CARDIOVASCULAR EFFECTS OF A NEW INOTROPIC AGENT, U.K. 14275, IN PATIENTS WITH CORONARY HEART DISEASE

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- 1 The chronotropic and inotropic properties of U.K. 14275, a phosphodiesterase inhibitor were assessed in patients with coronary heart disease.
- 2 Left ventricular function was assessed in eight patients with acute myocardial infarction using the non-invasive measurement of systolic time intervals.
- 3 Twelve patients with angina pectoris were studied during diagnostic coronary arteriography. Left ventricular function was assessed using a high fidelity catheter tipped transducer in the left ventricle.
- 4 In both groups of patients U.K. 14275 infused intravenously in doses of 32, 64, 128 and 256 $\mu\text{g kg}^{-1}$ bodyweight min^{-1} enhanced the contractile state of the left ventricle without altering the heart rate.

Introduction

The introduction of coronary care units has reduced the mortality from dysrhythmias complicating recent myocardial infarction but no impact has, as yet, been made on the mortality associated with left heart failure, hypotension and the reduced cardiac output state sometimes referred to as 'pump failure'. Sympathomimetic amines have been used in the management of such cases and also to provide inotropic support following cardiac surgery. Nor-adrenaline stimulates both α and β adrenergic receptors resulting in increased cardiac contraction and intense peripheral vasoconstriction with subsequent elevation of the arterial blood pressure but with increased myocardial oxygen consumption. Isoprenaline is a potent β -adrenoceptor stimulant and increases heart rate in addition to its inotropic action. The excessive tachycardia and the propensity to ventricular dysrhythmia produced by isoprenaline has stimulated research into pharmacological compounds which can exert inotropic effects but have no chronotropic action. Dobutamine has been shown both in man (Jewitt, Mitchell, Birkhead & Dollery, 1974) and in the experimental animal (Vatner, McRitchie & Braunwald, 1974) and (Willerson, Hutton, Watson, Platt & Templeton, 1976) to have such properties but, in patients after open heart surgery, it has been shown to have chronotropic properties similar to isoprenaline (Kersting, Follath, Moulds, Mucklow, McCloy, Shearer & Dollery, 1976).

1-Butyl-3 (1-(6,7-dimethoxyquinazolin-4-yl) piperidin-4-yl urea) (U.K. 14275, Pfizer Laboratories, Figure 1) is a new pharmacological compound which

inhibits cyclic AMP phosphodiesterase thus increasing cellular 3,5 cyclic AMP which should enhance the contractile state of the myocardium. Follath, Kersting, Lewis, Walden, Woolhouse & Dollery (1976) have shown in human volunteers that the intravenous infusion of U.K. 14275 resulted in an increase in myocardial contractility without significant alteration in heart rate or blood pressure.

The object of the present study was to assess the cardiovascular effects of U.K. 14275 in patients with coronary heart disease undergoing coronary angiography and in patients with recent myocardial infarction.

Methods

Twelve male patients with coronary heart disease undergoing coronary angiography were studied at the time of cardiac catheterization. The patients were all in sinus rhythm and β -adrenoceptor blocking agents had been discontinued 48 h prior to the investigation. Eight patients with acute myocardial infarction being treated in an intensive coronary care unit who were considered to have clinical evidence of left ventricular dysfunction as evidenced by tachycardia, additional heart sounds and lung base crepitations, were also studied by non-invasive techniques—the systolic time intervals. The nature of the study was carefully explained to each patient and their consent was obtained. Approval for the study had also been obtained from the hospital ethical committee.

Figure 1 The structure of U.K. 14275, 1-butyl-3-1-(6,7-dimethoxyquinazoline-4-yl) piperidin-4-yl urea.

Haemodynamic study

A high fidelity left ventricular (LV) pressure was obtained using a Millar transducer tipped catheter (PC-350). The catheter has a flat frequency response from 0–250 kHz. The LV pressure wave form was recorded on an f.m. instrumentation tape recorder and subsequently analysed on a PDP-8 computer. The computer digitized 8 s of recorded signal at a rate of 250 samples/second. The rate of rise of pressure dP/dt was then calculated between successive samples from end diastole to peak systole and dP/dt (max) and dP/dt over simultaneously developed pressure (P) was then determined for each beat analysed. The results presented are the mean values of all beats within an 8 s sample. Heart rate was obtained from a continuous recording of the electrocardiogram, systemic blood pressure was measured from the Miller catheter and cardiac output was determined using a dye-dilution technique (Waters Instrumentations DCR 701). All cardiac outputs were done in duplicate and the mean of the results was taken.

