Short Communication

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Evaluation of oral antidepressant drugs for adaptation to the simple suspension method

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ABSTRACT

Objective: Gavage administration of antidepressant drugs is required for some depressed patients with dysphagia. In the recent years, a simple suspension method has drawn increasing attention as a method that prevents changes in the stability and safety of various drugs. However, only 59 of the 354 orally administered antidepressant drugs (16.7%) approved in Japan by April 2013 have been examined with this method. In this study, we investigated whether 44 oral antidepressant drugs, which have not previously been tested for efficacy through gavage, could be adapted to the simple suspension method. **Materials and Methods:** Adaptability of antidepressants to the simple suspension method was assessed by incubating at room temperature a drug in 20 mL of warm water (at 55°C) in a 30 mL-syringe for 5 and 10 min. The ability of the decayed drugs to pass through the tubing was also examined. **Results:** Most of the 44 oral antidepressant drugs tested could be adapted to the simple suspension method. Unexpectedly, fluvoxamine maleate tablets, milnacipran hydrochloride tablets, and Cymbalta® capsules required 10 min or longer to decay. **Conclusions:** We were able to qualitatively assess all 44 oral antidepressant drugs. These results provide useful information for administration of oral antidepressant drugs to depressed patients using a simple suspension method.

Key words: Difficulty swallowing, gavage administration, generic drugs, oral antidepressant drugs, simple suspension method

INTRODUCTION

In the recent years, there has been a significant increase in the number of patients at medical institutions suffering from mental illnesses.[1] Depression is the most common among these diseases,[2,3] and since mental illness reduces activity in addition to affecting an individual's emotional state, it can lead to difficulty swallowing in some patients.[4,5] In such cases, it is necessary to administer medicine or nutrition via gavage administration through a gastric or intestinal stoma at the surface of the abdomen, or via a transnasal tube. Recently, the simple suspension method has garnered attention for its effectiveness and for the increased drug stability and safety associated with its use.[6-9] The method was devised by Kurata and Fujishima to reduce problems associated with gavage administration.[10] Porphyrization is used in association with conventional gavage administration but may alter the drug's physicochemical stability due to

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exposure to light, temperature, or humidity. Changes in the composition can occur if drugs are lost or intermingled when packages are split, or if there is adhesion to the mortar and pestle during processing.[11,12] In contrast, using a simple suspension method, the entire tablet or capsule is immersed into warm water for decay and suspension immediately before administration, which solves a variety of problems associated with porphyrization. Furthermore, institutions that have introduced the simple suspension method have confirmed the utility of this method noting increased efficiency in overall drug dispensation due to the elimination of the process of porphyrization.[13,14]

In Japan, tricyclic antidepressants and tetracyclic antidepressants are the pharmacotherapy of choice for depression. However, these antidepressant drugs not only block noradrenaline and serotonin transporters, but also inhibit central and peripheral receptors such as muscarinic acetylcholine receptors, histamine receptors, and α_1 adrenoreceptors. Therefore, they frequently cause side-effects including dry mouth, constipation, and drowsiness, and often cannot be used in patients and elderly people with symptoms such as glaucoma and enlarged prostate.[15] These drawbacks prompted the development of selective serotonin reuptake inhibitors (SSRI), which selectively block serotonin transporters and have a negligible effect on noradrenaline transporters and other receptors. Although SSRI drugs are safer and cause fewer side-effects than tricyclic and tetracyclic antidepressants, they are reportedly less effective than tetracyclic antidepressants in cases of severe depression. This suggested that the pathology of depression could not be explained simply by abnormalities of serotonergic neurotransmission.[16] These findings led to the development of serotonin and noradrenaline reuptake inhibitors, which affect other neurotransmitter systems in addition to the serotonergic system.

This study examined 44 antidepressant drugs that had not been previously investigated for their effectiveness using the simple suspension method. These 44 compounds were among the 354 antidepressant drugs on the market in Japan as of April 2013.[10] It is predicted that generic drug usage will increase in accordance with the Japanese Ministry of Health, Labor, and Welfare's target for raising the market share of generic drugs to at least 60% by the end fiscal 2017.[17] Thus, the adaptability of orally administered antidepressant drugs to simple suspension was examined, in anticipation of prescription changes that could occur in the future when transferring from brand name drugs to generic drugs.

MATERIALS AND METHODS

Drugs

Among the orally administered antidepressant drugs currently on the market in Japan, 44 drugs were selected from a list of 295 antidepressant drugs that were not previously approved for gavage administration,[10] and for which it was not known whether they could be adapted to the simple suspension method. Antidepressant drugs were defined in this study as those that are current on the National Health Insurance drug price list, are readily available, fall under the drug efficacy classification code 117, and that have been recorded as effective for depression according to patient surveys. Finally, drugs with the same name but different potencies or specifications were treated as different drugs.

