Br J clin Pharmac 1994; **37**: 347–353

Effects of acute β-adrenoceptor blockade with metoprolol on the renal response to dopamine in normal humans

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1 The present study investigated the contribution of adrenergic β_1-receptor stimulation to the cardiovascular and renal effects of low-dose dopamine in eight normal, water-loaded humans.

2 Metoprolol (100 mg) or placebo was administered orally at 08.00 h in a randomized, double-blind fashion on two different days. Renal clearance studies were performed during a 1 h baseline period, two 1 h periods with dopamine infusion (3 μg kg^{-1} min^{-1}), and a 1 h recovery period. Cardiac output was measured by an ultrasonic Doppler method, and lithium clearance (CL_{Li}) was used to estimate proximal tubular outflow.

3 Baseline values of heart rate, systolic pressure and mean arterial pressure decreased with metoprolol compared with placebo, but cardiac output, effective renal plasma flow (ERPF) and glomerular filtration rate (GFR) were not significantly changed. Metoprolol significantly decreased baseline CL_{Li} and sodium clearance (CL_{Na}) by 19% ($P < 0.01$) and 34% ($P < 0.01$), respectively.

4 Metoprolol blunted the dopamine-induced increases in heart rate and systolic pressure, but cardiac output increased to the same extent on both study days by 26% (placebo, $P < 0.05$) and by 31% (metoprolol, $P < 0.01$), respectively. With and without metoprolol, dopamine did not significantly change GFR, and the percentage increases in ERPF were similar on the two study days (40% ($P < 0.001$) and 42% ($P < 0.001$), respectively). Dopamine increased CL_{Li} and CL_{Na} by 31% ($P < 0.01$) and 114% ($P < 0.01$), respectively, with placebo, and by 36% ($P < 0.01$) and 114% ($P < 0.01$), respectively, with metoprolol. Values during infusion remained significantly lower with metoprolol compared with placebo.

5 It is concluded that adrenergic β_1-receptor activation contributes to the cardiac effects of dopamine in the present dose. However, cardiac output seemed to increase mainly as a response to a reduced peripheral resistance. The maintained percentage dopamine-induced increase in ERPF, CL_{Li}, and CL_{Na} is consistent with effects predominantly mediated via renal dopaminergic receptors. However, metoprolol decreased absolute values of CL_{Li} and CL_{Na} suggesting that a reduced adrenergic β_1-receptor activity may indirectly influence the natriuretic response to dopamine, probably by decreasing renal perfusion pressure.

Keywords dopamine effective renal plasma flow glomerular filtration rate lithium clearance metoprolol sodium clearance

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Introduction

Low-dose dopamine (1–5 μg kg^{-1} min^{-1}) increases renal blood flow and sodium excretion by stimulation of specific dopaminergic DA_1 receptors in the kidney [1, 2]. In addition, indirect effects secondary to the associated increase in cardiac output may contribute to the renal response of dopamine [3, 4]. Previous studies have indicated that a dose-dependent activation of adrenergic β_1-receptors becomes significant even during relatively low infusion rates (2–5 μg kg^{-1} min^{-1}) [5–7]. Therefore, an increase in cardiac contractility by an action of dopamine on β_1-adrenoceptors could in part be responsible for the beneficial renal effects [4]. In anaesthetized pigs, combined α- and β-adrenoceptor blockade abolished the dopamine-induced increase in heart rate and contractility, but the decrease in systemic and renal vascular resistance was not significantly affected [8]. In humans, it still remains unknown whether the increase in cardiac output after low-dose dopamine is primarily caused by stimulation of cardiac β_1-adrenoceptors or is merely a consequence of the vasodilating effect secondary to activation of vascular DA receptors. Furthermore, the dependence of renal effects upon cardiac β_1-stimulation is unknown.

The purpose of the present study was to test the hypothesis that acute β_1-adrenoceptor blockade with metoprolol in normal humans would abolish the dopamine-induced increase in cardiac output without affecting the renal vasodilating and natriuretic effects.

Methods

The study was approved by the regional scientific ethics committee. Eight healthy subjects (three females) aged 23–38 years gave informed consent and entered the study. Weight and height (means ± s.d.) were 70.6 ± 4.6 kg and 178 ± 6 cm, respectively.

