Comparison of Cardiorenal and Emetic Effects of Dopamine Prodrugs Docarpamine (TA-870) and Levodopa in Dogs

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(Received August 30, 1990)

Positive inotropic and renal vasodilatory effects of a novel dopamine prodrug, docarpamine, [N-(N-acetyl-L-methionyl)-3,4-bis(ethoxycarbonyl)dopamine; TA-870] and those of levodopa were compared in anesthetized dogs, and emetic effects of the two drugs were compared in conscious dogs.

Intraduodenal administrations of docarpamine and levodopa at 20 mg/kg produced similar increases in cardiac contractility. The maximal increases in the left ventricular \( dp/dt_{max} \) after docarpamine and levodopa were 36.6 ± 14.2 and 39.2 ± 12.1%, respectively. The two drugs also produced similar decreases in renal vascular resistance (21.2 ± 2.2 and 13.6 ± 3.4%, respectively) and increases in renal blood flow (27.9 ± 3.2 and 17.9 ± 5.2%, respectively), however, the duration of renal vasodilation after docarpamine was longer than that of levodopa.

Oral administration of the two drugs in conscious dogs produced vomiting. The ED_{50} value of the emetic effect for docarpamine was greater than 160 mg/kg, and that for levodopa was 11.0 mg/kg. The emesis was inhibited by pretreatment with a DA_{3} antagonist, domperidone.

In conclusion, docarpamine and levodopa produced similar cardiorenal effects, but the emetic effect of docarpamine was much weaker than that of levodopa. Docarpamine can be used as a selective dopamine prodrug for the peripheral circulation.

Keywords —- dopamine prodrug; docarpamine; N-(N-acetyl-L-methionyl)-3,4-bis(ethoxycarbonyl)dopamine (TA-870); levodopa; renal blood flow; cardiac contractility; vomiting; dog

Introduction

Docarpamine (TA-870) is a newly synthesized dopamine derivative developed as an oral dopamine prodrug. Docarpamine is absorbed well from the digestive tract and is hydrolyzed to dopamine mainly in the liver (Yoshikawa et al., unpublished observation) via a de-ethoxycarbonyl intermediate as shown in Fig. 1. The resulting dopamine in the blood increases myocardial contractility and renal blood flow by stimulating cardiac \( \beta_{1} \) receptors and renal DA_{1} receptors, respectively, in dogs and rats. Docarpamine elevates plasma free dopamine concentration after oral administration and improves cardiac function in patients with heart failure. It has also been reported that docarpamine elevates plasma free dopamine concentration after conversion by dopa-decarboxylase. On the other hand, levodopa is the biological precursor of dopamine, and oral ingestion of levodopa elevates plasma free dopamine concentration after conversion by dopa-decarboxylase. In this respect, levodopa can also be regarded as a dopamine prodrug. Furthermore, since levodo-

![Fig. 1. Metabolic Pathways from Docarpamine and Levodopa to Dopamine](image-url)

See references 4 and 5 for detailed explanations of the metabolic pathway of docarpamine.
Docarpamine and Levodopa

Docarpamine crosses the blood-brain barrier and is converted to dopamine in the brain; it has been used as an effective drug for akinesia and rigidity in Parkinson's disease. Applications of levodopa to cardiovascular disease have also been attempted.\(^7\)\(^-\)\(^9\) For example, Rajfer et al. have reported that oral administration of levodopa to patients with heart failure induced an increase in cardiac index and a decrease in systemic vascular resistance.\(^10\)\(^,\)\(^11\)

However, levodopa therapy has always been accompanied by nausea and vomiting. On the other hand, such adverse effects have not been reported when docarpamine is given to humans.\(^6\)\(^,\)\(^12\) This lack of adverse effects makes docarpamine very interesting, but we could not directly compare the therapeutic and adverse effects of docarpamine with those of levodopa, because of differences in the designs and conditions of previously reported studies. We therefore compared cardiovascular and emetic effects of docarpamine with those of levodopa in dogs.

