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Evaluation of easy-to-use containers for liquid medication

Abstract

Basic matters related to the method of dispensing oral-dose liquid medication and other prescription drugs in Japan have been set forth in the Dispensing Guidance issued by the Japan Pharmaceutical Association. However, accurate ways of dispensing vary among medical facilities and pharmacies. In case of oral-dose liquid medication such as antipyretics and expectorants often used for pediatric patients, the pharmacists often subdivide the liquid from a 500-mL glass container into smaller plastic containers and provides the subdivided liquid after dilution in a volume needed for a given patient. The present study was undertaken to evaluate the ease of use of several kinds of liquid medication containers and measuring devices during experimental measuring of phantom drug solution. The study was additionally designed to evaluate the extent of knowledge about the Child Resistance (CR) caps, and the ease or difficulty in removing such a cap. The collaborators to this study attached importance to the accuracy in measuring the liquid, the ease of reading the graduations and the design allowing hygienic handling as the factors determining the most easily usable liquid medication containers. The results additionally show that the recognition of the CR cap among people is not high at present.

Keywords: liquid medication, pediatric, plastic container, child resistance (CR), administration, device

Volume 12 Issue 2 - 2024

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Received: March 25, 2024 | **Published:** April 05, 2024

Introduction

In Japan, liquid medication containers are routinely used in clinical practices. Medical facilities and pharmacies often handle liquid medication containers used for oral-dose liquid medication, used for prevention and treatment of illnesses, and topical-dose liquid medication (disinfectants for prevention of infection).

Oral-dose liquid medication allows flexible dose level adjustment and this formulation of medication has been most frequently adopted for pediatric oral medication in Western countries.[1-3] In Japan, on the other hand, powder is a frequently used formulation of medication for children. During the neonatal and infantile periods, powdered medication is dissolved or suspended in water immediately before oral administration.[1] In Japan, medical care for symptoms, such as a cold and allergy, is also covered by the national health insurance (NHI), and drugs, such as antipyretics, antitussives, expectorants and adrenocortical steroids, are prescribed for patients complaining of such symptoms, with the costs covered by the NHI. Furthermore, in many local communities, the healthcare expenses for children before graduation from junior high school, or before graduation from senior high school in some local communities, covered by public funds. Those complaining of symptoms of a cold or allergy often visit general practitioners as outpatients. For children from the pre-school age to low grades of elementary school, the antipyretics, antitussives, expectorants, and adrenocortical steroids are often prescribed in the form of oral-dose liquid medication, which allow easier dose level adjustment, rather than powdered medication.

Basic matters related to the method of dispensing oral-dose liquid medication and other prescription drugs in Japan have been set forth in the Dispensing Guidance issued by the Japan Pharmaceutical Association. However, accurate ways of dispensing vary among medical facilities and pharmacies. In case of oral-dose liquid medication such as antipyretics and expectorants often used for pediatric patients, the pharmacists often subdivide the liquid from a 500-mL glass container into smaller plastic containers and provides the subdivided liquid after dilution in a volume needed for a given patient. In Japan, the oral-dose liquid medication is orally taken by roughly two methods: (1) the volume to be taken per dose (mL) is shown to the patient or his/her family, accompanied by instructions to measure this volume of the liquid with a cup or spuit (syringe); and (2) the dispensing pharmacist adds water to the liquid medication container up to the printed or embossed indicator line, followed by giving an instruction to the patient or his/her family to measure the liquid in a volume equivalent to one scale marked on the container (= volume to be taken per dose). Concerning syrup preparations, it has been reported that 66.4% of the facilities in Japan are providing syrup preparations after dilution corresponding to the graduations marked on the liquid medication container,[4] indicating that the widely adopted method of measuring oral-dose liquid medication in Japan is the one using the graduations marked on the liquid medication containers. Under the NHI healthcare service reimbursement system in Japan, there is a provision: "The drug containers used for medication are lent from the NHI-covered medical facilities to patients, as a rule. If they desire, they can purchase the container at the actual cost. However, if they have returned the container concerned and the main part of it can be re-used, the cost paid for the container needs to be refunded."[5] In this connection, a notification issued in the past from the Ministry of Health and Welfare (currently the Ministry of Health, Labour and Welfare) states: "If a reusable container, regardless of its material, has been returned by the patient, the NHI-covered medical facility (including the NHI-covered pharmacy) is required to refund the container's cost having been collected from the patient at the time of its return. It is not acceptable to collect the cost of the non-reusable container from the patient when the container is given to the patient."[6] At present, the actual cost of the plastic liquid medication container can be billed to