Each subject was investigated on two different occasions separated by an interval of at least 5 days. The lithium clearance method was used as an estimate of proximal tubular outflow [9, 10]. A test dose of lithium carbonate (600 mg, 16.2 mmol) was given orally at 22.00 h the evening before each study day. After an overnight fast, the subjects were randomized in a double-blind fashion to receive metoprolol (100 mg) or matched placebo tablets orally upon arrival to the laboratory at 08.00 h. Water diuresis was induced by orally administered water (200–300 ml every 20 min without an initial load). A venous catheter was inserted into an antecubital vein in each arm for infusion and blood sampling, respectively. Except for briefly standing when voiding every 20 min, the subjects were confined to a supine position. Steady state was considered to have been achieved when urine flow rates approximately equaled water intake. Thereafter, a 1 h baseline clearance period (period 1) was followed by an intravenous infusion of dopamine (3 μg kg^{-1} min^{-1}), which was given during two consecutive 1 h clearance periods (periods 2 and 3). Following cessation of the dopamine infusion, measurements were finally made in a 1 h recovery period (period 4).

Cardiac output was measured in periods 1, 3 and 4 by pulsed ultrasound Doppler and M-mode echocardiography. A 2 MHz pulsed doppler (Pedof, Norway) was used to measure the velocity of the blood stream in the ascending aorta with the transducer placed in the suprasternal notch. On each occasion, the stroke volume was calculated by multiplying the height of the integrate of maximum velocity (average of 30 consecutive beats) by the diameter of the ascending aorta as measured by M-mode echocardiography (average of 3 consecutive beats). Arterial blood pressure (measured by sphygmomanometry) and heart rate were measured for each period. Effective renal plasma flow (ERPF) and glomerular filtration rate (GFR) were measured by a constant infusion technique with urine collections, using [^{131}I]-hippuran and [^{99m}Tc]-diethylenetriaminepentaacetic acid (DTPA) in a total average dose of 0.10 MCi (3.6 MBq) and 0.73 MCi (27.0 MBq), respectively. After an equilibration period of at least 1 h, renal clearances of [^{131}I]-hippuran, [^{99m}Tc]-DTPA, lithium and sodium (CL_{Na}) were determined for periods 1, 2, 3 and 4, each calculated from the 1 h urinary excretion rates and the plasma values from three samples drawn at the start, the middle, and the end of each 1 h clearance period. Body weight was measured at arrival and at the end of periods 1, 3 and 4. Packed cell volume and plasma concentrations of renin (PRC) and aldosterone (PAC) were measured at the end of periods 1 and 3. Plasma concentration of dopamine was measured in period 3.

Activities of [^{131}I]-hippuran and [^{99m}Tc]-DTPA in plasma and urine were determined in a well-counter. Plasma and urinary lithium were measured by atomic absorption spectrophotometry (Model 403; Perkin-Elmer, Norwalk, CT, USA). Plasma sodium was measured with a Technicon RA 1000 instrument, and urinary sodium with a Technicon RA-XT instrument (Tarrytown, NY, USA). PRC was measured by a double antibody radioimmunoassay according to the principles described by Giese *et al.* [11]. Intra- and interassay coefficients of variation were 4% and 11%, respectively. PAC was measured as described by Lund *et al.* [12]. Intra- and interassay coefficients of variation were 4% and 23%, respectively. Plasma dopamine was determined by a radioenzymatic method with high performance liquid chromatography separation. Intra- and interassay coefficients of variation were 13% and 13%, respectively.

Cardiac output was calculated as stroke volume × heart rate. Mean arterial blood pressure (MABP) was calculated as the diastolic pressure plus one-third of the pulse pressure. Total vascular resistance in periods 1, 3 and 4 was estimated as MABP/cardiac output. Renal vascular resistance was determined as MABP divided by the renal blood flow calculated as ERPF/(1-packed cell volume fraction). ERPF, GFR, CL_{Li} and CL_{Na} were calculated by standard formulae. All clearance values were corrected to 1.73 m^2 body surface area. Fractional excretion rates of lithium (FE_{Li}) and sodium (FE_{Na}) were caluclated as CL_{Li}/GFR and CL_{Na}/GFR, respectively. Absolute and fractional proximal tubular reabsorption rates were calculated as GFR-CL_{Li} and 1-CL_{Li}/GFR, respectively.

