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Diuretic Action of the Novel Loop Diuretic Torasemide in the Presence of Angiotensin II or Endothelin-1 in Anaesthetized Dogs

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Abstract—The effects of torasemide (0·1 and 1 mg kg^{-1}, i.v.) and furosemide (3 mg kg^{-1}) on renal haemodynamics and excretory responses in the presence of angiotensin II and endothelin-1 was examined in anaesthetized dogs. Angiotensin II or endothelin-1 was continuously infused into the renal artery throughout the experiment and a bolus of torasemide or furosemide was injected into the bracheal vein. Continuous intrarenal arterial (i.r.a.) infusion of angiotensin II, at a dose of 5 ng kg^{-1} min^{-1}, increased renal vascular resistance (RVR) and decreased renal blood flow (RBF) and glomerular filtration rate (GFR), but had no effect on systemic mean arterial pressure (MAP). Urinary excretion of sodium ($U_{Na}V$) and urine flow (UF) were significantly decreased during angiotensin II infusion. Intravenous injections of torasemide in the presence of angiotensin II caused a dose-dependent increase in UF, $U_{Na}V$ and urinary excretion of potassium (U_KV), while a decrease in RVR was accompanied by an increase in RBF. U_KV was greater in the furosemide group than in the torasemide group, despite both groups having the same degree of aquaresis and natriuresis. Continuous i.r.a. infusion of endothelin-1, 1·5 ng kg^{-1} min^{-1}, produced effects similar to those of angiotensin II on renal haemodynamics; however, the onset of action was extremely slow compared with the effects produced by angiotensin II. Endothelin-1 caused a significant decrease in UF, $U_{Na}V$ and U_KV only at a later period, despite a relatively early depression of renal haemodynamics. Torasemide and furosemide also produced a sufficient diuretic action in this model. Overall, kaliuresis was greater in the furosemide group than in the torasemide group. The present study demonstrates that torasemide exhibited a significant diuretic action in the angiotensin II- or endothelin-1-induced renal impairment model, with less kaliuresis than furosemide at a concentration which caused the same degree of natriuresis.

Angiotensin II has been shown to be involved in the acute stage of renal impairment (Birbari & Hadar 1976; Haley & Johnson 1978). Angiotensin converting enzyme inhibitors protect renal function by reducing angiotensin II formation even during the later stages of this renal disorder (Meyer et al 1985), suggesting that angiotensin II may be a significant factor in the progression of renal disease.

Endothelin-1 is a recently discovered peptide which is the most potent vasoconstrictor yet described. On a molecular basis it is 10 times more potent than angiotensin II (Yanagisawa et al 1990). In experimental acute renal failure, induced by occlusion of the renal arteries followed by their reperfusion, plasma endothelin-1 levels were elevated, suggesting a possible involvement of endothelin-1 in the pathogenesis of renal failure (Shibouta et al 1990). Furthermore, there is increasing evidence (Nakamoto et al 1989; Tsuchiya et al 1989, 1990a, b; Miura et al 1990) that endothelin-1 elicits renal vasoconstriction following intrarenal arterial or systemic injection, and that this potent renal vasoconstriction may play an important role in glomerular injury. In patients with chronic renal failure (Warrens et al 1990), significant elevation of plasma endothelin-1 has been observed. These findings strongly suggest that angiotensin II and endothelin-1 are involved in the pathogenesis of renal failure.

Torasemide (1-isopropyl-3-{[4-(3-methyl-phenylamino) pyridine]-3-sulphonyl}urea) is a novel diuretic which is not structurally related to conventional diuretics. The main site of diuretic action of this drug has been determined to be the thick ascending limb of the loop of Henle (Wittner et al 1987). Torasemide has less kaliuretic, but more potent and longer-lasting diuretic properties than furosemide (Ghys et al 1985; Broekhuysen et al 1986).

This study was designed to examine the diuretic action of torasemide in an acute renal impairment model induced by continuous infusion of angiotensin II or endothelin-1 into the renal artery in anaesthetized dogs, and to compare its action with that of furosemide.