the patient only when the patient explicitly desires the container and, even when the patient desires the container, the medical facility or pharmacy often avoids billing the container's cost for the reason of procedural complexity or within the framework of patient services. It is plausible to imagine that many of the NHI-covered medical facilities and pharmacies, which do not bill the cost of the containers given to patients, are selecting the containers to be adopted through laying more emphasis on the price of the containers from wholesalers than on the usability or functionality of the containers. However, the usability and functionality of containers are closely related to the probability for accurate measurement of the liquid medication and hence associated with under- and over-doses of liquid medication through erroneous measuring. In Japan, no definite guidelines are available concerning not only liquid medication containers but also the measurement scales on the containers (e.g., cup and spuit), and the judgment about them has been assigned to NHI-covered medical facilities and pharmacies. It is unknown whether the measurement scales on the liquid medication containers are appropriate ones and are easy to use by parents, guardians or children.[7]

It has been reported that the incidence of erroneous drug administration to children by parents or guardians was much higher with the use of cups than with the use of spuits, spoons or syringes[8] and that many of the preventable adverse events related to medication in pediatric outpatients were often attributable to erroneous drug administration.[9] Furthermore, errors in administering liquid medication to children by parents or guardians have been occurring frequently, and it has been suggested that the practice of measuring the liquid with the use of a syringe and educational intervention for guardians are useful in reducing errors in liquid medication administration.[10] Although the circumstances surrounding the selection of liquid medication containers and measuring devices differ greatly between Japan and other countries, there are few published report concerning evaluation of the usability of different forms of liquid medication containers when used for the liquid medication dosing practice specific to Japan, i.e., the practice of adding water to the liquid medication container up to the printed or embossed indicator line at the pharmacy, followed by giving instructions to the patient or his/her family to orally take the liquid in a volume equivalent to one scale of the graduations marked on the container (= volume to be taken per dose).

The present study was undertaken to evaluate the ease of use of several kinds of liquid medication containers and measuring devices during experimental measuring of phantom drug solution by male and female adults having experienced with measuring liquid medication for their children before. The study was additionally designed to evaluate the extent of knowledge about the CR (child resistance) caps, a CR cap relatively unfamiliar in Japan, and the ease or difficulty in removing such a cap.

Material and methods

Study design

Collaborators for this study were recruited from inhabitants at Izumi Ward and Totsuka Ward of Yokohama City. Each collaborator was asked to open the cap of each liquid medication container (Containers A through D) and to record the time taken for measuring the liquid from the container into the cup in a volume equivalent to a single dose (one scale). After the liquid was added to the cup, the collaborator was asked to fill in the questionnaire. In addition, a questionnaire survey was conducted also concerning the CR cap opening time and the awareness about CR caps. In cases where the CR cap could not be opened in 30 seconds, explanation was given with the use of a leaflet attached to the CR cap and the time taken for opening the CR was recorded again.

Study population

This observational study of liquid medication containers and measuring devices was carried out by the Yokohama University of Pharmacy. The survey involved the individuals who, as guardians for their children, had experienced with measuring liquids from liquid medication containers to administer them to their children.