Non-invasive study

The systolic time intervals total electromechanical systole (QS_2), left ventricular ejection time (LVET), pre-ejection period (PEP) and ratio of PEP/LVET were measured from simultaneous high speed recordings of the electrocardiogram, phonocardiograms and carotid pulse wave tracing (Weissler, Harris & Schoenfeld, 1968). Each interval was measured to the nearest 5 ms mean values of six cardiac cycles being obtained. Blood pressure was measured by sphygmomanometer. The left ventricular filling pressure was measured by means of a flow-guided balloon catheter placed in the pulmonary artery (Swan, Ganz, Forrester, Marcus, Diamond & Chonetti, 1970). Heart rate was again measured from a continuous recording of the electrocardiogram.

Experimental protocol

In the haemodynamic study after baseline measure-

ments U.K. 14275 was infused intravenously at doses of 64, 128 and 256 $\mu\text{g kg}^{-1}$ bodyweight min^{-1} . The drug was dissolved in dextrose and infused over a 5–8 min period using a calibrated infusion pump (Sage Instruments). The dosage increments used in the patients with myocardial infarction were 16, 32, 64 and 128 $\mu\text{g kg}^{-1}$ bodyweight min^{-1} , each infusion level being given for 5 minutes.

Results

Haemodynamic study

Detailed results are noted in Table 1.

dP/dt (max) increased by 27% at the highest rate of infusion from 1518 ± 65 to 1936 ± 97 mmHg/s ($P < 0.02$). $dP/dt/P$ increased from 73.3 ± 3.0 to 82.2 ± 0.5 s^{-1} ($P < 0.02$). Left ventricular end diastolic pressure (LVEDP) did not change 10 ± 2 and 8 ± 1 mmHg. Heart rate was not significantly altered at any of the infusion rates 76 ± 2 to 77 ± 2 beats/min at 256 $\mu\text{g kg}^{-1}$ bodyweight min^{-1} . There was no significant change in the systemic blood pressure. Systolic blood pressure was 132 ± 9 at the start of the infusion and 129 ± 8 mmHg at the end. Diastolic blood pressure 79 ± 8 and 80 ± 6 mmHg and the mean blood pressure was 97 ± 8 and 96 ± 8 mmHg. Cardiac output increased from 5.9 ± 0.14 l/min to 6.3 ± 0.13 l/min ($P < 0.01$), at the 256 $\mu\text{g kg}^{-1}$ bodyweight min^{-1} infusion. There was an increase in stroke volume from 78 ± 18 to 85 ± 17 ml ($P < 0.01$).

Myocardial infarction group

The detailed results are found in Table 2.

The pre-ejection period (PEP) significantly shortened at the highest rate of infusion 128 $\mu\text{g kg}^{-1}$ bodyweight min^{-1} from 112 ± 6 to 91 ± 8 ms ($P < 0.05$) representing a 20% increase in left ventricular contractility. Similarly the ratio PEP/LVET shortened from 0.46 ± 0.05 to 0.34 ± 0.2 ($P < 0.05$). Heart rate was unchanged 76 ± 7 and 74 ± 5 beats/min. LVEDP was unaltered 12 ± 2 and 10 ± 3 mmHg. There was again no change in the systemic blood pressure, systolic blood pressure was 128 ± 8 mmHg at the start of the infusion and 126 ± 9 mmHg at the end, diastolic blood pressure was 80 ± 7 and 78 ± 6 mmHg mean blood pressure was 94 ± 6 and 95 ± 7 mmHg.