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Materials and Methods

Experimental procedures

For at least 1 week before the study adult mongrel dogs of both sexes, 10 to 14 kg, were maintained on standard laboratory chow with free access to tap water. The animals were anaesthetized with pentobarbitone sodium (25 mg kg^{-1}, i.v.) and supplemental doses of the anaesthetic were administered, as required, to maintain a stable anaesthesia. Animals were ventilated artificially with room air using a Harvard respirator through a tracheal tube inserted into the trachea. Polyethylene catheters were placed in the right brachial vein and artery for infusion of physiological saline, injection of drugs, and for blood sampling. A polyethylene catheter was inserted into the abdominal aorta via the right femoral artery, to about the level of the renal arteries, for continuous measurement of mean arterial pressure (MAP) with a pressure transducer (Statham P-50, Gould). The left kidney was exposed through a retroperitoneal flank incision and the renal artery was dissected free from the surrounding tissue. An electromagnetic flow probe (Nihon Kohden) was

attached to the renal artery to measure renal blood flow (RBF), using a square-wave flow meter (Nihon Kohden, MFV-2100). A polyethylene catheter was inserted into the left ureter for urine collection. A curved 23-gauge needle was inserted into the left renal artery for continuous infusion of angiotensin II or endothelin-1. After completion of the surgery, a priming dose of inulin (20 mg kg^{-1}) was given, followed by a sustained infusion of 0·9% NaCl (saline) containing 1·0% inulin at a rate of 2·0 mL min^{-1}. MAP and RBF were recorded continuously on a polygraph (Nihon Kohden, RM-6000).

After an equilibration period (1·5–2 h), urine samples were collected during two 10-min control periods. Following the control periods, continuous infusion of angiotensin II or endothelin-1 into the renal artery (i.r.a) was started and maintained throughout the experiment. Five minutes after the start of the respective peptide infusions, urine was collected for two consecutive 10-min clearance periods. After urine sampling during the two 10-min periods, torasemide (0·1 or 1 mg kg^{-1}) or furosemide (3 mg kg^{-1}) was intravenously injected 25 min after the start of the angiotensin II or endothelin-1 infusion. Five minutes after the injection of diuretic, urine was collected for two consecutive 10-min clearance periods. A single dose of torasemide or furosemide was given to each animal.

Analytical procedure

Urine and plasma inulin levels were measured by spectrofluorometry (FRF-5000, Shimadzu) according to the method of Vurek & Pegram (1966). Glomerular filtration rate (GFR) was estimated from the inulin clearance. Sodium and potassium were determined using an electrolyte autoanalyser (NAKL-2, Olympus Optical Co.). All data, except for MAP, are expressed as units per gram of kidney weight.

Drugs

Torasemide was synthesized by Boehringer Mannheim GmbH, Germany. Furosemide was purchased from Nakalai Tesque, Inc. (Kyoto, Japan). Both drugs were dissolved in 0·1 M $NaHCO_3$ solution and pH adjusted with the same volume of 0·1 M HCl solution. Angiotensin II and endothelin-1 (purchased from the Peptide Institute, Inc., Osaka, Japan) were dissolved in saline and were continuously injected into the left renal artery at rates of 5·0 and 1·5 ng kg^{-1} min^{-1}, respectively. Acute intravenous injections of torasemide (0·1 and 1 mg kg^{-1}) and furosemide (3 mg kg^{-1}) were performed at a volume of 1·0 mL kg^{-1}.

Statistical analysis

Data from the two control periods were combined and the mean values were calculated. Statistical analysis was performed using the Kruskal-Wallis non-parametric analysis of variance followed by a Williams-type multiple comparison test. In all comparisons, the difference was considered to be significant for $P<0·05$.