If analysis of variance for repeated measures showed unequal variances ($P < 0.05$), paired *t*-tests were used to analyze differences between period 1 (baseline) and periods 2, 3 and 4, respectively, and differences between corresponding periods on the two study days. Values are presented as means (95% confidence intervals).

Results

Systemic effects (Table 1)

Plasma dopamine concentrations during the second hour infusion period (period 3) were 108 (76–141) nmol l^{-1} and 106 (69–143) nmol l^{-1} with placebo and metoprolol, respectively. Heart rate in period 1 was significantly decreased by metoprolol. With placebo, dopamine increased heart rate, and values during infusion remained significantly higher compared with the study day with metoprolol, on which heart rate only transiently increased in period 3. Baseline values of stroke volume and cardiac output were not significantly changed by metoprolol, and dopamine infusion increased values to the same extent with and without metoprolol. Metoprolol decreased systolic blood pressure, and the dopamine-induced increase seen with placebo was abolished. Mean diastolic blood pressure did not differ between study days, but a significant decrease compared with baseline was observed during dopamine infusion with placebo. Metoprolol decreased baseline MABP, and values remained unchanged during dopamine infusion. With placebo, dopamine decreased MABP compared with baseline. Metoprolol did not change total vascular resistance and renal vascular resistance, and dopamine-induced decreases were similar on both study days.

Baseline values of PRC were 23 (6–40) miu l^{-1} after placebo and 22 (8–35) miu l^{-1} after metoprolol (NS), respectively, and values were not significantly changed by dopamine infusion [placebo: 31 (19–43) miu l^{-1}; metoprolol: 32 (18–45) miu l^{-1} (NS *vs* placebo)]. PAC were 207 (166–249) pmol l^{-1} and 275 (55–495) pmol l^{-1} after placebo in periods 1 and 3 (NS), respectively, and corresponding values after metoprolol were 236 (165–307) pmol l^{-1} and 352 (158–545) pmol l^{-1} (NS compared with baseline and with placebo).

Table 1 Haemodynamic effects of dopamine after pretreatment with metoprolol or placebo. Means (95% CI), $n = 8$. Period 1: baseline, periods 2 and 3: dopamine infusion (3 μg kg^{-1} min^{-1}), period 4: recovery. *, $P < 0.05$, **, $P < 0.01$, ***, $P < 0.001$ compared with baseline. $^{+}$, $P < 0.05$, $^{++}$, $P < 0.01$, $^{+++}$, $P < 0.001$ compared with placebo

	Period			
	1	*2*	*3*	*4*
Heart rate (beats min^{-1})				
Placebo	59(54–64)	65(58–71)*	65(58–72)*	60(55–66)
Metoprolol	52(46–57)$^{++}$	53(48–58)$^{+++}$	55(49–61)*$^{++}$	53(49–58)$^{++}$
Stroke volume (ml min^{-1})				
Placebo	94(59–129)	–	107(62–151)*	92(63–120)
Metoprolol	92(69–115)	–	106(79–132)**	95(71–119)
Cardiac output (l min^{-1})				
Placebo	5.2(3.4–7.0)	–	6.5(3.9–9.2)*	5.3(3.6–6.9)
Metoprolol	4.4(3.3–5.5)	–	5.8(4.0–7.5)**	4.8(3.5–6.0)
Systolic blood pressure (mm Hg)				
Placebo	109(103–115)	118(111–125)*	114(106–121)	106(100–113)
Metoprolol	100(93–106)$^{++}$	101(95–108)$^{+++}$	102(96–109)$^{++}$	101(94–107)$^{+}$
Diastolic blood pressure (mm Hg)				
Placebo	68(64–72)	63(58–68)**	58(52–64)***	64(61–67)*
Metoprolol	62(57–67)	60(55–64)	59(55–63)	63(59–68)
Mean arterial blood pressure (mm Hg)				
Placebo	81(77–85)	81(76–86)	77(71–82)**	78(74–82)
Metoprolol	75(70–79)$^{++}$	74(70–78)$^{+++}$	74(70–77)	76(72–80)
Total vascular resistance (mm Hg min l^{-1})				
Placebo	19(11–28)	–	16(7–25)***	18(10–26)
Metoprolol	19(13–24)	–	14(10–19)***	18(12–23)
Renal vascular resistance (mm Hg min l^{-1})				
Placebo	84(77–92)	71(61–81)*	60(51–69)***	74(64–84)*
Metoprolol	88(77–99)	67(57–76)*	62(51–72)**	84(74–94)