Liquid medication containers, measurement scale, and drug solution

Containers A through F were liquid medication containers (30 mL) of the same manufacturer. The drug solution tested was simple syrup JP (Kenei Pharmaceutical Co., Ltd., Osaka City, Osaka Prefecture, Japan). Of all test containers, only Containers A through D were used for measuring the liquid. In case of Containers A and B, the collaborator removed the cap, and the liquid was poured directly from the container into the cup in a volume equivalent to one scale. In case of Container C, the liquid was added to the cup with the use of a measuring spuit. In case of Container D, the liquid was poured the cup with the use of spuit integrated with the cap. Container A was the same as Container C, both having the same cap, but the way of measuring the liquid differed between these containers (Container A: direct measurement, Container C: measurement with the attached spuit).

Collaborators were told in advance that if an excess volume of the liquid has been added to the cup, the excess liquid may be returned to the container at their own discretion (they were told that if they used to decide returning the excess liquid from the cup into the container during their past attempts of administering liquid medication to their children, they are permitted to do such a returning procedure also in this study). Container D had a cap that was the same as that of Containers A and C except that the cap of Container D was integrated with the spuit. Container E had embossed graduations and was used only for the questionnaire survey. Container F was the same as Container E except for the cap design (the CR cap was adopted for Container F), and each collaborator actually performed the cap-opening test with this container (Figure 1, Table 1, 2).

Questionnaire

Table 2 shows the contents of the questionnaire.

Survey period

The survey was conducted between November 2022 and January 2023.

Data analysis

Statistical analysis employed JMP ver.14.3.0 (SAS Institute Inc.).

Ethical review

This study was started after having been reviewed and approved by the Yokohama University of Pharmacy Clinical Study Ethics Committee ("Protocol # C22002A" as per the updated guidelines of the Declaration of Helsinki (64th WMA General Assembly, Fortaleza, Brazil, October 2013). Informed consent was obtained in writing from each collaborator prior to the study.

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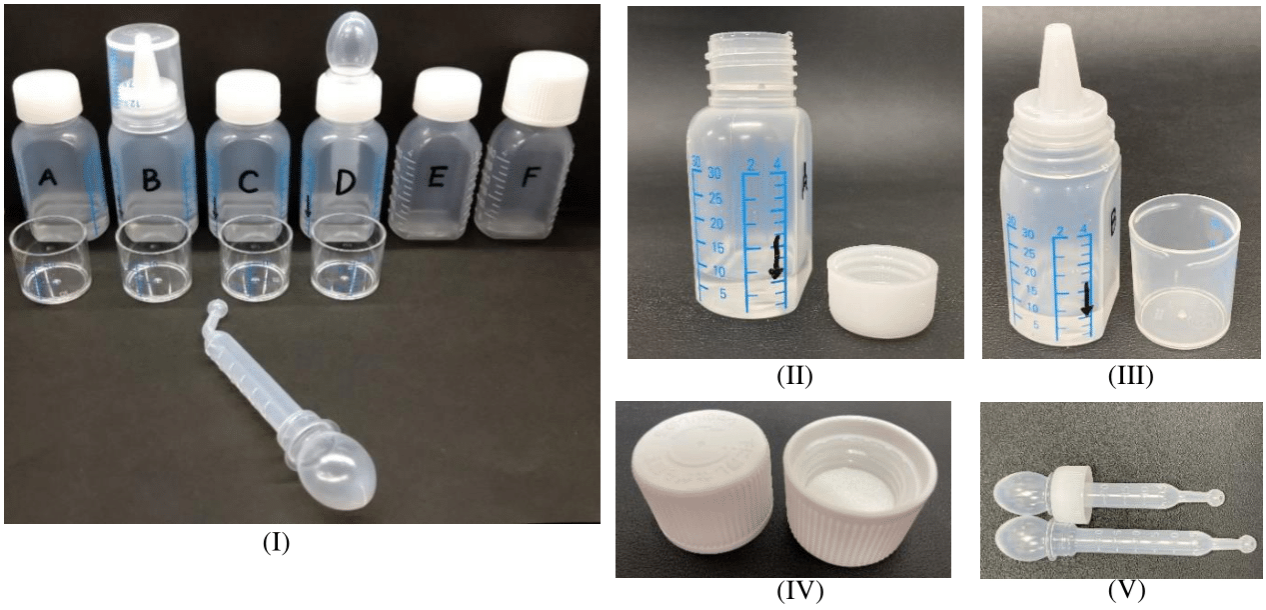

Figure 1 Liquid medication containers and measurement scale used.

