The effects of Rikkunshi-to on Parkinsonian patients with unstable effect of levodopa/carbidopa

Yukitaka HIYAMA,*[a] Hiroyori TOSA,[a] Katsutoshi TERASAWA,[a] Takashi SHIMADA,[a] Kozo TAKAHASHI,[a] Yutaka SHIMADA[a] and Hiroshi WATANABE[b]

[a]*Department of Japanese Oriental Medicine, University Hospital*
[b]*Section of Pharmacology, Research Institute for Wakan-Yaku, Toyama Medical and Pharmaceutical University*

(Received April 1, 1991. Accepted July 5, 1991.)

Abstract

Unstable effects (wearing-off and/or on-off phenomena) of levodopa/carbidopa (LD/CD) are at times observed in Parkinsonian patients. Irregular absorption of LD/CD (fluctuation of plasma levodopa levels) is considered to be a major reason for this. Recently, erratic gastric emptying has been proposed as being the determining cause of these unstable effects. Therefore, continuous duodenal infusion of LD/CD has been tried, but this is not a readily applicable procedure for the patients. For improving erratic gastric emptying seven Parkinsonian patients with unstable effect of LD/CD were treated with the Kampo medicine Rikkunshi-to, which is usually used for gastro-duodenal dysfunction.

Parkinsonian disability scores and percent on-time were improved as well as gastric emptying motility after the use of Rikkunshi-to. A reduction in the fluctuation of plasma levodopa levels also noticed. Our study suggests that Rikkunshi-to improves erratic gastric emptying and stabilizes the plasma levodopa levels, thus improving the motor fluctuations in Parkinsonian patients treatwd with LD/CD.

Key words Motor fluctuation in Parkinsonian patients, Erratic gastric emptying, Gastro-duodenal kinetic Kampo agent Rikkunshi-to, Reduction in fluctuations in motor and plasma levodopa levels.

Abbreviation Rikkunshi-to (Liu-Jun-Zi-Tang), 六君子湯.

Introduction

It is well known that an unstable effect (wearing-off and/or on-off phenomena) of levodopa/carbidopa is at times observed in Parkinsonian patients. Fluctuation of plasma levodopa concentration due to irregular absorption of levodopa/carbidopa is considered to be one of the reasons for this.[1,2] Recently, in order to achieve a stable plasma levodopa concentration, continuous duodenal infusion of levodopa/carbidopa[3] or controlled-release levodopa/carbidopa[4] has been tried in the treatment of Parkinson's disease.

In our study, a decreased gastric emptyng motility in Parkinsonian patients treated with levodopa/carbidopa was noticed. Therefore we supposed that improving the decreased gastric emptying motility would tend to stabilize the plasma levodopa concentration and thus also stabilize the effect. For this purpose we used the Kampo medicine Rikkunshi-to combination with levodopa/carbidopa.

Methods

Patients : Seven subjects suffering from Parkinson's disease with an unstable effect of levodopa/carbidopa (motor fluctuations) were entered into the study. The wearing-off phenomenon was noticed in all patients and the on-off phenomenon occurred in patients 3, 5, 6 and 7 (Table I).

*〒 930-01 富山市杉谷2630
富山医科薬科大学附属病院和漢診療部 檜山幸孝
2630, Sugitani, Toyama 930-01, Japan

Journal of Medical and Pharmaceutical Society for WAKAN-YAKU 8, 83－88, 1991

Table I Patient profiles and L-DOPA dose.