Results

Intrarenal arterial infusion of angiotensin II (5·0 ng kg^{-1} min^{-1}, i.r.a.) caused a significant decrease in RBF (about 40%) and GFR (about 30%) and elevation in renal vascular resistance (RVR) without having an effect on MAP (Fig. 1). Urine flow (UF) and urinary sodium ($U_{Na}V$) and potassium (U_KV) excretion were also significantly decreased (Fig. 2).

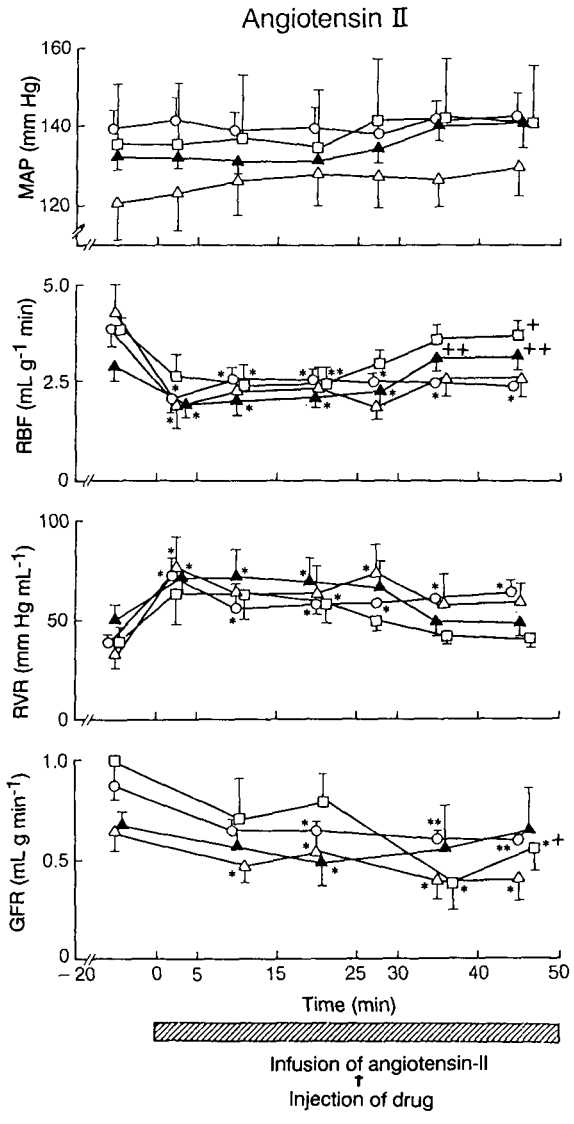

FIG. 1. Effects of intravenous administration of vehicle (1 mL kg^{-1}, ○, n = 4), torasemide (0·1 mg kg^{-1}, △, n = 4; 1 mg kg^{-1} ▲, n = 4) and furosemide (3 mg kg^{-1}, □, n = 5) on renal haemodynamics in anaesthetized dogs in the presence of angiotensin II. Drugs were intravenously injected 25 min after the start of continuous infusion of angiotensin II. Mean arterial pressure (MAP), renal blood flow (RBF), renal vascular resistance (RVR) and glomerular filtration rate (GFR) are plotted as a function of experimental time. Points and bars represent mean ± s.e. *, ** represents a significant difference from the value of the pretreatment period at $P<0·05$, 0·01, respectively. $^{+}$, $^{++}$ represents a significant difference from the value at 25 min after the start of continuous infusion of angiotensin II at $P<0·05$, 0·01, respectively.

The effects of angiotensin II on RBF and GFR were eliminated in the diuretic drug groups. In particular, both diuretics significantly increased RBF which had been decreased by continuous intrarenal arterial infusion of angiotensin II.

Torasemide, at doses of 0·1 and 1 mg kg^{-1}, elicited a marked and dose-dependent increase in UF, $U_{Na}V$ and U_KV.