Tools

Terumo syringes (30 mL; Terumo Corp.), were used to dispense drugs. The recently developed Kangaroo™ tubes were used for enteral feeding (8 Fr/120 cm; Japan Covidien Co.).

Experimental conditions

All testing was done at room temperature (25.8 ± 0.48°C), with relative constant humidity (64.0 ± 6.98%), and illumination (1070.4 ± 49.5 lux).

Decay-suspension test

The plunger was removed from the syringe, the drug (1 tablet or 1 unopened capsule) placed inside, and the plunger replaced. Distilled water (20 mL, 55°C) was sucked into the syringe, and it was left at room temperature for 5 min, with the cap replaced back onto the tip. Then, the syringe was rotated 90° and back again, and the drug's decay and suspension status was checked. The syringe was left for another 5 min, and the same operations were repeated (Figure 1a).

Tube passage test

The suspension produced from the decay-suspension test was injected into an 8 Fr tube from the injection end at a speed of about 2-3 mL/s. Samples without clear decay and suspension were regarded as nonadaptable. Following injection of the drug, approximately 20 mL of distilled water was drawn up into the syringe and used to clean the tube. If no drug remained in the tube, it was determined that the drug passed through the tube properly (Figure 1b).

Assessment of suitability for gavage administration

The determination as to whether a drug could be adapted to gavage administration was based on the results of the 3 independent decay-suspension and tube-passage tests. In order for a drug to be determined suitable for gavage administration, it was required that the drug achieved previously established criteria in at least 2 out of the 3 repetitions. Adaptability of an experimental drug was specified by classification into the following categories, according to a handbook of gavage administration: Adaptable 1, decay and suspension occur within 10 min, and the tube-passage is possible through an 8 Fr tube; Adaptable 2, breaking the tablet's coating allows decay and suspension to occur within 10 min with the tube passage achieved through an 8 Fr tube.[10]

RESULTS

This study examined 44 orally administered antidepressant drugs for their adaptability to the simple suspension method. A summary of the results of the decay-suspension and the tube passage tests, as well as a final evaluation of each drug is shown in Table 1.

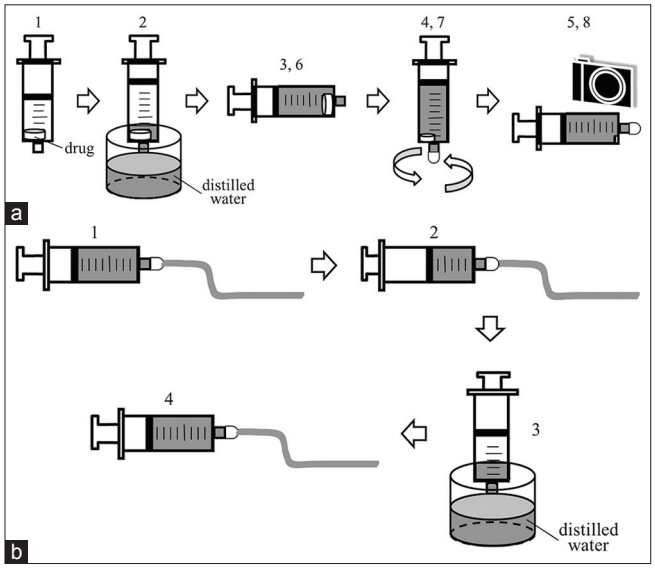

Figure 1: Analysis of adaptability of various drugs to the simple suspension method using the test for decay, suspension, and tube passage. (a) Test for decay and suspension; 1. Place the drug into the syringe, 2. Aspirate distilled water (approximately 55°C) using the syringe, 3. Incubate the syringe at room temperature for 5 min, 4. Rotate the syringe 90°, 5. Check the status of the drug, 6. Incubate the syringe at room temperature for 5 min, 7. Rotate the syringe 90°, 8. Check the status of the syringe. (b) Test for tube passage; 1. Inject the suspension into the feeding tube (approximately 2-3 mL/min). 2. Check the tube passage to the feeding tube (i.d. 2.7 mm), 3. Aspirate distilled water (at approximately 55°C) using the syringe, 4. Check the tube passage to the feeding tube

In the decay-suspension test of the 44 drugs, 38 drugs decayed after suspended in warm water within 10 min and passed through an intubation tube (Adaptable 1). The drugs that did not meet these criteria were the fluvoxamine maleate tablet (75 mg; TCK®), the fluvoxamine maleate tablet (75 mg; EMEC®), and milnacipran hydrochloride tablets (12.5 mg, 15 mg, 25 mg, and 50 mg; Nichi-Iko®). After breaking the tablet coating, the fluvoxamine maleate tablet (75 mg; TCK®), the fluvoxamine maleate tablet (75 mg; EMEC®), and the milnacipran hydrochloride tablets (12.5 mg, 15 mg, 25 mg, and 50 mg; Nichi-Iko®) decayed and suspended within 10 min, and also passed through an intubation tube (Adaptable 2). Interestingly, only the Cymbalta capsule (20 mg®) did not either decay or suspend (Figure 2). This is consistent with the results reported by Takemoto *et al.*[18]

