Antihypertensive Effect of CS-905, a Novel Dihydropyridine Calcium Blocker, in Conscious Hypertensive Dogs

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Abstract—CS-905, (±)-3-(1-diphenylmethylazetidin-3-yl)5-isopropyl 2-amino-1,4-dihydro-6-methyl-4-(m-nitrophenyl)-3,5-pyridine-dicarboxylate, is a novel dihydropyridine calcium blocker. Both CS-905 and nicardipine, when administered orally, produced a dose-dependent fall of blood pressure in conscious perinephritic hypertensive dogs. Unlike the hypotensive effect of nicardipine, that of CS-905 has a gradual onset and is long-lasting, with little increase in the heart rate and plasma renin activity (PRA). The lack of both tachycardia and increase of PRA is probably mostly due to the slow onset of antihypertensive action following CS-905.

Dihydropyridine Ca antagonists represented by nifedipine and nicardipine have been demonstrative to be effective antihypertensive drugs (1, 2). We have already reported that CS-905, unlike nicardipine, has a gradual and long-lasting antihypertensive action with little tachycardia in SHR (3). The present study was designed to assess the antihypertensive effect of CS-905 and nicardipine in conscious hypertensive dogs. We also investigated the effect on the renin angiotensin system after a single oral administration of CS-905 or nicardipine by measuring plasma renin activity (PRA).

Hypertension was induced by the method of Page (4). Male beagle dogs weighing 9–11 kg were anesthetized with sodium pentobarbital, 30 mg/kg, i.v. After the left kidney was exposed by retroperitoneal approach, the connective tissue was removed, and the kidney was wrapped in a sheet of cellophane. The right kidney was wrapped in an identical manner a month after the first operation. A month after the second surgery, the mean blood pressure of the dogs reached about 150 mmHg, and the animal was prepared with an aortic cannula inserted via the left femoral artery for blood sampling and for measuring blood pressure and heart rate. The distal end of the cannula was routed subcutaneously to the flank and exteriorized. The animal was fitted with a jacket to protect the cannula. After the animal was permitted 2–3 days for surgical recovery and training, the aortic cannula was connected to a pressure transducer (Nihon Kohden, TP-200T), and the blood pressure and heart rate in the conscious state were continuously recorded on a pen-writing oscilloscope (Nihon Kohden, RJG-4128). After blood pressure and heart rate became stabilized, the drugs suspended in 0.3% CMC solution were administered by gavage at a dose of 1 or 3 mg/kg. Blood pressure and heart rate were monitored for up to 8 hr after the drug was administered. Blood samples in a volume of 1 ml were collected in cooled test tubes containing 1 mg/ml of EDTA 2 Na, at 0.5 hr before and at 0.5, 2, 4 and 7 hr after administration. After the blood was centrifuged (2000×g for 20 min at 4°C), plasma was collected for the PRA assay. PRA was determined with a kit purchased from Dinabot Labs. When the blood pressure did not return to the control levels at 8 hr, measurements of blood pressure, heart rate, and PRA were performed at 24 hr.

The two-kidney perinephritic hypertensive
dog used in this study is a model of chronic hypertension, but the pathogenesis of this hypertension is poorly understood. Campbell et al. has reported that this model is not dependent on increased activity of the renin angiotensin system during the maintenance of elevated blood pressure (5). In agreement with this report, PRA in the present study was within the normal range (below about 2 ng Al/ml/hr).

Both CS-905 and nicardipine, when administered orally, produced a dose-dependent fall of blood pressure in the conscious perinephritic hypertensive dog (Figs. 1 and 2). However, there was a great difference in the blood pressure lowering actions of these drugs: After nicardipine, blood pressure reached a nadir 15 min after administration and returned near the pre-administration level in 4 to 8 hr (Fig. 1), whereas CS-905 produced a gradual and long-lasting reduction of blood pressure (Fig. 2). These differences may be explained on the basis of the difference in association and dissociation rates of these compounds with calcium channels or the difference in the rate of absorption from the gastrointestinal tract (3).

Calcium entry blockers are expected to increase PRA because calcium ion inhibits renin secretion by a direct action on the juxtaglomerular cell in vitro (6). Many investigators have observed that dihydropyridine Ca blockers increase PRA by a single oral administration (7–9). In the present study, nicardipine also produced an increase of PRA (Fig. 1). However, it is difficult to determine whether the increase of PRA is caused by the direct action of a Ca blocker on the juxtaglomerular cells, because the renin release in the whole animal is primarily controlled by changes in blood pressure, ionic composition of the fluid and sympathetic activity. CS-905 at a dose of 1 mg/kg produced a sustained reduction of blood pressure from 2 to 6 hr, but did not affect PRA (Fig. 2). Long-term adminis-

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**Fig. 1.** Time courses of the changes in heart rate (HR), mean blood pressure (MBP) and plasma renin activity (PRA) after a single oral administration of nicardipine at 1 or 3 mg/kg in conscious renal hypertensive dogs. Asterisks indicate a statistically significant difference at \( P < 0.05 \) from the control values before administrations by the paired \( t \)-test. Values are means±S.E. from five dogs.

**Fig. 2.** Time courses of the changes in heart rate (HR), mean blood pressure (MBP) and plasma renin activity (PRA) after a single oral administration of CS-905 at 1 or 3 mg/kg in conscious renal hypertensive dogs. Asterisks indicate a statistically significant difference at \( P < 0.05 \) from the control values before administrations by the paired \( t \)-test. Values are means±S.E. from five dogs.
tration of Ca blockers does not produce alterations in any of the components of the renin angiotensin system in clinical settings (10). We have already reported that chronic administration of CS-905 lowered PRA in SHR (11), and a similar effect has been reported for nifedipine (12). These findings suggest that the increased renin release by acute administration of Ca blockers may be caused not only by direct action on the juxtaglomerular cell but also by other mechanisms such as reflex sympathetic excitation due to a decrease in blood pressure.

Another evidence supporting this notion is that PRA was increased only when heart rate was increased in the present study (Figs. 1 and 2). Heart rate, like PRA, was not always increased when blood pressure was lowered, as shown in the case of CS-905 at 1 mg/kg, p.o. (Fig. 1). Nifedipine at lower and higher doses increased both PRA and heart rate, whereas CS-905 raised PRA only when blood pressure was greatly lowered and heart rate was increased (Fig. 2).

A possible reason for the differential responses to nifedipine and CS-905 is as follows: 1) nifedipine produced a greater peak decrease of blood pressure than CS-905, 2) CS-905 lowered blood pressure at a much slower rate than nifedipine. The intensity of baroreceptor reflexes is determined not only by the degree of hypotension but also by the rate of blood pressure fall (13). Indeed, nifedipine at 1 mg/kg, p.o., produced a greater increase in heart rate and PRA than CS-905 at 3 mg/kg, p.o., although both agents lowered blood pressure to a similar degree at their peak effects (Figs. 1 and 2).

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