Renal haemodynamics (Table 2)

Baseline ERPF was not significantly changed by metoprolol. The percentage increase in ERPF during dopamine infusions (placebo: 40%, metoprolol: 42%) were similar and there were no significant differences between infusion periods. However, ERPF in the recovery period (period 4) was significantly decreased with metoprolol compared with placebo. Neither dopamine nor metoprolol significantly changed GFR.

CL_{Li} and proximal tubular function (Table 3)

Metoprolol decreased CL_{Li} in period 1, but baseline FE_{Li} was not significantly changed. Dopamine increased CL_{Li} by 31% with placebo and by 36% with metoprolol, respectively, and values during infusion remained significantly lower with metoprolol compared with placebo. A similar pattern was observed for FE_{Li}. Calculated absolute proximal reabsorption rate did not differ between study days and remained unchanged during dopamine infusion. With and without metoprolol, dopamine decreased fractional proximal reabsorption, but values during infusion were significantly higher on the study day with metoprolol.

Excretion of sodium and water (Table 4)

Metoprolol decreased baseline values of CL_{Na} and urine flow rate, but FE_{Na} remained unchanged. Values increased during dopamine infusion by 114%, 46% and 103%, respectively, with placebo, and by 114%, 36% and 101%, respectively, with metoprolol. However, the absolute values remained significantly depressed with metoprolol in period 2.

Table 2 Effects of dopamine on effective renal plasma flow (ERPF) and glomerular filtration rate (GFR) after pretreatment with metoprolol or placebo. Means (95% CI), $n = 8$. Period 1: baseline, periods 2 and 3: dopamine infusion (3 μg kg^{-1} min^{-1}), period 4: recovery. *, $P < 0.05$, **, $P < 0.001$ compared with baseline. $^{+}$, $P < 0.01$ compared with placebo

	Period			
	1	*2*	*3*	*4*
ERPF (ml min^{-1})				
Placebo	545(476–614)	715(657–773)**	762(679–884)**	642(565–719)*
Metoprolol	497(434–559)	660(565–754)*	709(633–784)**	551(511–592)$^{+}$
GFR (ml min^{-1})				
Placebo	114(102–126)	117(111–124)	116(105–126)	110(103–116)
Metoprolol	105(94–115)	111(100–121)	110(103–118)	101(96–107)

Table 3 Effects of dopamine on lithium clearance (CL_{Li}), fractional lithium excretion (FE_{Li}), absolute proximal reabsorption rate (APR) and fractional proximal reabsorption (FPR) after pretreatment with metoprolol or placebo. Means (95% CI), $n = 8$. Period 1: baseline, periods 2 and 3: dopamine infusion (3 μg kg^{-1} min^{-1}), period 4: recovery. *, $P < 0.05$, **, $P < 0.01$ compared with baseline. $^{+}$, $P < 0.05$, $^{++}$, $P < 0.01$ compared with placebo

	Period			
	1	*2*	*3*	*4*
CL_{Li} (ml min^{-1})				
Placebo	30(26–34)	38(33–43)**	40(34–45)**	32(27–38)
Metoprolol	24(22–26)$^{++}$	30(25–35)*$^{+}$	33(29–38)**$^{+}$	27(24–31)**
FE_{Li} (%)				
Placebo	27(24–30)	32(28–37)**	34(29–39)**	29(25–33)
Metoprolol	24(21–27)	27(23–31)*$^{+}$	30(26–35)**$^{+}$	27(24–31)
APR (ml min^{-1})				
Placebo	84(74–94)	79(72–86)	76(67–85)	77(71–83)
Metoprolol	80(70–90)	81(72–90)	77(68–86)	74(66–82)
FPR (%)				
Placebo	73(70–76)	68(64–72)**	66(61–71)**	70(66–74)
Metoprolol	76(73–79)	73(69–77)*$^{+}$	70(65–75)**$^{+}$	73(69–77)*