(I) Containers used (A-D: Each collaborator measured the liquid using the cup shown in front of the container in a volume equivalent to one scale of graduation; C: Measured into the cup using the spuit shown in front of the container) ; (II) Each collaborator measured the liquid in a volume equivalent to one scale of graduations from the container filled with the liquid in a volume equivalent to 3 scales of graduations marked with the arrow. ; (III) Container B's nozzle and cap; (IV) CR cap; (V) (Lower): Spuit for use in measuring from Container C, (Upper): Spuit integrated with the cap for Container D

Table 1 Characteristics of liquid medication containers and measurement scale

Container	Opening upon cap removal	Graduation on container surface	Measure using cup	Material	Manufacturer's price for a minimum package unit (excluding tax)
A	Wide	Printed	Directly from container	Container: Polypropylene (PP) Cap: polyethylene (PE)	35 Yen/piece (including cap)
B	Inner stopper nozzle	Printed	Directly from container	Container & Cap: Polypropylene (PP) Inner stopper: polyethylene (PE)	59 Yen/piece (including cap)
C	Wide	Printed	With an attached spuit (capacity 3 mL, with embossed graduations at intervals of 0.5 mL)	Container: Polypropylene (PP) Cap: polyethylene (PE) Spuit: Low Density Polyethylene (LDPE)	Container: 35 Yen/piece (including cap) Spuit: 30 yen/piece
D	Wide	Printed	With a spuit integrated with cap (capacity 2 mL, with embossed graduations at intervals of 0.5 mL)	Container: Polypropylene (PP) Cap: polyethylene (PE) Spuit: Low Density Polyethylene (LDPE)	48.2 Yen/piece (including spuit integrated with cap)
E	Wide	Embossed	-	Container: Polypropylene (PP) Cap: polyethylene (PE)	25 Yen/piece (including cap)
F	Wide	Embossed	-	Container: Polypropylene (PP) CR cap Outer cap: polyethylene (PE) Inner cap: Polypropylene (PP)	41 Yen/piece (including CR cap)

a) 1 The capacity of each container is 30 mL.

b) 2 Inner diameter of the opening of Container A, C, D, E and F upon cap removal: 1.9 mm (actually measured)

c) 3 Cup: Capacity 10 mL, 22 Yen/piece (excluding tax)

d) 4 The top of CR cap carried the following embossed information

   i. Arrow in direction of cap opening "Rotate while compressing downwards"

   ii. Arrow in direction of cap closing "Fasten tight"

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Table 2 Questionnaire for collaborators

I. Usability of Containers A to D * NRS: Numeric Rating Scale
- a. Ease of measuring the liquid (NRS)
- b. Ease of cap opening/closing (NRS)
- c. Do you think this container allows hygienic handling? (NRS)
- d. Free comments (advantages)
- e. Free comments (disadvantages)
- f. Free comments (improvement-requiring points)

II. Most easily usable container among Containers A to D (comprehensive evaluation of shape/manipulability of container and measurement scale, easy to measure) and reason for selection (free comments)

III. Among Containers A to E, which is more desirable in terms of graduations?
Reason for your selection (free comments)

IV. Between Containers C and D, which is more desirable in terms of spuit?
Reason for your selection (free comments)

V. Containers A to E
- a. Containers you have handled before (multiple answers acceptable)
- b. 2. Container you had handled most frequently before (one container to be selected)