DISCUSSION

This study established that, with the exception of the Cymbalta capsule (20 mg®), 43 of the drugs examined could be adapted to the simple suspension method. However, the tablet coating needed to be broken for the fluvoxamine maleate tablet (75 mg; TCK®), the fluvoxamine maleate tablet (75 mg; EMEC®), and the milnacipran hydrochloride tablets (12.5 mg, 15 mg, 25 mg, and 50 mg; Nichi-Iko®). The reasons for these experimental outcomes are discussed below.

First, the fluvoxamine maleate tablet (TCK®) contains the disintegrating agent carmellose for the 25 mg and 50 mg dosage forms, while its 75 mg form does not, which may have caused discrepancies in the ability of these drugs to decay.[19] Next, the greater mass of the fluvoxamine maleate table (75 mg; EMEC®) required more time for water to permeate to the core of the

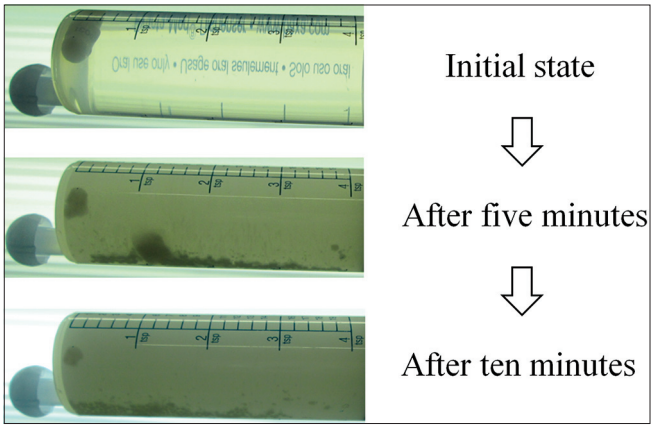

Figure 2: External appearance of Cymbalta capsule (20 mg®) immediately after initiating the decay and suspension procedures after 5 min and after 10 min