No.	Sex	Age	Contraction period	Stage	Motor fluctuation wearing-off	Motor fluctuation on-off	L-DOPA (mg/day)
1	F	63	2 yrs 0 mon.	II	+	−	300
2	F	46	2 6	II	+	−	450
3	F	58	3 2	III	+	+	400
4	M	74	2 4	III	+	−	300
5	M	66	9 3	IV	+	+	400
6	M	70	5 10	IV	+	+	500
7	M	55	6 9	III	+	+	450

Table II Rikkunshi-to

Medicinal plants	Weight (g)	Origin
Ginseng Radix	2.0	South Korea
Hoelen	3.0	North Korea
Atractylodis Rhizoma	3.0	China
Aurantii Nobilis pericarpium	4.0	Japan
Pinelliae Tuber	4.0	China
Glycyrrhizae Radix	1.0	China
Zingiberis Rhizoma	1.0	China
Zizyphi Fructus	2.0	China

All subjects were admitted to our hospital and have been undergoing thorough examinations from one week before the start of the study.

Protocol : Effects of Rikkunshi-to were examined two weeks after combined use of the agent and levodopa/carbidopa. No additional drugs were used. The dosage and schedule of levodopa/carbidopa remained constant for a period beginning one month prior to and throughout the study.

Preparation of Rikkunshi-to : Rikkunshi-to was prepared as a 300 ml decoction (40°C), gently boiling the crude ingredients in 600 ml of water for 40 minutes just before administration (Table II). These ingredients used were purchased from Tochimoto Tenkai-do (Osaka, Japan).

Clinical assessment : An independent observer examined the patients every hour from 6 A. M. to 9 P. M. Tremor, rigidity and akinesia were each scored on a scale of 0 (absent) to 4 (very severe) and combined to yield an overall Parkinsonian disability score.

Symptoms were self-assessed and were scored on a scale of 0 (absent) to 4 (very severe). A decrease in more than two grades of symptomatic score were considered as improvement.

Evaluation of gastric emptying motility : The gastric emptying motility was evaluated by acetaminophen absorption.[4] Two ml. of plasma was sampled 45 minutes after the administration of 1.5 gr. of acetaminophen. Plasma acetaminophen concentration was measured by fluorescent polarization immunoassay (FPIA).

Plasma levodopa measurements : The plasma levodopa concentration was determined by high pressure liquid chromatography (HPLC) with electrochemical detection (ECD). An EICOM EP-10 solvent delivery system and an EICOM ECD-100 electrochemical detector equipped with a glassy carbon electrode were employed. The voltage was set at 400 mV versus an Ag/AgCl reference electrode. The detector range was 80 nA f. s. for the quantification of levodopa. The recorder used was a SEKONIC SS 250F dual pen data module. The analytical column was a TSK-gel ODS-80, 5-μm packing. The mobile phase

consisted of 0.05 M phosphate buffer solution containing 10 μM EDTA and 0.2 mM sodium octylsulfate to which a volume of methanol equal to 8 % (v/v)of the degassed buffer volume had been added (pH 3.15). The mobile phase was filtered through a 0.45-μm cellulose membrane filter (Millipore, Milford, MA, U. S. A.) and vacuum-degassed. Chromatography was performed at 1,400 lb./in^2 at a flowrate of 0.9 ml/min. The temperature of the analytical column was kept at 28°C. Blood was collected in sodium EDTA kept at 4°C, immediately centrifuged at 3,000 r/min for 5 min, and the plasma kept frozen at -80°C until analysis. Dihydroxybenzylamine (10 μg / ml), an internal standard used to correct for catechol recoveries, was added to 1 ml of plasma, and catechols were partially purified by adsorption onto alumina and desorbed with 100 μl of 0.1 M perchloric acid.

Statistics : Data was analyzed by a two-tailed Wilcoxon U-test. Paired U-test was employed when appropriate.

Results

Parkinsonism

Parkinsonian disability scores decreased significantly from 2.25 ± 0.38 with the use of levodopa/carbidopa only to 1.03±0.13 with the combined use of Rikkunshi-to and levodopa/carbidopa ($p<0.05$) (Fig. 1a). Percent on-time increased significantly from 60±8.3 to 92±3.5 ($p<0.01$) (Fig. 1b). Gastric discomfort, nausea and poor appetite improved in 4 patients/5 patients, 3/3 and 5/7, respectively.