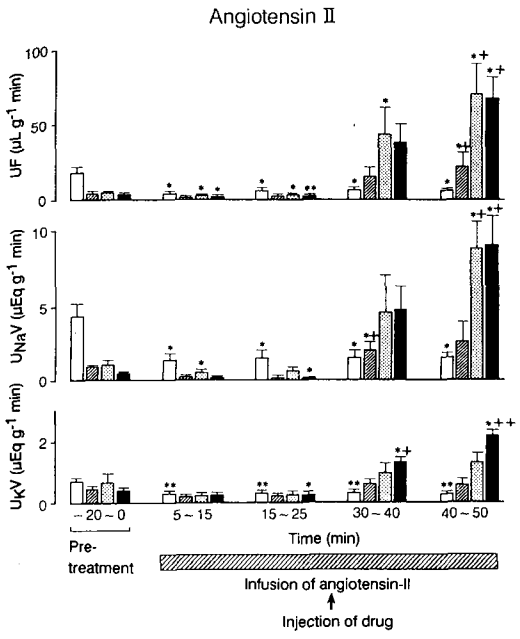

FIG. 2. Renal excretory response of vehicle (1 mL kg^{-1}, □, n = 4), torasemide (0·1 mg kg^{-1}, ▨, n = 4; 1 mg kg^{-1}, ▩, n = 4) and furosemide (3 mg kg^{-1}, ■, n = 5) in anaesthetized dogs in the presence of angiotensin II. Drugs were intravenously injected 25 min after the start of continuous infusion of angiotensin II. Urine formation (UF), urinary sodium volume ($U_{Na}V$) and urinary potassium volume (U_KV) are plotted as a function of experimental time. Points and bars represent mean ± s.e. *, ** represents a significant difference from the value of the pretreatment period at $P < 0.05$, 0·01, respectively. +, ++ represents a significant difference from the value 25 min after the start of continuous infusion of angiotensin II at $P < 0.05$, 0·01, respectively.

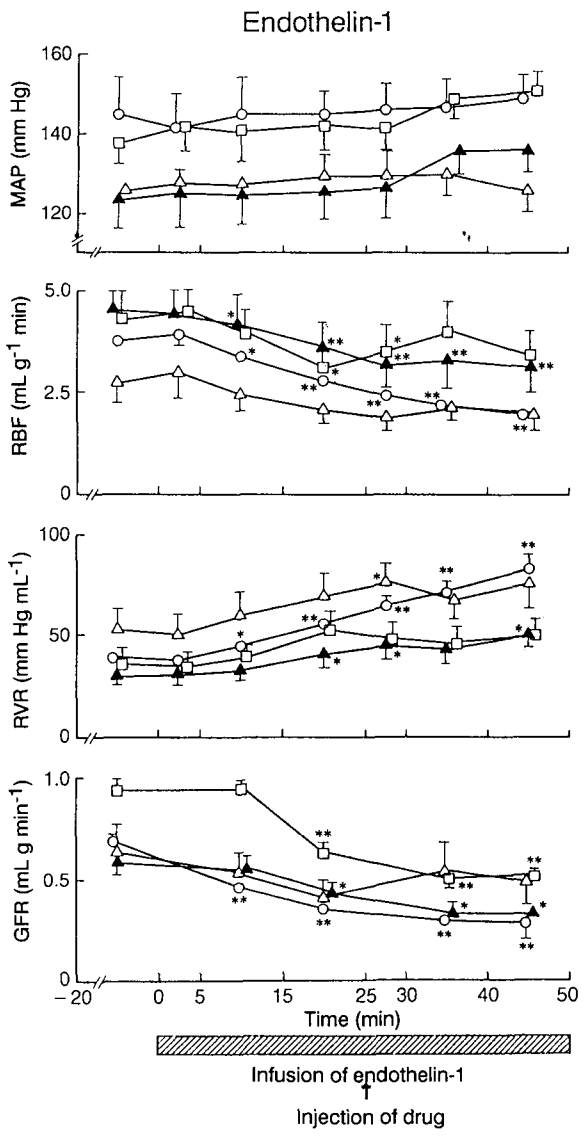

FIG. 3. Effects of intravenous administration of vehicle (1 mL kg^{-1}, ○, n = 4), torasemide (0·1 mg kg^{-1}, △, n = 4; 1 mg kg^{-1}, ▲, n = 4) and furosemide (3 mg kg^{-1}, □, n = 5) on renal haemodynamics in anaesthetized dogs in the presence of endothelin-1. See Fig. 1 for details.

