SOME ASPECTS OF THE CARDIOVASCULAR PHARMACOLOGY OF UK 14,275 IN PATIENTS WITH CORONARY ARTERY DISEASE

K. JENNINGS, P.G. JACKSON, M. MONAGHAN & D.E. JEWITT

Cardiac Department, King's College Hospital, London, SE5

- 1 A phosphodiesterase inhibitor, UK 14,275 (Pfizer) was administered intravenously to six patients with suspected coronary artery disease under-going diagnostic cardiac catheterisation to assess its inotropic activity.
- 2 Intracardiac haemodynamic measurements included pulmonary and systemic arterial pressure. Left ventricular end diastolic pressure and left ventricular $dP/dt_{\max}$ were also measured, in addition to cardiac output using the indocyanine green dye technique.
- 3 UK 14,275 resulted in a significant increase in LV $dP/dt_{\max}$ and cardiac output.
- 4 No chronotropic action was observed using this agent.
- 5 This agent may have potential therapeutic value in the management of cardiovascular failure associated with low cardiac output.

Introduction

Following cardiac surgery or myocardial infarction, advanced cardiovascular failure associated with a low cardiac output is a profound problem resulting in a high mortality (Lown, Vassaux, Hood, Fakhro, Kaplinsky & Roberge, 1967; Dietzman, Ersek, Lillihei, Castaneda & Lillihei, 1969; Moffitt, Molnar & McGoon, 1971). The use of catecholamines in the management of these patients is limited by other, unwanted cardiovascular effects. Isoprenaline, the most commonly employed agent in this situation improves cardiac output but its positive inotropic activity is associated with positive chronotropic effects (Litwak, Kuhn, Gadboys, Lukban & Sakurai, 1968). Thus this agent results in improved cardiac output at the expense of increased heart rate and a higher incidence of cardiac arrhythmias. Increases in myocardial oxygen demands are undesirable in patients with coronary artery disease. Since heart rate is a major determinant of myocardial oxygen consumption (Sonnenblick & Skelton, 1971), the increase in heart rate associated with isoprenaline administration is a significant disadvantage (Maroko, Libby & Braunwald, 1973). Furthermore, hypotension may persist because of its peripheral vasodilating effects. On the other hand, noradrenaline results in peripheral vascular vasoconstriction and increased external cardiac work (Allwood, Cobbold & Ginsberg, 1963). An inotropic agent which augmented left ventricular function without increasing heart rate, the incidence of arrhythmias, or external cardiac work, would have clear therapeutic advantages.

Figure 1 The structure of UK 14,275, 1-butyl-3-(1-(6,7-dimethoxyquinazoline-4-yl) piperidin-4-yl) urea.

UK 14,275 is pharmacologically unique in that it is a cyclic AMP phosphodiesterase inhibitor some 20 times as potent as theophylline and this is thought likely to be the cause of its inotropic activity (Figure 1). In spontaneously beating guinea pig atria, UK 14,275 displayed dose related, positive inotropic effects without significant chronotropic change. In this respect, it resembled ouabain, but differed from isoprenaline and theophylline, which increased both force and frequency of contraction. Unlike the cardiac glycosides, however, it did not inhibit $\text{Na}^+\text{-K}^+$ ATPase and in contrast to isoprenaline, did not affect adenyl cyclase activity (Danilewicz, Evans, Ham & Thomson, 1976; Alabaster, Blackburn, Joice, Massingham & Scholfield, 1977). In anaesthetized and

Table 1 Summary of symptoms and findings in six patients

<i>Patient</i>	<i>Age (years)</i>	<i>Symptoms</i>	<i>Clinical findings</i>	<i>ECG</i>	<i>Angiographic findings</i>
HU	69	Angina — 2 years	Ectopics	Infero-lateral ischaemic changes. Ventricular ectopics	Poor LV function Complete block RCA. 90% block L. anterior descending. 90% proximal stenosis circumflex
NM	48	Angina — 5 years	Raised lipids	Changes of old inferior infarct plus anterior ischaemia	High LVEDP post angiography. 90% block RCA. Proximal stenosis of anterior descending
OK	64	Dyspnoea Angina 2 infarcts	Arcus senilis	Antero-lateral ischaemia	Very poor LV function
PD	54	Angina — 10 days	Arcus senilis	Normal	Two stenoses RCA (30% and 50%). 30% block L. anterior descending. 30% block in circumflex. Normal LV function
EW	63	Angina — 8 months Hypertension	BP 155/90	Normal	90% block L. anterior descending. Normal LV function
CM	60	Angina 3 years Dyspnoea	Arcus senilis	Severe anterior ischaemic changes	90% block RCA 90% stenosis LCA Normal LV function

RCA right coronary artery; LCA left coronary artery.

conscious dogs infusions of UK 14,275 produced positive inotropic effects with increases in rate which were much less than those evoked by a dose of isoprenaline which produced equivalent inotropic changes. This inotropic response was achieved with only a minor change in myocardial oxygen consumption (Danilewicz *et al.*, 1976).