Table 1: Results of tests for decay, suspension and tube passage

No.	Drug name	Test for decay and suspension						Final result		Final evaluation
		After 5 minutes			After 10 minutes			Test for decay and suspension	Tube-passage test	
		N=1	N=2	N=3	N=1	N=2	N=3			
1	Amplit® tablet 25 mg	×	×	×	O	×	O	O	O	apply 1
2	(G) Etizolam tablet 0.5 mg「Nichi-Iko」	O	O	O	O	O	O	O	O	apply 1
3	(G) Etizolam tablet 1 mg「Nichi-Iko」	O	O	O	O	O	O	O	O	apply 1
4	Abilify® tablet 3 mg	O	O	O	O	O	O	O	O	apply 1
5	Abilify® tablet 12 mg	O	O	O	O	O	O	O	O	apply 1
6	Cymbalta® capsule 20 mg	×	×	×	×	×	×	×	-	inappropriate
7	Zyprexa® tablet 2.5 mg	×	×	O	O	O	O	O	O	apply 1
8	(G) Dezolam tablet 0.5 mg	O	O	O	O	O	O	O	O	apply 1
9	(G) Dezolam tablet 1 mg	O	O	O	O	O	O	O	O	apply 1
10	Toledomin® tablet 12.5 mg	×	×	O	O	O	O	O	O	apply 1
11	(G) Paroxetine tablet 5 mg「SAWAI」	O	O	O	O	O	O	O	O	apply 1
12	(G) Paroxetine tablet 5 mg「MEIJI」	×	O	O	O	O	O	O	O	apply 1
13	(G) Paroxetine tablet 5 mg「TCK」	×	O	O	O	O	O	O	O	apply 1
14	(G) Paroxetine tablet 5 mg「Nichi-Iko」	O	O	O	O	O	O	O	O	apply 1
15	(G) Paroxetine tablet 10 mg「SAWAI」	×	O	O	O	O	O	O	O	apply 1
16	(G) Paroxetine tablet 10 mg「MEIJI」	O	O	O	O	O	O	O	O	apply 1
17	(G) Paroxetine tablet 10 mg「TCK」	×	O	O	O	O	O	O	O	apply 1
18	(G) Paroxetine tablet 10 mg「Nichi-Iko」	O	O	O	O	O	O	O	O	apply 1
19	(G) Paroxetine tablet 10 mg「EE」	O	×	O	O	O	O	O	O	apply 1
20	(G) Paroxetine tablet 20 mg「SAWAI」	×	O	O	O	O	O	O	O	apply 1
21	(G) Paroxetine tablet 20 mg「MEIJI」	O	×	×	O	O	O	O	O	apply 1
22	(G) Paroxetine tablet 20 mg「TCK」	O	O	O	O	O	O	O	O	apply 1
23	(G) Paroxetine tablet 20 mg「Nichi-Iko」	×	×	O	O	O	O	O	O	apply 1
24	(G) Paroxetine tablet 20 mg「EE」	×	×	O	O	O	O	O	O	apply 1
25	(G) Fluvoxamine maleate tablet 25 mg「TCK」	×	×	×	O	O	O	O	O	apply 1
26	(G) Fluvoxamine maleate tablet 25 mg「EMEC」	×	×	×	O	O	O	O	O	apply 1
27	(G) Fluvoxamine maleate tablet 25 mg「Nichi-Iko」	O	O	O	O	O	O	O	O	apply 1
28	(G) Fluvoxamine maleate tablet 50 mg「TCK」	×	×	×	O	O	O	O	O	apply 1
29	(G) Fluvoxamine maleate tablet 50 mg「EMEC」	×	×	×	O	O	O	O	O	apply 1
30	(G) Fluvoxamine maleate tablet 50 mg「Nichi-Iko」	O	O	O	O	O	O	O	O	apply 1
31	(G) Fluvoxamine maleate tablet 75 mg「TCK」	×	O	O	O	O	O	O	O	apply 2
32	(G) Fluvoxamine maleate tablet 75 mg「EMEC」	O	O	O	O	O	O	O	O	apply 2
33	(G) Fluvoxamine maleate tablet 75 mg「Nichi-Iko」	×	O	O	O	O	O	O	O	apply 1
34	(G) Milnacipran hydrochloride tablet 12.5 mg「Nichi-Iko」	O	×	O	O	O	O	O	O	apply 2
35	(G) Milnacipran hydrochloride tablet 15 mg「Nichi-Iko」	O	×	O	O	O	O	O	O	apply 2
36	(G) Milnacipran hydrochloride tablet 25 mg「Nichi-Iko」	O	×	O	O	O	O	O	O	apply 2
37	(G) Milnacipran hydrochloride tablet 50 mg「Nichi-Iko」	O	×	O	O	O	O	O	O	apply 2
38	(G) Mozun tablet 0.5 mg	×	×	×	O	O	O	O	O	apply 1
39	(G) Mozun tablet 1 mg	O	O	×	O	O	O	O	O	apply 1
40	(G) Risperidon tablet 1 mg「YOSHITOMI」	O	O	O	O	O	O	O	O	apply 1
41	(G) Risperidon tablet 2 mg「YOSHITOMI」	O	O	O	O	O	O	O	O	apply 1
42	Reflex® tablet 15 mg	×	×	O	O	O	O	O	O	apply 1
43	Lexapro® tablet 10 mg	O	O	O	O	O	O	O	O	apply 1
44	Remeron® tablet 15 mg	×	×	O	O	O	O	O	O	apply 1

(G): Generic drug, O: complete decay, ×: part of decay or non-decay, -: Not done

tablet, resulting in the observed dose-dependent lengthening of decay times. Also, when one of the additives, pregelatinized starch, comes in contact with water, its viscosity increases, albeit weakly. Therefore, larger tablet sizes are thought to require more time to decay.[20] With milnacipran hydrochloride tablets (12.5 mg, 15 mg, 25 mg, and 50 mg; Nichi-Iko®), the tablet-capsule porphyrization handbook[21] states that porphyrization is "possible under certain conditions." This indicates that in the cases of gavage administration of drugs even

with the same ingredients it is necessary to consider the effect of prescription changes such as a replacement with larger dosage forms. Finally, although the enterosoluble granule drug Cymbalta capsule (20 mg®) can be dissolved in solvents at pH higher than 5.5, dissolution requires at least 30 min, which is thought to be the reason why we did not observe decay and suspension of this drug within 10 min.[18,22] Drugs in the Adaptable 2 category were not tested, since the tablet-capsule porphyrization handbook[21] indicated that porphyrization of these drugs was not achievable (noted as "×," not possible "O").

CONCLUSIONS

In this study, the decay-suspension test and the tube passage test were performed on 44 orally administered antidepressant drugs to clarify which can be adapted to gavage administration, and the mechanistic limitations underlying the results were discussed. This study contributes to lowering the risks of tube blockage and drug incompatibility prior to gavage administration. Furthermore, taking into consideration that Japan is an aging society with a low birthrate, these results are expected to help maintain and improve the quality-of-life of depressed elderly patients, as well as their caregivers, and to generally promote safety in medical care.

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