Materials and Methods

Cardiorenal Effects — Six mongrel dogs of either sex weighing between 12.0 and 17.4 kg were used. Each dog was anesthetized with 30 mg/kg i.v. of pentobarbital-Na (PB). The trachea was intubated with a balloon-cuffed endotracheal tube and the dog was artificially ventilated (15 ml/Kg/stroke, 18—20 stroke/min) with room air delivered from an animal respirator (model 100, Takashima Co., Tokyo, Japan). A femoral vein was cannulated and PB was continuously infused into the vein at a rate of 4 mg/kg/h to maintain anesthesia. A catheter was placed in the abdominal aorta via the right femoral artery and arterial blood pressure was measured with a pressure transducer which was connected to the catheter. Mean blood pressure was measured with a resister-capacitance circuit (time constant 3 s). A sensor of microtip catheter transducer (Millar micro-tip catheter pressure transducer, Millar Instruments Inc., Houston, U.S.A.) was placed in the left ventricle via the left common carotid artery for measurement of left ventricular pressure. The first differential of the left ventricular pressure \((dP/dt)\) was obtained with an analogue differentiator (EQ-601G, Nihon Kohden, Tokyo, Japan), and the contractile state of the myocardium was assessed using the maximum value of the left ventricular \(dP/dt\) \((LVdP/dt_{\text{max}})\). Heart rate was measured with a cardiotachometer triggered by the ventricular pressure pulses. The left renal artery was exposed through a left flank incision, and the probe of an electromagnetic flowmeter (MVF-2100, Nihon Kohden) was attached around the artery for measurement of renal blood flow. All the measurements were recorded on a recticorder (WR-3101, Graphtec Corporation, Tokyo, Japan). Renal vascular resistance (RVR) was calculated by the following equation: RVR (mmHg·min/m) = mean arterial blood pressure (MAP, mmHg)/renal blood flow (RBF, mL/min).

Both docarpamine and levodopa, suspended in 5 ml water with a small amount of Tween 80, were administered to each dog at 20 mg/kg through a catheter placed in the duodenum. In three of the six dogs, docarpamine was administered first, then levodopa was administered after a recovery period of at least 3 h. This order was reversed in the other three dogs.

Emetic Effect — Six beagles of either sex were used. The dogs fasted overnight and were given a small amount of standard dog food 1 h before administration of the test compound. Docarpamine at 20, 40, 80 or 160 mg/kg or levodopa at 5, 10, 20 or 40 mg/kg was orally administered in a gelatin capsule with 50 ml of water. After the administration, the dog was placed in a cage and was observed for general symptoms and vomiting for 2 h. The various doses of docarpamine and levodopa were administered to each dog at intervals of 2 or 3 d in a randomized order.

Drugs — Docarpamine was synthesized at the Research Laboratory of Applied Biochemistry of Tanabe Seiyaku Co., Ltd. Levodopa and domperidone were purchased from Kyowa Hakko Co., Ltd.

Statistics — Data were expressed as the means ± S.E. Analysis of variance (randomized block method) followed by Dunnett’s test used for comparisons between a baseline value and plural experimental values. The Litchfield–Wilcoxon method was used to calculate the
Fig. 2. Cardiovascular Effects of Docarpamine and Levodopa in Anesthetized Dogs

Docarpamine and levodopa were intraduodenally administered to the same dogs at 20 mg/kg●, docarpamine 20 mg/kg i.d.; ■, levodopa 20 mg/kg i.d. Baseline values were as follows. Docarpamine: MAP 133.3 ± 7.2 mmHg, RBF 128.3 ± 19.5 ml/min, RVR 1.139 ± 0.145 mmHg·min/ml, heart rate (HR) 154.3 ± 9.7 beats/min, LVdp/dt max 2942 ± 469 mmHg/s. Levodopa: MAP 135.8 ± 4.1 mmHg, RBF 146.7 ± 22.5 ml/min, RVR 1.017 ± 0.123 mmHg·min/ml, HR 160.7 ± 7.4 beats/min, LVdp/dt max 3183 ± 412 mmHg/s. a) p < 0.05, b) p < 0.01 vs. baseline value.

ED50 value of the vomiting response.

Results

Cardiorenal Effects

Figure 2 shows the effects of docarpamine and levodopa on cardiac contractility and renal blood flow. Intraduodenal administrations of docarpamine and levodopa produced similar increases in LVdp/dt max. The increases peaked at 30 min, and returned to baseline levels at 90—120 min. The maximal increases in LVdp/dt max after docarpamine and levodopa were 36.6 ± 14.2% (from 2942 ± 469 to 3900 ± 588 mmHg/s, p < 0.01) and 39.2 ± 12.1% (from 3183 ± 412 to 4333 ± 490 mmHg/s, p < 0.01), respectively.

