ANTAGONISM OF KW-5338 (DOMPERIDONE) AGAINST EMESIS AND DEPRESSION OF INTESTINAL MOTILITY INDUCED BY L-DOPA

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KW-5338 (domperidone), a new dopamine antagonist, is considered to be an agent to cross the blood-brain barrier with difficulty. The antagonistic activities of KW-5338 against L-DOPA were investigated. KW-5338 showed a strong anti-emetic action against L-DOPA induced emesis in beagle dogs (ED₅₀ = 0.056 mg/kg (p.o.)) and restored the L-DOPA induced depression of intestinal motility to some extent, while it did not antagonize anti-tremorine activities of L-DOPA and trihexyphenidyl in mice. These results suggest that KW-5338 prevents side effects of L-DOPA such as nausea, vomiting and constipation, without reduction in therapeutic effects of L-DOPA in Parkinson’s disease.

Keywords — domperidone; L-DOPA; metoclopramide; dopamine antagonist; anti-emetic action; tremorine; trihexyphenidyl; Parkinson’s disease; intestinal motility

INTRODUCTION

KW-5338 (domperidone) is a new antinauseant and gastrokinetic drug which has been reported to be effective in nausea, vomiting, dyspepsia and gastroesophageal reflex.1–5) Pharmacologically, KW-5338 is a strong dopamine antagonist.

Recently, it was found in “in vitro” binding assays that KW-5338 had a specific affinity to dopamine receptors in the striatum, but this substance was practically devoid of central effects associated with neuroleptic agents because it did not reach dopamine receptors in the striatum in “in vivo” tests.6,7)

On the other hand, L-DOPA that crosses the blood-brain barrier to change to dopamine in the brain is an effective drug for akinesia and rigidity in Parkinson’s disease.8–10) Such side effects as nausea, anorexia and constipation were observed in L-DOPA treatment.

Therefore, it can be supposed that KW-5338 will prevent side effects of L-DOPA without reduction in therapeutic effects of L-DOPA. Reyntjens10) reported that KW-5338 inhibited the L-DOPA induced nausea without producing extrapyramidal side effects in clinical tests. The aim of the present study is to investigate whether KW-5338 would interfere with L-DOPA therapeutic effect (anti-tremorine) and block its side effects (emesis and depression of intestinal motility) in animal tests.

MATERIALS AND METHODS

Animals and Materials — Beagle dogs (female) weighing 7 to 11 kg and mice (male, dd-strain) were used. In dog experiments, KW-5338 (Fig. 1) and metoclopramide (Yamanouchi Pharmaceutical Co., Ltd.) were diluted with lactose. In mouse experiments, they were suspended in 0.3% carboxymethylcellulose. L-DOPA (Kyowa Hakko Kogyo Co., Ltd.), tremorine 2HCl (Aldrich Chemical Co., Ltd.) and trihexyphenidyl HCl (Lederle Japan Ltd.) were used.

Effects of KW-5338 on L-DOPA Induced Emesis — The dose of L-DOPA that could reproduce vomiting in beagle dogs was determined to be 25 mg/kg (p.o.). The latency time from L-DOPA administration to the first vomiting and the frequency of vomiting were observed in a calm place. Vomiting counted only when the chyme
was vomited out. L-DOPA was administered when such drugs as KW-5338 and metoclopramide showed the maximum effects, and animals were observed for 60 minutes after L-DOPA administration.

**Effects of KW-5338 on the Depressed Motility of the Small Intestine** — Mice fasted for 18 hours, were administered orally with charcoal meal (acacia 10% and active carbon 5% suspended solution) and were sacrificed 20 minutes after administration. The small intestine was isolated in its whole length from the pylorus to the caecum. The length from the pylorus to the front of the traversing carbon was measured and the percent motility was calculated as follows:

\[
\text{percent motility} = \frac{\text{carbon-traversed length (cm)}}{\text{whole length (cm)}} \times 100
\]

L-DOPA was administered subcutaneously 60 minutes before charcoal meal administration.

**Effects of KW-5338 on the Anti-tremorine Activity of L-DOPA and Trihexyphenidyl** — Mice receiving subcutaneous administration of 25 mg/kg of tremorine, showed tremor of head, limbs and tail with autonomic symptoms such as watery salivation, diarrhea and lacrimation. KW-5338, metoclopramide, L-DOPA or trihexyphenidyl was given orally or subcutaneously at suitable intervals before tremorine injection, and the combined effects of KW-5338 and L-DOPA or trihexyphenidyl were evaluated by observing the presence or complete absence of tremor, salivation, diarrhea and lacrimation for 2 hours after its injection.

