In pharmacological *in vitro* experiments similar concentrations when added to the medium increased the contractile force of kitten papillary muscles by about 20% and prolonged the action potential duration (APD) of guinea-pig papillary muscles by about 15%, whereas lower concentrations (0.03 μmol l^{-1}) were without effect on APD (Scholtysik *et al.*, 1985).

In conclusion, single oral doses of DPI are well tolerated and elicit dose-dependent positive inotropic and negative chronotropic effects with a duration of action of several hours. These data show that DPI is distinctly different from other nonglycosidic, noncatecholamine inotropic agents with respect to its cardiovascular effects as well as its kinetic properties, and suggest that DPI merits further investigations to study its usefulness for the treatment of congestive heart failure.

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