The drugs also decreased renal vascular resistance and increased renal blood flow. The maximal decreases in renal vascular resistance after docarpamine and levodopa were 21.2 ± 2.2% (from 1.139 ± 0.145 to 0.884 ± 0.091 mmHg·min/ml, p < 0.01) and 13.6 ± 3.4% (from 1.017 ± 0.123 to 0.869 ± 0.100 mmHg·min/ml, p < 0.01), respectively. The maximal increases in
renal blood flow after the two drugs were
27.9 ± 3.2% (from 128.3 ± 19.5 to 161.3 ± 21.0
ml/min, $p < 0.01$) and 17.9 ± 5.2% (from
146.7 ± 22.5 to 169.3 ± 20.7 ml/min, $p < 0.01$),
respectively. The renal vasodilation and aug-
mented blood flow following docarpamine last-
ed for more than 3 h, while these effects of
levodopa returned to baseline levels within 90
min. Although docarpamine transiently elevat-
ed blood pressure (8.8 ± 5.2%, from 133.3 ± 7.2
to 143.8 ± 6.1 mmHg, $p < 0.05$) and decreased
heart rate (14.8 ± 5.2%, from 154.3 ± 9.7 to
132.0 ± 12.9 beats/min, $p < 0.05$), levodopa did
not cause significant changes in the blood pres-
sure and heart rate at this dose.

**Emetic Effect**

Table I shows the emetic effects of docarpa-
mine and levodopa. Oral administration of
docarpamine at 160 mg/kg produced nausea and
vomiting in two dogs out of six. Lower doses of
docarpamine did not produce vomiting at all.

In contrast, oral administration of levodopa
at 5, 10, 20 and 40 mg/kg produced dose-
dependent vomiting. In particular, the vomiting
occurred at 5 mg/kg in one dog, and the ED$_{50}$
value of the emetic effect was 11.0 mg/kg.

The emetic effects of 160 mg/kg docarpamine
and of 20 mg/kg levodopa were inhibited by
pretreatment with the DA$_2$ dopamine an-
tagonist, domperidone.

**Discussion**

We have previously reported a detailed
dose–response analysis of cardiovascular effects
of docarpamine in anesthetized dogs.$^{3}$ In that
study, docarpamine at 2 mg/kg i.d. significantly
increased renal blood flow, and from 7 to 12
mg/kg it also increased cardiac contractility. In
another unpublished study, intraduodenal doses
of docarpamine at 11.2 and 33.5 mg/kg elevat-
ed plasma free dopamine concentrations to 68
and 157 ng/ml, respectively, in anesthetized
dogs. Furthermore, in another preliminary study
in anesthetized dogs, 10 mg/kg intraduodenal
levodopa significantly increased renal blood
flow, but the duration of the effect was short.
Levodopa at 20 mg/kg produced a clear and rela-
tively sustained increase in renal blood flow and
a significant increase in cardiac contractility. It
therefore appears that 20 mg/kg is sufficient for
both docarpamine and levodopa to elevate
plasma levels of free dopamine and to produce
increases in renal blood flow and cardiac con-
tractility in dogs.

In the present study, we compared the effects
of intraduodenal administrations of 20 mg/kg
docarpamine and levodopa in the same anesthe-
tized dogs. These drugs produced similar in-
creases in renal blood flow and cardiac contractility (Fig. 2). Although the renal
vasodilatory effect caused by docarpamine was
somewhat greater than that caused by levodopa, the difference between the effects of the two drugs was not marked. However, the effect of docarpamine lasted much longer than that of levodopa.