Gastric emptying motility

Decreased gastric emptying motility was improved with the combined use of Rikkunshi-to and levodopa/carbidopa compared to the levels without treatment (Fig. 2).

Plasma levodopa levels

Fluctuation of plasma levodopa concentration indicated as percent deviation from the mean levodopa levels were clearly reduced (Fig. 3a). Maximum and minimum values in peak to peak of percent deviation from the mean dopa levels were significantly reduced from 290±68 and 117 ±31 to 114±47 and 19±21, respectively ($p<0.01$) (Fig. 3b).

Discussion

In Japan, the Kampo medicine called Rikkunshi-to is used for the following symptoms : epigastralgia, gastric discomfort and nausea, as well as for the following diseases : chronic gastritis and impairment of gastrointestinal functions. These symptoms and diseases are frequently observed in Parkinsonian patients treated with levodopa/carbidopa. We noticed chronic atrophic gastritis in all subjects, and then confirmed the improvement

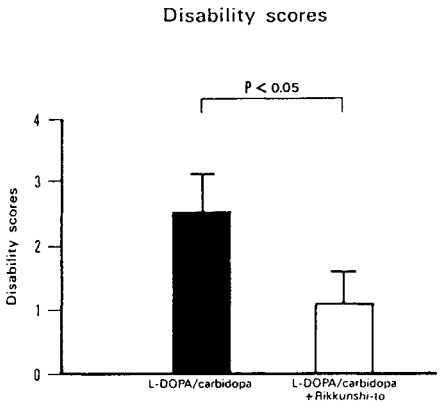

Fig. 1a Parkinsonian disability scores decreased significantly with the combined use of Rikkunshi-to and LD/CD. Each value indicates the mean± S.D.

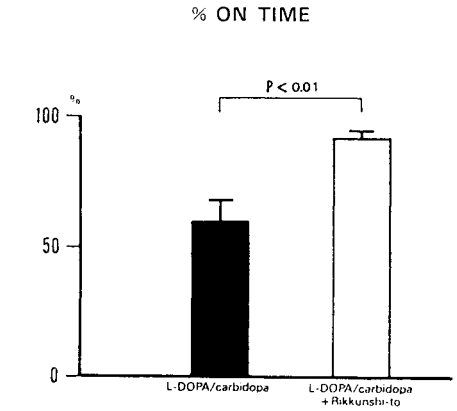

Fig. 1b Percent on time (effective time of LD/CD) increased significantly with the combined use of Rikkunshi-to and LD/CD. Each value indicates the mean±S.D.

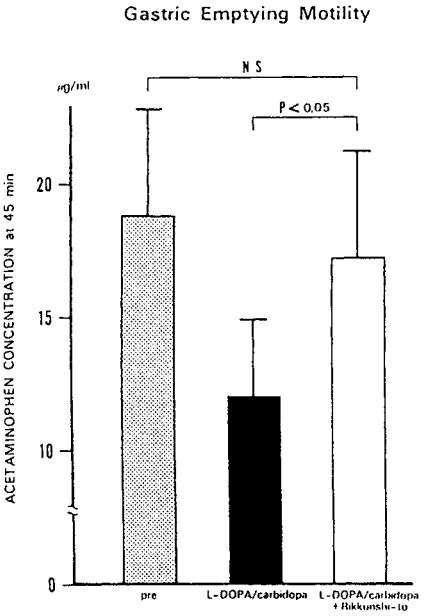

Fig. 2 Decreased gastric emptying motility after LD/CD was improved with the combined use of Rikkunshi-to and LD/CD. Each value indicates the mean±S.D.