A volunteer study performed non-invasively in this unit, using systolic time intervals confirmed a significant inotropic effect after UK 14,275 which was not associated with a rate increase (Jackson, Jackson, Kitson & Jewitt, 1977). These findings confirm those reported in a similar study performed by Follath, Kersting, Lewis, Walden, Woolhouse & Dollery (1976).

The purpose of the present study was to investigate the haemodynamic effects of UK 14,275 in patients with coronary artery disease at the time of routine diagnostic catheterization.

This work was presented at the November 1976 meeting of the British Cardiac Society.

Methods

Six male patients with coronary artery disease and angina were studied. Their clinical details are illustrated in Table 1. Previous maintenance therapy with digoxin, diuretics and warfarin was continued but no patient had received beta-adrenergic blocking agents during the 72 h before the study. All patients were in sinus rhythm at the time of investigation. Informed consent was obtained in every case.

Haemodynamic study

The electrocardiogram lead II was recorded for heart rate; left ventricular end diastolic pressure, pulmonary and systemic arterial pressures were recorded using fluid filled catheters attached to Statham strain gauge transducers whose signals were filtered and amplified and recorded on a Mingograph console. Left ventricular $dP/dt_{\max}$ was recorded using a Millar catheter tip manometer and cardiac output measured using the indocyanine green dye dilution technique with a Gilford densitometer. Duplicate dye dilution curves were performed at each dosage level. Values for pulmonary and systemic vascular resistances, cardiac index and stroke volume index were derived employing the following formulae:

Cardiac index (CI) = cardiac output (CO)/body surface area (BSA) ($\text{l min}^{-1} \text{m}^{-2}$)

Stroke volume index (SVI) = SV/BSA (ml m^{-2})

Systemic vascular resistance (SVR) = $(BP - RA)/CO \times 80$ ($\text{dyn} \cdot \text{s cm}^{-5}$)

Pulmonary vascular resistance (PVR) = $(PA - PCW)/CO \times 80$ ($\text{dyn} \cdot \text{s cm}^{-5}$)

Figure 2 Mean $\pm$ s.e. mean changes in heart rate following infusion with UK 14,275 at $128 \mu\text{g kg}^{-1} \text{min}^{-1}$ and $256 \mu\text{g kg}^{-1} \text{min}^{-1}$.

Drug infusion

Following a 10 min control infusion of 5% dextrose, UK 14,275 was administered in the dose of $128 \mu\text{g kg}^{-1} \text{min}^{-1}$ and $256 \mu\text{g kg}^{-1} \text{min}^{-1}$, to a total volume of 440 ml for the heaviest patient. Each infusion was separated by a 10 min period.

Statistical analysis employed the Student's *t*-test for paired data.

Results

The mean control haemodynamic values $\pm$ 1 s.e. mean and those following UK 14,275 infusion are presented in Table 2.

Heart rate, P-R interval and QT_c

Heart rate did not change significantly. The mean control value being 76 ± 7 beats/min and after the higher dose 78.8 ± 9 beats/min (Figure 2). The P-R interval remained unchanged but the QT_c was prolonged in five of the six patients following the higher dose infused. The QT interval, corrected for heart rate lengthened from 0.35 ± 0.02 to 0.44 ± 0.02 s ($P < 0.05$). The range was 0.29 to 0.42 s and 0.34 to 0.49 s respectively. Mean arterial pressure did not change significantly. The mean arterial pressure on

control infusion was 79.0 ± 13.9 mmHg falling to 72.3 ± 3.2 mmHg at the higher infusion dose. This was not significant. Mean systolic pressure was 115 mmHg falling to 108 mmHg and the mean diastolic pressure 64 mmHg falling to 56 mmHg at the higher dose. This diastolic fall was significant at the 2% level.

LVEDP fell from a mean level during the control infusion of 11.3 ± 2.9 to 9.8 ± 3.9 mmHg following the higher concentration of UK 14,275. This was significant at the 5% level.