Free dopamine concentrations in plasma after oral administration of docarpamine and its cardiorenal effects have also been studied in humans. Recently, Yoshikawa et al.\textsuperscript{12} reported that the mean maximal concentrations of free dopamine in plasma after oral administration of 750 and 1500 mg of docarpamine to nine healthy volunteers were 63 and 127 ng/ml, respectively. Kubota et al.\textsuperscript{9} reported that one hour after a single oral dose of 1200 mg docarpamine, the mean plasma free dopamine level peaked at $144.6 \pm 43.4$ ng/ml in patients with congestive heart failure. The dose of docarpamine improved left ventricular fractional shortening and mean circumferential velocity on M-model echocardiography. Renal plasma flow and glomerular filtration rate improved with docarpamine, and urine volume and sodium excretion increased. In these studies, there were no reports of any adverse effects such as nausea or vomiting in either volunteers or patients.

On the other hand, Rajfer et al.\textsuperscript{11} reported that 1500 to 2000 mg of levodopa given orally to 14 patients with heart failure elevated plasma concentrations of dopamine to a maximum of $43 \pm 16$ ng/ml at 0.5 h and increased the cardiac index. The plasma concentration of dopamine correlated significantly with the changes in the cardiac index. They also reported that the most common adverse responses observed in their patients were nausea and vomiting.

In the present study, docarpamine and levodopa produced similar effects on cardiac contractility and renal blood flow. From this result and our preliminary pharmacokinetic study, mentioned above, we estimated that the plasma free dopamine concentration in the peripheral circulation in the dogs was elevated to roughly 70—150 ng/ml. On the other hand, the potencies of the emetic effects of docarpamine and levodopa were very different. The ED$_{50}$ value of the emetic effect of levodopa was 11.0 mg/kg, while that of docarpamine was greater than 160 mg/kg in conscious dogs.

It has been suggested that levodopa induces emesis by activating DA$_2$ dopamine receptors located in the chemoreceptor trigger zone (CTZ) of the medulla, via dopamine which is generated from levodopa.\textsuperscript{13,14} Indeed the emetic effects of levodopa and docarpamine in the present study were antagonized by the DA$_2$ dopamine receptor antagonist domperidone. Since the area postrema, which includes the CTZ, is easily penetrated by dyes and other substances,\textsuperscript{15} it has been generally assumed that there is either a weak barrier between the peripheral circulation and the CTZ, or that the CTZ is located outside the blood-brain barrier.

In the present study, if the DA$_2$ receptor in the CTZ was stimulated by dopamine, the free dopamine concentrations around the DA$_2$ receptors in that zone must have been considerably different after administration of the two dopamine prodrugs. This would be inconsistent with the similar cardiorenal effects of the two drugs if the CTZ were located on the peripheral side of the blood-brain barrier.

It is well known that peripherally administered dopamine does not cross the blood-brain barrier, but levodopa does, and changes dopamine levels in the brain. Regarding this fact, our colleagues have found that orally administered docarpamine does not affect locomotor activity in rats with unilateral 6-hydroxydopamine lesions of the nigrostriatal dopamine pathway, which is a prototype of brain dopaminergic neurons, even at a dose of 1000 mg/kg (Fukuchi et al. unpublished observation). This indicates that docarpamine and its metabolic intermediate (i.e., de-ethoxycarbonyl docarpamine) does not cross the blood-brain barrier. As mentioned above, it has been generally assumed that the CTZ is either within a weak part of the blood-brain barrier or is outside of it. Although we have no direct evidence as to which of these two is true, the present results can be explained easily by the former.

Several lines of evidence support the existence of a weak barrier. Many investigators have reported that when levodopa is administered to patients with Parkinson's disease in combination with an extracerebral dopa-decarboxylase inhibitor, carbidopa, to minimize the peripheral adverse effects, the patients still developed nausea...
and vomiting.\textsuperscript{16--18} This suggests that the CTZ is not entirely on the peripheral side of the blood-brain barrier. Furthermore, Rajfer \textit{et al.} reported that when a small dose of metoclopramide, a dopamine receptor antagonist that does cross the blood-brain barrier, was administered to patients in whom emesis was associated with ingestion of levodopa, the nausea and emesis were suppressed.\textsuperscript{11}

In conclusion, the two dopamine prodrugs docarpanine and levodopa produced similar cardio-renal effects but the emetic effect of docarpanine was much weaker than that of levodopa. The difference in emetic effects can be explained by assuming the existence of a weak blood-brain barrier between the peripheral circulation and the CTZ. Docarpanine can be used as a selective dopamine prdrug for the peripheral circulation.

\textbf{References}