VI. Please answer the factor(s) determining the ease of using liquid medication containers (NRS)
- a. Graduations on the container surface
- b. Shape of the container
- c. Presence/absence of inner stopper nozzle
- d. Shape of the cap
- e. Ease of cap opening/closing

VII. Please answer the following questions about the Container F's CR (Child Resistance) cap
- a. Do you know what the CR cap is?
- b. Have you used any CR cap before?
- c. Do you want to use the CR cap from now on?
- d. Free comments (advantages)
- e. Free comments (disadvantages)
- f. Free comments (correction-requiring points)

Results

Collaborators

During this study, evaluation was made by 40 collaborators. Of all collaborators, 90.0% (36) were female and 10.0% (4) were male. Their median age was 45 (IQR: 41.3-49.0). The median pinching power of the dominant hand of collaborators was 13.3 kg (IQR: 11.1-17.0).

Parameters of measuring the liquid from liquid medication containers

Time taken for measuring

The median time spent by collaborators for measuring the liquid from liquid medication containers was 22 seconds (IQR: 19.25-28) for Container A, 28.5 seconds (IQR: 21-40) for Container B, 34 seconds (IQR: 29-39.75) for Container C and 33.5 seconds (IQR: 25-45) for Container D. There was no correlation between the age of collaborators and the time spent for measuring the liquid from each container or between the pinching power and the time spent for measuring the liquid from each container (Table 3).

Other parameters

Of the 40 collaborators, 4 spilled the liquid during the measuring procedure. There was no collaborator who spilled the liquid from two or more containers. Spilling occurred during measuring from Container C by 3 collaborators and from Container D by one collaborator. Of the 40 collaborators, 10 returned the excess measured liquid into the container. There was no collaborator who returned the excess measured liquid into two or more containers. Returning of the excess measured liquid was done into Container C by 6 collaborators, into Container D by 3 collaborators and into Container A by one collaborator.

Table 3 Correlation of age and pinching power to the time taken for measuring from each container (Spearman's rank correlation coefficient)

vs.	Time taken for measuring from each container							
	A		B		C		D	
	rs	P	rs	P	rs	P	rs	P
Age	0.1	0.538	0.037	0.822	0.155	0.341	0.027	0.867
Pinching power (Kg)	0.1	0.539	-0.175	0.282	-0.094	0.565	0.015	0.927

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Usability of Containers A through D

Figure 2 shows the results of liquid medication container usability evaluated by the collaborators. In evaluation of "ease of measuring the liquid," the median numeric rating scale (NRS) score was highest (7.5) with Container C, followed by Container D (7), Container B (6) and Container A (5). This score differed significantly between Container A and B, between Container A and C, and between Container A and D. In evaluation of "ease of cap opening/closing," the median NRS score was highest with Container A and B (6.5), followed by Container D (6) and Container C (5.5). This score did not differ significantly between any two of the containers. To the inquiry "Do you think this is a container allowing hygienic handling?", the median NRS score was highest with Container D (8), followed by Container B (7), Container A (5) and Container C (4.3). This score differed significantly between Container A and D, between Container B and C, and between Container C and D (Figure 2). Table 4 gives the free comments of collaborators about each container. On each container, positive, negative and correction-requesting comments were given.