The increase in dP/dt showed a linear relationship to the log of plasma concentration of U.K. 14275 (Figure 2). Plasma drug concentrations were determined by extraction from plasma ethyl acetate, the extract then being chromatographed by thin layer chromatography (t.l.c.) and the quantity of the drug measured by direct absorption densitometry on the t.l.c. plate (Department of Drug Metabolism, Pfizer Limited, Sandwich). There was a dose related decrease

Table 1 Mean $\pm$ s.e. mean results from haemodynamic study

Dosage regime	Heart rate (beats/min)	Systolic BP (mmHg)	Diastolic BP (mmHg)	Mean BP (mmHg)	Cardiac output (l/min)	Stroke volume (ml)	LVEDP (mmHg)	dP/dt (max) (mmHg/s)	dP/dt/P (s ⁻¹)
Control	71 $\pm$ 5	130 $\pm$ 8	80 $\pm$ 6	97 $\pm$ 7	—	—	9 $\pm$ 3	1590 $\pm$ 233	85.8 $\pm$ 2.5
64 μ g kg ⁻¹ bodyweight min ⁻¹ n=5	74 $\pm$ 5	131 $\pm$ 9	81 $\pm$ 7	86 $\pm$ 7	—	—	9 $\pm$ 3	1738 $\pm$ 332*	89.8 $\pm$ 2.2*
Control	72 $\pm$ 6	130 $\pm$ 8	82 $\pm$ 7	98 $\pm$ 7	—	—	9 $\pm$ 3	1439 $\pm$ 91	84.1 $\pm$ 1.6
128 μ g kg ⁻¹ bodyweight min ⁻¹ n=6	74 $\pm$ 7	132 $\pm$ 9	80 $\pm$ 6	97 $\pm$ 8	—	—	10 $\pm$ 4	1667 $\pm$ 101*	91.1 $\pm$ 2.0*
Control	76 $\pm$ 2	132 $\pm$ 9	79 $\pm$ 8	97 $\pm$ 8	5.9 $\pm$ 0.1	78 $\pm$ 18	10 $\pm$ 2	1518 $\pm$ 65	73.3 $\pm$ 3.0
256 μ g kg ⁻¹ bodyweight min ⁻¹ n=6	77 $\pm$ 2	129 $\pm$ 8	80 $\pm$ 6	96 $\pm$ 8	6.4 $\pm$ 0.1**	85 $\pm$ 17**	8 $\pm$ 1	1936 $\pm$ 97*	82.2 $\pm$ 4.0*

* $P < 0.02$; ** $P < 0.01$.Table 2 Mean $\pm$ s.e. mean results of non-invasive study

Dosage regime	Heart rate (beats/min)	Systolic BP (mmHg)	Diastolic BP (mmHg)	Mean BP (mmHg)	PEP (s)	PEP/LVET
Control	81 $\pm$ 4	126 $\pm$ 7	80 $\pm$ 6	95 $\pm$ 5	101 $\pm$ 10	0.41 $\pm$ 0.03
16 μ g kg ⁻¹ bodyweight min ⁻¹ n=4	80 $\pm$ 4	127 $\pm$ 8	82 $\pm$ 7	96 $\pm$ 6	99 $\pm$ 18	0.39 $\pm$ 0.02
Control	81 $\pm$ 4	130 $\pm$ 9	84 $\pm$ 8	97 $\pm$ 8	101 $\pm$ 10	0.41 $\pm$ 0.26
32 μ g kg ⁻¹ bodyweight min ⁻¹ n=7	79 $\pm$ 4	132 $\pm$ 10	85 $\pm$ 9	96 $\pm$ 7	94 $\pm$ 9	0.37 $\pm$ 0.03
Control	82 $\pm$ 5	129 $\pm$ 6	83 $\pm$ 7	95 $\pm$ 6	96 $\pm$ 5	0.40 $\pm$ 0.03
64 μ g kg ⁻¹ bodyweight min ⁻¹ n=4	80 $\pm$ 5	131 $\pm$ 5	82 $\pm$ 6	96 $\pm$ 6	83 $\pm$ 6	0.34 $\pm$ 0.01
Control	76 $\pm$ 7	128 $\pm$ 8	80 $\pm$ 7	94 $\pm$ 6	112 $\pm$ 6	0.45 $\pm$ 0.05
128 μ g kg ⁻¹ bodyweight min ⁻¹ n=4	72 $\pm$ 5	126 $\pm$ 9	78 $\pm$ 6	95 $\pm$ 7	91 $\pm$ 8***	0.34 $\pm$ 0.02***

*** $P < 0.05$.

Figure 2 The relationship between the percentage change in left ventricular dP/dt and log of plasma concentration of U.K. 14275. No activity is evident with plasma levels less than 2 µg ml⁻¹.