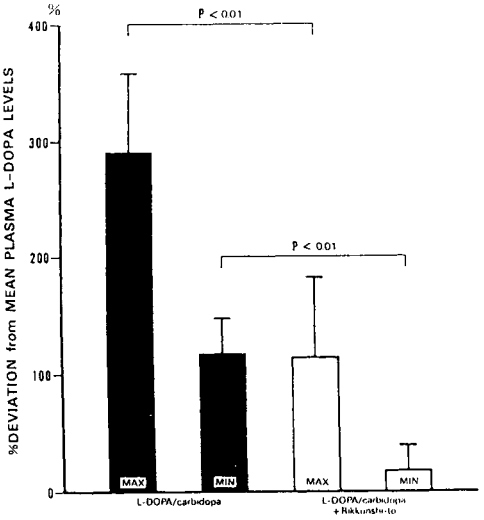

Fig. 3b Maximum and minimum values in peak to peak of percent deviation from the mean LD levels were significantly reduced after the combined use of Rikkunshi-to and LD/CD. Each value indicates the mean±S.D.

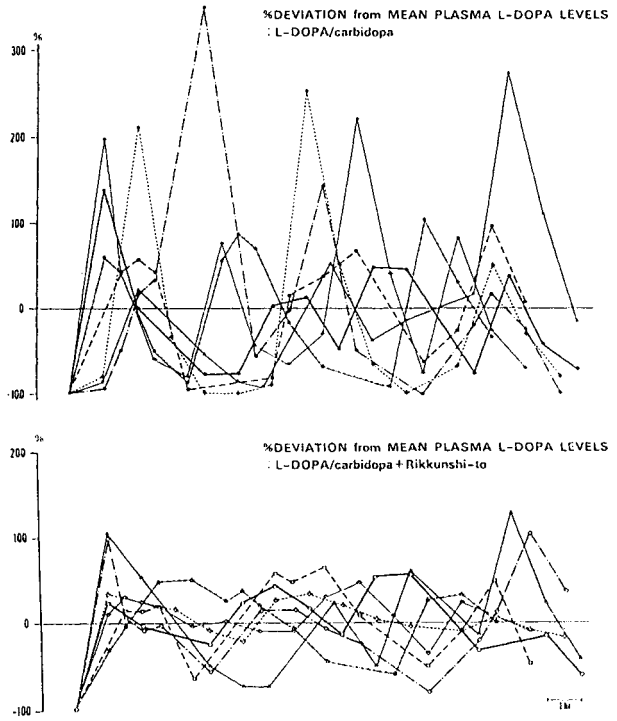

Fig. 3a Fluctuation of plasma LD concentration indicated as percent deviation from the mean LD levels were clearly reduced with the combined use of Rikkunshi-to and LD/CD.

of this condition after the combined use of Rikkunshi-to by gastroendoscopy. In other words, Rikkunshi-to improved the gastritis as well as the accompanying symptoms. For such cases, antiemetic and kinetic agents (*i.e.* metoclopramide, domperidone, cisapride) are generally used, but they are particularly difficult to use for Parkinsonian patients because of their anti-dopaminergic character. During our long-term experience in treating Parkinsonian patients with Rikkunshi-to, there was never a need for the use of antiemetic agents.

It is suggested that stabilizing the plasma levodopa concentration will moderate the motor fluctuations such as wearing-off and/or on-off phenomenon.[1,2,5] Maintenance of steady plasma levodopa levels by the continuous intravenous infusion of levodopa appears very effective in stabilizing motor fluctuations,[5,6] but this procedure is still experimental and is inconvenient for actual practice. Therefore, other approaches for stabilizing plasma levodopa, such as continuous duodenal infusion of levodopa, has been reported.[2,7] Most levodopa absorption appears to take place in the proximal small intestine,[8] meaning that erratic gastric emptying may contribute to unsteady levodopa absorption and the resulting fluctuating plasma levodopa levels.[7]

Neither of the above two procedures appears feasible for long-term therapy. Recent reports of controlled-release levodopa/carbidopa preparations also suggest beneficial effects, especially in patients with the wearing-off phenomenon.[3,9] Such controlled-release would be conducive to maintaining steady plasma levodopa levels in cases that are not bothered by erratic gastric emptying. However, with such preparations the problem with erratic emptying still remains unsolved. In contrast, our observations suggest that the use of Rikkunshi-to could lead to a solution of the problem of erratic gastric emptying and associated unstable plasma levodopa levels. The relatively stable plasma levels of levodopa may be due to an improvement of its absorption from the small intestine when combined with Rikkunshi-to.