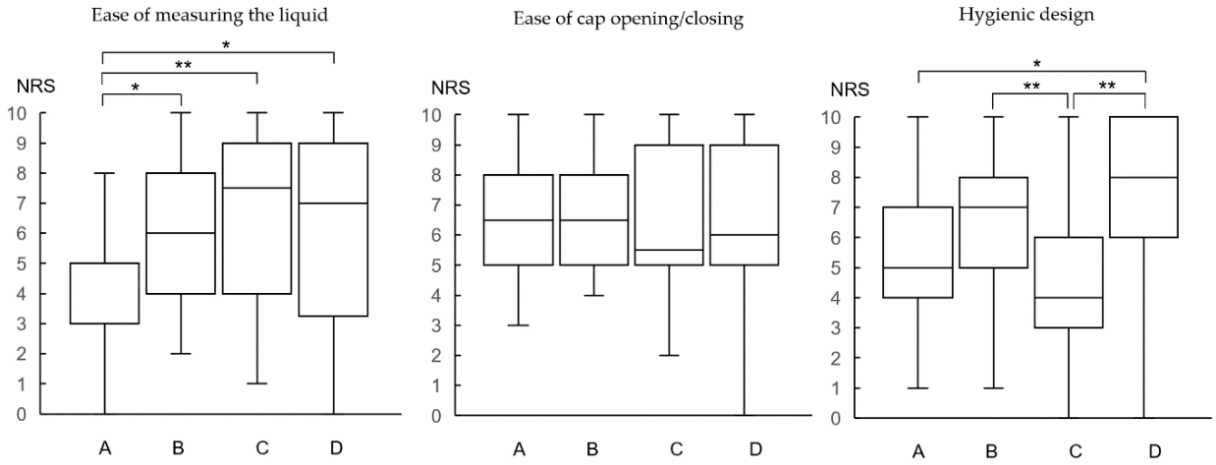

Figure 2 Evaluation of usability of liquid medication containers.

Median score of Container A in evaluation of "ease of measuring the liquid" is 5 (n=40, Steel-Dwass test **P<0.01, *P<0.05).

Table 4 Free comments of collaborators about each container

	Positive comments (number of collaborators)	Negative comments (number of collaborators)	Correction-requesting comments (number of collaborators)
Container A	• Easy to measure (8) • Easy to open/close cap (6) • Simple and easy (5) • Dripping unlikely (2) • Spilling unlikely (2) • Can be measured at once (1) • Error in measuring unlikely (1) • Compact (1)	• Troublesome with the need of checking container's graduations repeatedly (14) • Spilling likely (7) • Cannot return the liquid (6) • Excess measuring likely when in a hurry or depending on the liquid type (5) • Not hygienic (5) • Concerned with dripping (2) • Upon falling over, the content is lost at once (1) • Difficult to use (1)	• Should be designed so that the liquid goes out little by little (1)
Container B	• Easy to adjust each droplet (17) • Massive spilling unlikely (11) • Nozzle allows easy measuring (8) • Hygienic (4) • Cap large and easy to open (2) • Even a child can use (2) • Easy to carry (2) • Dripping unlikely (2) • Can feel assured with tight cap closure (1) • Simple (1)	• Difficult to return the liquid (19) • Time-consuming (17) • Container-compressing power needed (9) • The volume is changed by the liquid falling from the nozzle into the container (6) • Cap too hard to allow easy opening/closing (5) • Not hygienic (3) • Difficult to understand how to open the cap by rotating (2) • Liquid goes out just by placing the container upside down (1) • Cannot read the graduations unless the container is placed on desk (1) • Cap is likely to open without intention (1) • Difficult in placing (1)	• A type of cap which can be closed in a snapping motion is desirable (2) • Easier to measure if graduations can be read also in an upside-down position (1)

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Table 4 Continued...