Figure 3 The relationship between the percentage change in the duration of the pre-ejection period with increasing infusion rates of U.K. 14275. Mean ± s.e. mean for each level shown.

in the PEP with infusion rates of 16, 32, 64 and 128 µg kg⁻¹ bodyweight min⁻¹ (Figure 3).

Side effects

There was a modest degree of venous irritation in two of the twenty patients to whom U.K. 14275 was infused intravenously.

No adverse biochemical effects were found, nor was evidence of hepatic or renal damage obtained.

Discussion

The data obtained from this study would suggest that U.K. 14275 has a significant inotropic action on patients with coronary heart disease with little or no effect on heart rate. The invasive measurements of dP/dt (max) and dP/dt/P have been shown to be acceptable indices of myocardial contractility, to be relatively insensitive to changes in pre-load or after-load and to be particularly applicable in the interpretation of directional haemodynamic changes produced by a drug or other intervention (Furnival, Linden & Snow, 1970); (Mason, Braunwald, Covell, Sonnenblick & Ross, 1971) and (Vatner, Higgins, Patrick, Franklin & Braunwald, 1971). In this study the heart rate was unaltered, left ventricular end diastolic pressure was unchanged as was systemic blood pressure, and thus the highly significant

increases in dP/dt (max) and dP/dt/P indicated that U.K. 14275 has a positive inotropic action. This was further confirmed by the significant increases in cardiac output and stroke volume.

Although U.K. 14275 appears to exert a positive inotropic action in patients with angina pectoris its clinical application might be more relevant to an acute situation such as recent myocardial infarction. It seemed appropriate to evaluate the drug in this clinical context. The assessment of left ventricular function in these ill patients was carried out by measurement of systolic time intervals using a noninvasive technique. In the absence of changes in preload and afterload the duration of pre-ejection period is determined by the rate of rise of left ventricular pressure (dP/dt) (Talley, Meyer & McNay, 1971). The ratio of PEP/LVET correlates closely with the ejection fractions measured by ventriculography (Garrard, Weissler & Dodge, 1970). In the present study there was significant shortening of the PEP and a decrease in PEP/LVET indicating enhanced contractility. Again this was associated with no change in heart rate nor in preload and afterload. Thus U.K. 14275 exerts a positive inotropic effect in the patients with recent myocardial infarction. These changes in myocardial contractility in both groups of patients were dose-related and were maximum at the highest infusion rate.

These results are similar to those found experimentally in the anaesthetized dog where cardiac output and L.V. dP/dt increased progressively with

the dose administered (Follath *et al.*, 1976). The only difference was the transient effect of the drug in both groups of patients in contrast to the persistence of the inotropic action for some 30 min found in the experimental study.

Pharmacological agents which have an inotropic but not a chronotropic effect might be useful in the management of the low output state complicating recent myocardial infarction or cardiac surgery. Dobutamine, reported to have a powerful inotropic action in patients undergoing diagnostic cardiac catheterization but with little increase in heart rate (Jewitt *et al.*, 1974) was found to have no advantage over isoprenaline in the post-operative cardiac surgical patient (Kersting *et al.*, 1976).

Cardiogenic shock complicating pump failure is now the principal cause of death in patients being treated in the coronary care unit and one of the major areas of cardiovascular research is directed towards protection of the ischaemic myocardium and limitation of the ultimate areas of myocardial necrosis. Experimentally factors which augment myocardial

oxygen consumption have been shown to extend the area of ischaemic injury and of ultimate necrosis. These factors include isoprenaline, ouabain and tachycardia (Maroko, Kjekshus, Sobel, Watanase, Covell, Ross & Braunwald, 1971) and (Redwood, Smith & Epstein, 1972). Dobutamine has been shown in both the anaesthetized and conscious dog, with myocardial ischaemia, to increase myocardial contractility as much if not more than myocardial blood flow and if heart rate were to increase in addition, then the extent of myocardial damage would be greater (Willerson *et al.*, 1976). Thus, despite the lack of effect on heart rate, U.K. 14275 should be used with caution in patients with acute myocardial infarction unless there is evidence of left ventricular dysfunction.

The main potential use for this new inotropic agent would appear to be in the management of patients with established coronary heart disease, who have ventricular dysfunction and chronic cardiac failure.

Supplies of the drug were obtained from Pfizer Research Laboratories, Sandwich, Kent.

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