Conclusion

Combining the use of Rikkunshi-to with levodopa/carbidopa is efficacious for those Parkinsonian patients who suffer from the effects of instability which sometimes accompany the treatment with levodopa/carbidopa.

Acknowledgement

We express our gratitude to Mr. A. Gerz for his critical reading of this manuscript. This work was supported in part by a research fund from Japan Foundation For Aging and Health.

和文抄録

L-DOPA 製剤により治療中のパーキンソン病患者には on-off 現象など L-DOPA の効果が不安定になることが知られている。この原因の一つとして L-DOPA の腸管からの吸収の障害が想定されており，最近では空腸への経管投与や吸収を安定させる目的で controlled-release carbidopa/levodopa 剤が試みられている。また，パーキンソン病患者では消化管機能低下がしばしば認められるが，L-DOPA の効果が不安定になっている患者では胃排出能低下があり，これが L-DOPA 製剤服用によりさらに悪化する事をわれわれは確認した。このことより，低下した胃排出能を改善することが L-DOPA の効果を安定させることにつながるのではないかとの仮説を立てた。この目的に合致する漢方方剤として六君子湯を併用しその効果を検討した。対象は L-DOPA 製剤により治療中のパーキンソン病患者 7 名で L-DOPA の効果が不安定となっているものを選んだ。六君子湯併用により臨床的には L-DOPA 投与の効果が安定し ADL の改善が得られ，胃排出能の改善ならびに血中 L-DOPA 血中濃度の安定化も確認された。

References

1) Eriksson, T., Magnusson, T., Carlsson, A. *et al.*: "On-off"phenomenon in Parkinson's disease : correlation to the concentration of dopa in plasma. *J. Neural. Transm.* **59**, 229-240, 1984.

2) Sage, J. I., Schuh, L., Heikkila, R. E. *et al.*: Continuous duodenal infusions of levodopa : plasma concentra-

tions and motor fluctuations in Parkinson's disease. *Clin. Neuropharmacol.* **11**, 36-44, 1988.

3) Jesse, M. C. Lyn Breck, R. N., Henn, K. *et al.*: Controlled-release levodopa/carbidopa. II. Sinemet CR4 treatment of response fluctuations in Parkinson's disease. *Neurology* **37**, 1607-1612, 1987.

4) Heading, R.C., Nimmo, J., Prescott, L.F. *et al.*: The dependence of paracetamol absorption on the rate of gastric emptying. *Br. J. Pharmacol.* **47**, 415-421, 1973.

5) Mouradian, M. M., Juncos, J. L., Fabbrini, G. *et al.*: Motor Fluctuations in Parkinson's Disease : Pathogenic and Therapeutic Studies. *Ann. Neurol.* **22**, 475-479, 1987.

6) Hardie, R. J., Lees, A. J. and Stern, G. M. : ON-OFF FLUCTUATIONS IN PARKINSON'S DISEASE. *Brain* **107**, 487-506, 1984.

7) Kurlan, R., Rubin, A. J., Miller, C. *et al.*: Duodenal delivery of levodopa for on-off fluctuations in parkinsonism: preliminary observations. *Ann. Neurol.* **20**, 262-265, 1986.

8) Bianchine, J.R., Calimlim, L. R., Morgan, J. P. et *al.*: Metabolism and absorption of L-3, 4-dihydroxyphenylalanine in patients with Parkinoson's disease. *Ann. NY. Acad. Sci.* **179**, 126-140, 1971.

9) Hutton, J. T., Albrecht, J. W., Roman, G. C. *et al.*: Prolonged Serum Levodopa Levels With Controlled-Release Carbidopa / Levodopa in the Treatment of Parkinson's Disease. *Arch. Neurol.* **45**, 5-57, 1988.