Furosemide (3 mg kg^{-1}) significantly increased UF and $U_{Na}V$ in a similar manner to torasemide (1 mg kg^{-1}), while the U_KV was greater in the furosemide group than in the torasemide group.

Continuous infusion of endothelin-1 (1·5 ng kg^{-1} min^{-1}) caused a significant decrease in RBF (about 45%) and GFR (about 40%) and an increase in RVR (about 90%, Fig. 3) without having an effect on MAP (like angiotensin II), while no significant effect was observed in UF, $U_{Na}V$ and U_KV (Fig. 4) in the 25 min following the start of continuous infusion of endothelin-1 (unlike angiotensin II). The changes induced by endothelin-1 infusion were manifested slowly and progressively, in comparison with that of angiotensin II.

In the endothelin-1 model, i.v. torasemide injection, 0·1 and 1 mg kg^{-1}, elicited a dose-dependent increase in UF, $U_{Na}V$ and U_KV with little effect on RBF, RVR and GFR. Furosemide also caused a significant increase in UF, $U_{Na}V$ and U_KV at a dose of 3 mg kg^{-1}. The excretory response in $U_{Na}V$ and U_KV was greater in the furosemide group than in the torasemide group, and the difference in U_KV was notable.

Overall, both drugs exhibited a stronger diuretic action in the presence of endothelin-1 than in the presence of angiotensin II.

Discussion

This study was designed to examine the diuretic action of the novel loop diuretic torasemide in a canine model of acute renal failure induced by intrarenal arterial infusion of angiotensin II or endothelin-1.

The results demonstrate that intrarenal infusion of angiotensin II or endothelin-1 elicits an antidiuretic action by renal vascular contraction (increase in RVR). Specifically, the decrease in GFR resulted mainly from the decrease in RBF. There is much evidence that angiotensin II exerts an antidiuretic action by decreasing RBF in man (Hollenberg et al 1972) and in experimental animals (Cannon et al 1966; Porush et al 1967). In addition to these actions of angiotensin II on renal haemodynamics, a direct action on tubular function has been reported, namely a stimulatory action of the reabsorption of sodium and water in the proximal tubules (Harris & Young 1977; Schuster et al 1984) or in the ascending limb of the loop of Henle (Healy & Elliot 1970).

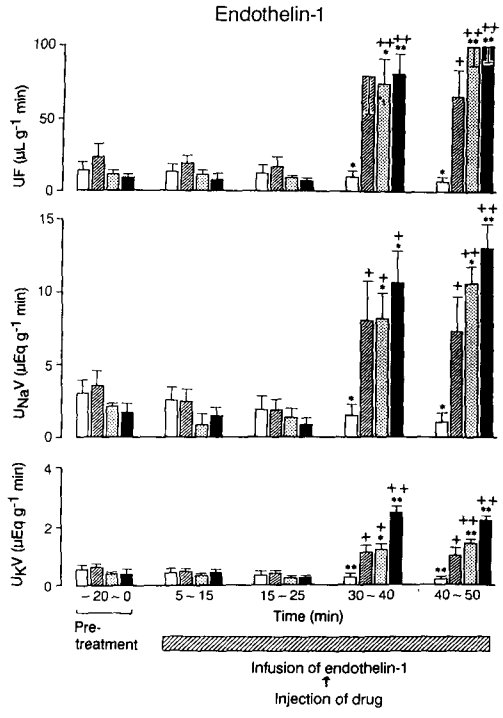

FIG. 4. Renal excretory response of vehicle (1 mL kg^{-1}, □, n=4), torasemide (0·1 mg kg^{-1}, ▨, n=4; 1 mg kg^{-1}, ▩, n=4) and furosemide (3 mg kg^{-1}, ■, n=5) in anaesthetized dogs in the presence of endothelin-1. See Fig. 2 for details.