Discussion

The present study investigated cardiovascular and renal effects of low-dose dopamine after acute pretreatment with the cardioselective β_1-adrenoceptor blocking agent metoprolol or placebo. The decrease in heart rate, seen in all subjects after metoprolol, indicates a significant effect on cardiac β_1-receptors by the present dose (100 mg). However, metoprolol (and other cardioselective β-adrenoceptor blockers) to some extent also inhibits β_2-receptors [13, 14], and concomitant effects on those receptors in peripheral tissues may therefore have influenced the present results. Stroke volume (and cardiac output) was determined non-invasively by simultaneous measurements of the velocity of the blood in aorta and its diameter by pulsed ultrasound doppler and M-mode echocardiography, respectively. Although a number of potential errors may contribute to inaccuracy, this combined technique has been found to agree reasonably with the thermodilution method [15]. Previous studies of the reproducibility under similar conditions indicated that changes in blood flow velocity greater than 10–12% may be detected [16].

The use of lithium clearance as an index of proximal tubular outflow to the thin descending limp of Henle relies on the assumptions that lithium is reabsorbed in parallel with sodium and water in the proximal tubules, but not reabsorbed or secreted in the distal tubules [9]. Based on direct measurements by *in vivo* micropuncture techniques in rats [10, 17] and indirect evidence obtained by diuretic drug effect studies in man [9, 18, 19], it is now generally agreed that the lithium clearance method provides a reasonable, 'whole kidney' measure of end-proximal volume delivery in man under normal physiological conditions [20]. Recently, the lithium test doses used in clearance studies similar to the present one were shown to increase baseline sodium excretion on the study day, but the subsequent response to dopamine remained unchanged [21]. In the present study, the lithium test doses may therefore have interfered with baseline CL_{Na}, but experimental conditions were similar on the two study days.

As previously found in patients with essential hypertension, metoprolol in the present study decreased sodium excretion [22]. The concomitant decrease in lithium clearance suggests that the antinatriuretic effect of metoprolol was a consequence of a decreased outflow from the proximal tubules. As suggested by the unchanged proximal tubular reabsorption rate, this effect of metoprolol was not likely to reflect specific tubular actions. Previous studies on renal haemodynamics after administration of β-adrenoceptor blocking agents have demonstrated that the decreases mostly are small in the range of 10–20% [13, 14, 22], and neither did the present changes in ERPF and GFR reach statistical significance. However, calculation of the statistical power reveals that the probabilities of erroneously rejecting true differences equal to or above 15% between placebo and metoprolol were 16% and 11% for ERPF and GFR, respectively. Thus, the non-significant results may represent type II errors. Taken together, the results most probably reflects an antinatriuretic effect secondary to the decreased arterial pressure, but also small decreases in ERPF, not detectable in the present study, may have contributed. The acute renal effects of β-adrenoceptor blocking agents are apparently not maintained, since long-term therapy does not normally cause sodium and water retention [23]. This may reflect the achievement of a new steady state secondary to intrarenal compensatory mechanisms, and, in addition, inhibition of aldosterone subsequent to the suppression of renin release following prolonged treatment has been proposed to play a role [23].

Consistent with the view that chronotropic and inotropic effects of dopamine are mediated by stimulation of cardiac β_1-receptors [1, 4, 6–8, 24], the dopamine-induced increase in heart rate and systolic blood pressure was significantly attenuated by meto-

Table 4 Effects of dopamine on sodium clearance (CL_{Na}), fractional sodium clearance (FE_{Na}) and urine flow rate after pretreatment with metoprolol or placebo. Means (95% CI), $n = 8$. Period 1: baseline, periods 2 and 3: dopamine infusion (3 μg kg^{-1} min^{-1}), period 4: recovery. *, $P < 0.05$, **, $P < 0.01$, ***, $P < 0.001$ compared with baseline. $^{+}$, $P < 0.05$, $^{++}$, P 0.01 compared with placebo