**RESULTS**

**Effects of KW-5338 on L-DOPA Induced Emesis** — L-DOPA at a dose of 25 mg/kg (p.o.) produced vomiting in all control dogs. The latency of vomiting in 14 dogs was 6.7 ± 0.6 minutes (mean ± S.E.) and the frequency of vomiting was 4.6 ± 0.5 times per dog. KW-5338 at 0.04 mg/kg (p.o.) protected 2 out of 5 dogs from vomiting, and in the other 3 dogs, it prolonged the latency and decreased the frequency of vomiting. KW-5338 at 0.32 mg/kg (p.o.) completely blocked emesis (Table I). Its ED₅₀ was 0.056 mg/kg (p.o.).

Metoclopramide protected 1 out of 5 dogs and 5 out of 6 dogs from vomiting at 0.63 mg/kg (p.o.) and 25 mg/kg (p.o.), respectively. The ED₅₀ was 1.4 mg/kg (p.o.).

These results showed that KW-5338 was 25 times as potent as metoclopramide.

**Effects of KW-5338 on the Depressed Motility of the Small Intestine** — The percent motility of

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<th>TABLE I. Effects of KW-5338 and Metoclopramid on L-DOPA Induced Emesis in Beagle Dogs</th>
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a) L-DOPA 25 mg/kg, p.o.
b) ED₅₀ values and 95% confidence limits were calculated by Litchfield-Wilcoxon method.
Antagonism of KW-5338 against L-DOPA

charcoal meal in the control (normal) group was \(63.6 \pm 1.5\%\) (mean \(\pm\) S.E.) \((n = 36)\). It was decreased to \(57.5 \pm 3.1\%\) by L-DOPA at 100 mg/kg (s.c.) and to \(37.4 \pm 1.4\%\) at 300 mg/kg (s.c.) \((n = 36)\).

KW-5338 \((0.3 \text{ mg/kg (p.o.)})\) restored the motility depressed by L-DOPA to some extent. The responses to KW-5338 were dose-related. KW-5338 at 100 mg/kg (p.o.) accelerated the motility and restored it to \(51.1\%\) \((p < 0.001)\) (Fig. 2).

Metoclopramide \((0.3 \text{ mg/kg (p.o.)})\) did not affect significantly the depressed motility and at the highest dose \((100 \text{ mg/kg})\), it potentiated the depression (Fig. 3).

Effects of KW-5338 on the Anti-tremorine Activity of L-DOPA and Trihexyphenidyl — Control animals to which tremorine had been injected subcutaneously exhibited, within 20 minutes after injection, severe tremor with watery salivation followed by lacrimation. Diarrhea was observed in 40 to 60% of them after 60 to 90 minutes.

L-DOPA at 300 to 600 mg/kg (p.o.) hardly affected tremor, watery salivation and lacrimation induced by tremorine, but at the highest dose \((1000 \text{ mg/kg (p.o.)})\), it produced viscous salivation and slightly blocked tremor and lacrimation. KW-5338 did not affect tremor, watery salivation and lacrimation induced by tremorine but

![Chemical Structure of KW-5338 (Domperidone)](image1)

**FIG. 1. Chemical Structure of KW-5338 (Domperidone)**

![Effects of KW-5338 on L-DOPA Induced Inhibition of Charcoal Meal Transport in Mice](image2)

**FIG. 2. Effects of KW-5338 on L-DOPA Induced Inhibition of Charcoal Meal Transport in Mice**

![Effects of Metoclopramide on L-DOPA Induced Inhibition of Charcoal Meal Transport in Mice](image3)

**FIG. 3. Effects of Metoclopramide on L-DOPA Induced Inhibition of Charcoal Meal Transport in Mice**
TABLE II. Effects of KW-5338 and Metoclopramide on Anti-tremorine Action of L-DOPA in Mice

<table>
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<tr>
<th>L-DOPA (mg/kg, p.o.)</th>
<th>KW-5338 (mg/kg, p.o.)</th>
<th>Metoclopramide (mg/kg, p.o.)</th>
<th>No. of mice</th>
<th>Tremor</th>
<th>Watery salivaion</th>
<th>Diarrhea</th>
<th>Lacrima- tion</th>
<th>L-DOPA induced viscous salivaion</th>
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a) Tremorine dihydrochloride 25 mg/kg, s.c.
b) Values in parenthesis represent inhibitory percent.
c) KW-5338 was given orally 90 minutes before tremorine injection.
d) Metoclopramide or L-DOPA was given orally 30 minutes before tremorine injection.