Thus, it is considered that angiotensin II is partly involved in the renal insufficiency.

There is increasing evidence suggesting that a depressive effect on renal haemodynamics is involved in the antidiuretic action of endothelin-1 (Miller et al 1989; Hoffman et al 1990), however, its action on the renal tubular function is unclear (Ferrario et al 1989; Miura et al 1990).

In contrast, elevation of the plasma endothelin-1 content is observed in patients with chronic renal failure (Warrens et al 1990), and cyclosporin, which is known to cause renal impairment, elicits endothelin-1 production in $LLCPK_1$ cultured renal tubular cells (Nakahama 1990). Furthermore, the presence of the endothelin-1 receptor (Jones et al 1989; Kohzuki et al 1989; Martin et al 1989; Neuser et al 1990) and the synthesis of endothelin-1 (Kitamura et al 1989; Kosaka et al 1989) have been confirmed in both cultured renal cells and the intact kidney. These findings strongly suggest the involvement of endothelin-1 in renal insufficiency.

In this study, i.r.a. infusion of endothelin-1 caused a significant decrease in UF, $U_{Na}V$ and U_KV only at a later period, despite a significant decrease in RBF and GFR at a relatively early period, suggesting that the tubular effect of this peptide is considerably weaker than that of angiotensin II. The renal haemodynamic action of endothelin-1 is manifested slowly and continued to grow stronger for a longer time than those actions of angiotensin II.

The significant decrease in RBF during i.r.a. infusion of angiotensin II or endothelin-1 was eliminated by torasemide or furosemide i.v. injection, and urine formation was significantly increased. In general, loop diuretics are known to cause an increase in RBF mediated by an increase in the synthesis of renal prostaglandins (Nies et al 1983). The increase in RBF seems to be a part of the diuretic action of loop diuretics, but the primary diuretic mechanism is inhibition of the reabsorption of sodium in the ascending limb of the loop of Henle. Loop diuretics exhibit a strong diuretic action even in the presence of indomethacin pretreatment, which impairs the increase in RBF (Pedrinelli et al 1980; Nies et al 1983). There is evidence (Herchueltz et al 1989) that the diuretic action of torasemide is decreased by pretreatment with indomethacin at a similar level to furosemide. This strongly suggests that torasemide also elicits an increase in renal blood flow via the stimulation of prostanoid formation in the kidney, in a similar fashion to furosemide. The diuretic action of torasemide is due to inhibition of water and electrolyte reabsorption in the distal tubule including the ascending limb of the loop of Henle, as demonstrated by microperfusion and micropuncture techniques (Hermes & Heidenreich 1985). We also confirmed the diuretic profile of torasemide as a loop diuretic using renal clearance and stop-flow methods in anaesthetized dogs (Uchida et al 1991). In this study, torasemide and furosemide caused a significant diuretic action even in the presence of angiotensin II or endothelin-1 by the inhibition of water and electrolyte reabsorption at the ascending limb of the loop of Henle.

Both diuretics tend to exhibit stronger diuresis in the presence of endothelin-1 than in the presence of angiotensin II. This phenomena might be related to the peptides' different actions on the tubules.

Torasemide produces less loss of potassium than other loop diuretics (Ghys et al 1985; Lillian & Puschett 1988). In this study, the kaliuresis of torasemide was lower than that of furosemide, despite similar aquaresis and natriuresis, especially in the angiotensin II-induced renal insufficiency model.

In summary, torasemide and furosemide exhibited significant diuresis actions in these renal impairment models induced by the intrarenal arterial infusion of angiotensin II or endothelin-1. The diuretic action of torasemide was more potent than that of furosemide, and kaliuresis of torasemide was lower than that of furosemide.

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