	Period			
	1	*2*	*3*	*4*
CL_{Na} (ml min-1)				
Placebo	1.20(0.97–1.43)	2.57(1.63–3.50)**	2.57(1.48–3.66)**	1.27(0.83–1.70)
Metoprolol	0.80(0.58–1.01)$^{++}$	1.45(0.94–1.96)*$^{+}$	1.71(1.14–2.27)**	0.94(0.64–1.25)
FE_{Na} (%)				
Placebo	1.09(0.83–1.35)	2.16(1.36–2.96)**	2.22(1.35–3.10)**	1.07(0.72–1.42)
Metoprolol	0.78(0.57–0.99)	1.31(0.86–1.76)*$^{+}$	1.57(1.00–2.14)**	0.96(0.65–1.27)
Urine flow rate (ml min^{-1})				
Placebo	13.4(11.9–14.8)	19.0(16.2–21.9)***	18.7(14.6–22.8)*	10.9(7.9–14.0)
Metoprolol	10.7(9.7–11.7)$^{+}$	13.9(12.1–15.7)*$^{++}$	14.7(10.1–19.1)	12.2(10.8–13.6)

prolol. However, the effects on overall cardiac performance as reflected by stroke volume, cardiac output and total peripheral resistance remained unaffected. Our results in humans confirm those of Van Woerkens *et al.* [8], where adrenergic blockade in pigs abolished the effects of dopamine on heart rate and contractility but not on vascular resistance of various organs. In patients with idiopathic dilated cardiomyopathy [7], dopamine (2 and 4 $\mu g\ kg^{-1}\ min^{-1}$) elicited a dose-dependent increase in left ventricular contractility, which together with a reduced afterload was concluded to contribute to the increase in cardiac index. In our normal subjects, the dopamine-induced increase in cardiac output seemed to occur mainly as a response to a reduced peripheral resistance, independent of effects of β_1-receptors on cardiac contractility and heart rate.

In the present and other studies, dopamine increased ERPF and decreased renal vascular resistance. This effect can be largely explained by a direct vasodilatating action on renal arterioles secondary to stimulation of vascular DA_1 receptors [2, 25]. Indirect effects secondary to a primarily dopamine-induced increase in cardiac output has also been proposed to play a role [3]. However, in the present study, pretreatment with metoprolol did not alter the percentage increase in ERPF. It therefore seems unlikely that inotropic effects of dopamine mediated via β_1-receptor stimulation indirectly contributes to the increase in ERPF. In agreement with this, a comparison of dopamine and the β_1-adrenoceptor agonist dobutamine in equipotent doses producing similar increases in cardiac output demonstrated that only dopamine increased ERPF [26]. The present results suggest that the increase in cardiac output was secondary to the vasodilating effects of dopamine, which has been demonstrated not only in renal vessels, but also in the circulation of the brain, adrenals and splanchnic organs [2, 8].

Dopamine is well known to have a natriuretic effect, and the present increases in CL_{Li} and CL_{Na} on the study day with placebo were of similar magnitude as previously found [19, 26–29]. The increase in proximal tubular outflow (CL_{Li}), which has also been found by micropuncture studies in rats given the dopaminergic DA_1 agonist fenoldopam [30], may be either secondary to the renal vasodilatation or to specific tubular effects on sodium reabsorption or both [2, 26, 27, 30]. The percentage dopamine-induced increase in sodium and water excretion was not affected by metoprolol, and also the trends in the renal handling of lithium remained the same. However, the absolute, maximal values were significantly depressed. Although a direct effect of acute β-adrenoceptor blockade on tubular reabsorption cannot be excluded, the results most probably reflect an indirect, haemodynamic effect of metoprolol secondary to the decrease in arterial pressure.

In conclusion, the increase in heart rate and systolic pressure seen with dopamine in the present dose can be attributed to activation of adrenergic β_1-receptors. However, cardiac output seemed to increase mainly as a response to a reduced peripheral resistance. The maintained percentage dopamine-induced increase in ERPF, CL_{Li}, and CL_{Na} is consistent with effects predominantly mediated via renal dopaminergic receptors, and argues against a contribution of indirect haemodynamic effects on the renal response to dopamine following increased cardiac contractility. However, metoprolol decreased absolute values of CL_{Li} and CL_{Na} suggesting that a reduced adrenergic β_1-receptor activity may indirectly influence the natriuretic response to dopamine, probably by decreasing renal perfusion pressure.

This work was supported by grants from Astra, Denmark, and MEDA, Denmark. Metoprolol and placebo tablets were kindly donated and prepared for double-blind administration by Astra, Denmark.

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(Received 24 August 1993, accepted 21 December 1993)