Changes in LV $dP/dt_{\max}$ are illustrated in Table 2. From a control value of 1332 ± 138 mmHg s^{-1} the level increased to 1733 ± 299 mmHg s^{-1} after UK 14,275 $128 \mu g kg^{-1} min^{-1}$ and to 2004 ± 360 mmHg s^{-1} after $256 \mu g kg^{-1} min^{-1}$. This increase was statistically significant ($P < 0.005$). These changes are illustrated in Figure 3.

Cardiac output, stroke volume index and vascular resistance

Cardiac output rose from a mean control value of 3.0 ± 0.4 l/min to 3.5 ± 0.6 l/min during UK 14,275 infusion of $128 \mu g kg^{-1} min^{-1}$, increasing to 3.7 ± 0.5 l/min at the $256 \mu g kg^{-1} min^{-1}$ dose level. The latter value was significant ($P < 0.01$).

Cardiac index increased from a mean value of 1.3 ± 0.3 l $min^{-1} m^{-2}$ by 0.7 ± 0.3 at the higher dose level ($P < 0.05$). Stroke volume index increased to 27.5 ± 4.5 ml m^{-2} from a mean control value of 22 ± 3 ml m^{-2} at the $256 \mu g kg^{-1} min^{-1}$ level ($P < 0.05$). Changes in cardiac output and stroke volume are shown in Figure 4.

Total peripheral resistance fell significantly from a mean control value of 2218 ± 256 by 300 ± 116 dyn cm^{-5} at $128 \mu g kg^{-1} min^{-1}$ and by 592 ± 176 dyn

Figure 3 Mean $\pm$ s.e. mean changes in LV $dP/dt_{\max}$ following UK 14,275 infusion.

cm^{-5} at $256 \mu g kg^{-1} min^{-1}$ ($P < 0.05$ and $P < 0.02$ respectively).

The pulmonary vascular resistance fell from a mean control value of 133 ± 24 by 40 ± 28 dyn cm^{-5} but this was not significant.

Side effects

No side effects attributable to UK 14,275 were observed during or following this study. Full biochemical and haematological screening performed

Table 2 Mean $\pm$ s.e. mean effects of UK 14,275 infusions on six patients

	Control	UK 14,275	
		$128 \mu g kg^{-1} min^{-1}$	$256 \mu g kg^{-1} min^{-1}$
Heart rate (beats/min)	76 ± 7.3	$+1.17 \pm 1.62$	$+2.8 \pm 2.4$
MAP (mmHg)	79 ± 13.9	-2.0 ± 1.8	-7 ± 3.2
Systolic pressure (mmHg)	115	-3.83 ± 2.7	-7.8 ± 4.1
Diastolic pressure (mmHg)	64	-2.5 ± 1.8	$** -8.5 \pm 2.3$
PAP (mmHg)	14.7 ± 2.1	-1.5 ± 0.8	-2.2 ± 1.1
LVEDP (mmHg)	11.3 ± 2.87	-1.42 ± 0.76	$* -1.5 \pm 0.7$
dP/dt (mmHg/s)	1332 ± 138	$+401 \pm 168$	$**** +672 \pm 87$
CO (l/min m^{-2})	3.1 ± 0.4	$+0.5 \pm 0.3$	$*** +0.67 \pm 0.2$
CI (l/min m^{-2})	1.3 ± 0.3	$+0.2 \pm 0.2$	$* +0.7 \pm 0.3$
SVI (ml m^{-2})	22 ± 31	$+2.5 \pm 2.5$	$* +5.2 \pm 2$
SVR (dyn cm^{-5})	2218 ± 256.5	$* -300 \pm 116$	$** -592 \pm 176$
PVR (dyn cm^{-5})	133 ± 24	-5.7 ± 14.2	-40.4 ± 28.7

* $P < 0.05$; ** $P < 0.02$; *** $P < 0.01$; **** $P < 0.005$.

Figure 4 Mean $\pm$ s.e. mean changes in cardiac output (●) and stroke volume (■) following UK 14,275 infusion. ** $P < 0.01$ from control; * $P < 0.05$ from control.

before, at 24 h and 1 week following the study included ANF, full blood count, urinalysis and SMA₁₂.

Discussion

This haemodynamic study confirms previous experimental work in both conscious and anaesthetized animals (Danilewicz *et al.*, 1976; Follath *et al.*, 1976). We have demonstrated a 24% increase in cardiac output and a 43% improvement in LV $dp/dt_{\max}$. This improvement in cardiac performance was achieved without a substantial rise in heart rate. The QT_c was significantly prolonged in five of the six patients while the P-R interval remained unchanged. However, no arrhythmias developed following the infusions.