TABLE III. Effects of KW-5338 and Metoclopramide on Anti-tremorine Action of Trihexyphenidyl in Mice

<table>
<thead>
<tr>
<th>Trihexy- phenidyl (mg/kg, s.c.)</th>
<th>KW-5338 (mg/kg, p.o.)</th>
<th>Metoclo- pramide (mg/kg, p.o.)</th>
<th>No. of mice</th>
<th>Tremor</th>
<th>Watery salivaion</th>
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a) Tremorine dihydrochloride 25 mg/kg, s.c.
b) Values in parenthesis represent inhibitory percent.
c) Trihexyphenidyl was given subcutaneously just before tremorine injection.
Antagonism of KW-5338 against L-DOPA

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depressed diarrhea at 10 to 100 mg/kg (p.o.) (Table II).

In the group on the combination of KW-5338 and L-DOPA, tremor did not change when
compared with the L-DOPA group. The viscous salivation induced by L-DOPA was prevented by
KW-5338 at 100 mg/kg (p.o.). Metoclopramide showed almost the same effects as KW-5338 but
metoclopramide, in contrast to KW-5338, potentiated L-DOPA induced viscous salivation
(Table II).

Trihexyphenidyl significantly prevented tremor; that is, it blocked tremor by 54% at 3
mg/kg (s.c.) and completely at 5 mg/kg (s.c.). KW-5338 and metoclopramide did not interfere
with the tremor decreasing activity of trihexyphenidyl (Table III).

DISCUSSION
L-DOPA is an effective drug for akinesia and rigidity in Parkinson's disease.5-10 Trihexyphenidyl, an anti-cholinergic drug, is often used with L-DOPA for tremor, another symptom of Parkinson's disease.

Lotti, Clark11 and Peng12 reported that dopamine, which is a decarboxylated L-DOPA, activated the chemoreceptor trigger zone and induced nausea and vomiting.

KW-5338 is a very potent and selective dopamine antagonist. In the [3H] haloperidol
binding assay, KW-5338 was found to bind with high affinity to the site of dopamine antagonist in
the striatum.7 However, it was actually devoid of central effects associated with neuroleptic agents
because it hardly crossed the blood brain barrier.6

KW-5338 showed a very strong antagonistic activity against emesis induced by L-DOPA 25
mg/kg (p.o.). Its ED50 was 0.056 mg/kg (p.o.). KW-5338 is 25 times as potent as meto-
clopramide. We have found that it has also a strong antiapomorphine (emesis) activity in
beagle dogs. The ED50 was 0.034 mg/kg (p.o.).13
It is 27 times as potent as metoclopramide in the antagonistic test against apomorphine emesis. The potency ratio of KW-5338 to metoclopramide against L-DOPA emesis is almost equal to that
against apomorphine emesis. These data might suggest that KW-5338 prevents L-DOPA emesis
and apomorphine emesis by its dopamine antagonistic activity at the level of the chemore-
ceptor trigger zone which is outside the blood-
brain barrier.

Reyntjens et al.1) said that dopamine played
some role in gastrointestinal depression. Nakamura et al.14) reported that L-DOPA depressed
motility of the small intestine in mice and that the
effect was blocked by benserazide (L-DOPA
de carboxylase inhibitor), indicating that motility
depression of the small intestine might be induced
by dopamine, a metabolite of L-DOPA.

In the present study, KW-5338 improved the
depression of charcoal meal transit induced by L-
DOPA. Therefore, the dopamine antagonistic
property of KW-5338 played an important role
in acceleration of intestinal motility.

It is said that tremor induced by tremorine is
similar to one of the symptoms of Parkinson's disease.15) KW-5338 did not block the tremor
decreasing activity of L-DOPA and trihexypheni-
dyl in this test. Metoclopramide showed almost
the same effects as KW-5338, except on the L-
DOPA induced viscous salivation which was pre-
vented by KW-5338 but strengthened by meto-
clopramide.

These results suggest that KW-5338 might
prevent such L-DOPA induced side effects as
nausea, vomiting and constipation without in-
terfering with central action of L-DOPA in
Parkinson's disease.

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