There was an associated reduction in left ventricular filling pressure, but mean arterial pressure was not significantly altered. This positive inotropic response was demonstrated in patients whose resting cardiac output ranged from 1.9 to 4.1 l/min. Total peripheral resistance fell significantly at both concentrations. Although pulmonary vascular resistance

fell at each infusion concentration, the differences from control did not reach statistical significance.

It is well known that angiography may cause impairment of left ventricular performance (Friesinger, Schaffter, Criley, Gaertner & Ross, 1965; Rahimtoola, Gau & Raphael, 1970). In this study the control haemodynamic values prior to UK 14,275 infusion were at preangiographic levels following a 45 min interval between the angiogram and the study.

Clearly in patients with coronary artery disease, increases in myocardial oxygen demands are undesirable. The inotropic effects of isoprenaline, the most commonly used agent in the low cardiac output syndrome, are achieved with a concomitant increase in heart rate. Since heart rate is a major determinant of myocardial oxygen consumption (Sonnenblick & Skelton, 1971) this is a significant disadvantage as is the tendency to precipitate cardiac arrhythmias. The use of agents which increase heart rate such as isoprenaline or increase systemic vascular resistance such as noradrenaline, may have a deleterious effect on the ischaemic left ventricle (Gunnar, Loeb, Pietras & Tobin, 1967; Mueller, Ayres, Gregory, Gianelli & Grace, 1970; Maroko, Libby & Braundwald, 1973).

The magnitude of the increase in LV $dp/dt_{\max}$ observed after UK 14,275 in the presence of a fall in diastolic pressure (there was not a significant fall in mean arterial pressure), makes it unlikely that the improvement in cardiac function was due to reduced afterload alone. The level of change in LV $dp/dt_{\max}$ associated with a fall in LVEDP suggests an increase of myocardial contractility. Reduction of afterload *per se* would be expected to reduce LV $dp/dt_{\max}$ (Gleason & Braunwald, 1962; Mason, 1969). The fact that LV $dp/dt_{\max}$ in the present study, increased despite a small reduction in afterload probably indicates improved contractility.

The present findings with UK 14,275 contrast with the effects of ouabain in patients without cardiac failure, when an increase in LV $dp/dt_{\max}$ is produced in association with a reduction in LVEDP and a minor increase in peripheral resistance (Rahimtoola, DiGilio, Sinno, Loeb, Rosen & Gunnar, 1971). Cardiac output did not change.

The demonstrated inotropic effect of UK 14,275 in man may be compared with that reported following other clinically used inotropic agents. Isoprenaline and dopamine have been reported to produce a 37% and 43% increase in cardiac output respectively (Holloway *et al.*, 1975). In these studies heart rate rose by 28% from control values following isoprenaline but did not increase significantly in dopamine treated patients. Dobutamine has been shown to significantly increase cardiac output by 42% above control values without increasing heart rate significantly (Jewitt *et al.*, 1974). The clinical value of dobutamine and dopamine in the management of advanced cardiovascular failure following cardiac surgery or myocardial infarction is being actively investigated at present (Jewitt *et al.*,

1974; Holloway *et al.*, 1975; Akhtar, Mikulic, Cohn & Chaudhry, 1975). Their precise clinical role in therapy has not yet been established. Future studies comparing the parenteral effects of UK 14,275 with these agents in patients with cardiac failure will be necessary.

Cardiac glycosides are the only agents commonly

prescribed for their inotropic effect in chronic cardiac failure. Since UK 14,275 has been demonstrated to possess inotropic activity following oral administration (Danilewicz *et al.*, 1976), future studies comparing it directly with cardiac glycosides will be necessary in order to establish whether or not UK 14,275 orally in man is an effective inotropic agent.

References

- AKHTAR, N., MIKULIC, E., COHN, J.N. & CHAUDHRY, M.H. (1975). Haemodynamic effects of dobutamine in patients with severe heart failure. *Am. J. Cardiol.*, **36**, 202–205.
- ALABASTER, C.T., BLACKBURN, K.J., JOICE, J.R., MASSINGHAM, R. & SCHOLFIELD, P.C. (1977). Abstract—British Pharmacological Society. April 1977.
- ALLWOOD, M.J., COBBOLD, A.F. & GINSBERG, J. (1963). Peripheral vascular effects of noradrenaline, isopropyl-noradrenaline and dopamine. *Br. med. Bull.*, 132–136.
- DANILEWICZ, J., EVANS, A.G., HAM, A.L. & THOMSON, C. (1976). *British patent number 1460389*.
- DIETZMAN, R.H., ERSEK, R.A., LILLIHEI, C.W., CASTANEDA, A.R. & LILLIHEI, R.C. (1969). Low output syndrome: recognition and treatment. *J. thorac. cardiovasc. Surg.*, **57**, 138–150.
- FOLLATH, F., KERSTING, F., LEWIS, G.R.J., WALDEN, R.J., WOOLHOUSE, N.M. & DOLLERY, C.T. (1976). Cardiovascular effects of a new inotropic drug in dog and normal man. *Clin. Pharmac. Ther.*, **20**, 24–30.
- FRIESENGER, G.C., SCHAFFTER, J., CRILEY, M., GAERTNER, R.A. & ROSS, R.S. (1965). Haemodynamic consequences of the injection of radiopaque material. *Circulation*, **31**, 730–740.
- GLEASON, W.L. & BRAUNWALD, E. (1962). Studies on the first derivative of the ventricular pressure pulse in man. *J. clin. Invest.*, **41**, 80–91.
- GUNNAR, R.M., LOEB, H.S., PIETRAS, R.J. & TOBIN, J.R. (1967). Ineffectiveness of isoproterenol in shock due to acute myocardial infarction. *J. Am. med. Ass.*, **202**, 1124–1128.
- HOLLOWAY, E.L., STINSON, E.B., DERBY, G.C. & HARRISON, D.C. (1975). Action of drugs in patients early after cardiac surgery. Comparison of isoproterenol and dopamine. *Am. J. Cardiol.*, **35**, 656–659.
- JACKSON, P.G., JACKSON, G., KITSON, D., JEWITT, D.E. The inotropic effect of UK 14,275, a phosphodiesterase inhibitor in man. *Br. J. clin. Pharmac.*, **5**, 7–11.
- JEWITT, D.E., MITCHELL, A., BIRKHEAD, J. & DOLLERY, C. (1974). Clinical cardiovascular pharmacology of dobutamine, a selective inotropic catecholamine. *Lancet*, **ii**, 363–367.
- LITWAK, R.S., KUHN, L.A., GLADBOYS, H., LUKBAN, S.B. & SUKURAI, H. (1968). Support of myocardial performance after open cardiac operations by rate augmentation. *J. thorac. cardiovasc. Surg.*, **56**, 484–496.
- LOWN, B., VASSAUX, C., HOOD, W.B., FAKHRO, A.M., KAPLINSKY, E. & ROBERGE, G. (1967). Unresolved problems in coronary care. *Am. J. Cardiol.*, **20**, 494–508.
- MAROKO, P.R., LIBBY, P. & BRAUNWALD, E. (1973). Effect of pharmacological agents on the function of the ischaemic heart. *Am. J. Cardiol.*, **32**, 930–936.
- MASON, D.T. (1969). Usefulness and limitations of the rate of rise of intraventricular pressure (dP/dt) in the estimation of myocardial contractility in man. *Am. J. Cardiol.*, **23**, 516–527.
- MOFFITT, E.A., MOLNAR, G.D. & McGOON, D.C. (1971). Myocardial and body metabolism in fatal cardiogenic shock after valvular replacement. *Circulation*, **44**, 237–244.
- MUELLER, H., AYRES, S.H., GREGORY, J.J., GIANELLI, S. Jr. & GRACE, W.J. (1970). Haemodynamics, coronary blood flow, and myocardial metabolism in coronary shock, response to L-norepinephrine and isoproterenol. *J. clin. Invest.*, **49**, 1885–1902.
- RAHIMTOOLA, S.H., GAU, G.T. & RAPHAEL, M.J. (1970). Cardiac performance after diagnostic coronary arteriography. *Circulation*, **41**, 537–544.
- RAHIMTOOLA, S.H., DIGILIO, M.M., SINNO, M.Z., LOEB, H.S., ROSEN, K.M. & GUNNAR, R.M. (1971). Effects of ouabain on impaired left ventricular function during convalescence after acute myocardial infarction. *Circulation*, **44**, 866–876.
- SONNENBLICK, E.H. & SKELTON, C.L. (1971). Oxygen consumption of the heart: physiological principles and clinical implications. *Mod. Conc. Cardiov. Dis.*, **40**, 9–16.

(Received January 24, 1977)