	Positive comments (number of collaborators)	Negative comments (number of collaborators)	Correction-requesting comments (number of collaborators)
Container C	• Can measure accurately (14) • Can read graduations while placing the container on desk (12) • Child can play with the spuit (1) • Can compress the spuit with small power (1) • Spuit carries graduations on surface (1) • Can place the liquid directly from spuit into mouth (1) • Easy to aspirate the drug (1) • Spuit is large (1) • No fear of spilling (1) • Spuit is light (1)	• Difficult in finding a place for storage after use (29) • Troublesome (14) • Liquid cannot be completely pushed out from spuit (7) • Difficult to read graduations due to the bubbles going out from the spuit (6) • Spuit is likely to be lost (3) • The compressing part of spuit is hard and difficult to compress (2) • The spuit tip is curved, making it difficult to push out the liquid (2) • Container is difficult to hold unless it is inclined (2) • Small adjustment difficult (2) • Increasing the waste (2) • Time-consuming (2) • Not hygienic (2) • Much time taken until the spuit restored its original shape after being compressed (1) • Cannot understand the need of spuit (1) • Take some time until becoming familiar (1) • Graduations difficult to read (1)	• More convenient if liquid can be taken with a single push (1) • More convenient is the spuit can stand on itself (1)
Container D	• Hygienic (25) • East to carry (23) • No difficulty in storage (23) • Easy to measure (11) • Small adjustment easy (7) • Time-saving (7) • Can read the graduations while placing the container on desk (4) • Spuit-washing can be saved (4) • Easy is cap opening/closing (2)	• Spuit cannot reach the bottom of container (11) • Difficult in measuring (9) • Causing a feeling of being caught (6) • Troublesome (6) • Graduations difficult to read when bubbling (4) • Liquid remains lightly within the spuit (4) • Dripping likely (3) • Container likely to fall over when the cap is closed (1) • Much time taken until the spuit restores its original shape after being compressed (1) • Spuit tip is round, making aspiration difficult (1) • Some power needed when aspirating the liquid with the spuit (1) • Not ecologically friendly (1) • Not hygienic (1)	• More convenient if the liquid can be taken out by a single action (4)

Most easily usable container among Containers A through D (comprehensive evaluation of the shape, manipulability and easy to measure of the container and the measurement scale)

All of the 40 collaborators answered the question about the most easily usable container. Container B was answered most frequently (40.0%, 16 collaborators), followed by Container D (37.5%, 15 collaborators), Container C (12.5%, 5 collaborators) and Container A (10.0%, 4 collaborators). Thus, 77.5% of all collaborators selected Container B or D as the most easily usable container. In this procedure during which each collaborator was asked to select one out of the Containers A though D as "the most easily usable container," there was no significant difference in the representative value of age or pinching power between any two of the collaborator groups having selected each container (A, B, C or D) (Kruskal-Wallis test: age $p=0.14$, pinching power $p=0.59$).

Table 5 shows the free comments about "the most easily usable container" selected by individual collaborators.

Table 6 shows the coefficient of correlation of age and pinching power with each parameter of the liquid medication containers (ease of measuring the liquid, ease of cap opening/closing, and hygienic design). For Container D, a weak negative correlation was noted between age and ease of cap opening/closing.

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Table 5 Free comments on "the most easily usable container" selected by individual collaborators

	Positive comments (number of respondents)
Container A	• Liquid can be orally taken smoothly without trouble (1) • Easiest in returning the excess measured liquid (1) • Familiar with its use (1) • Accurate measuring possible (1)
Container B	• Small adjustment easy (9) • Spilling unlikely (7) • Nozzle allows easy measuring (5) • Unlikely to lose the measuring cup (3) • Cap is large and easy to grip (3) • No fear of dripping (3) • Hygienic (2) • Better if the liquid does not go out unless the container is compressed in an upside-down position (1) • Better if the nozzle is shortened and designed to allow the liquid to go out while placing the container upside down (1) • Better if returning the excess measured liquid more easily (1) • Power not needed (1)
Container C	• Easy to use because measuring is possible while reading the graduations (2) • Small adjustment easy (2) • Better if designed to reduce the likelihood for losing the spuit (1) • Easy to measure (1) • Easy to administer the liquid to the patient (1) • Hygienic (1)
Container D	• Spuit can be stored together (9) • Hygienic (8) • Dripping less likely than the spuit of Container C (7) • Easy to measure (7) • Convenient because measuring can be done at once (5) • No need of washing the spuit (4) • No fear of spilling (1)

Table 6 Coefficient of correlation of age and pinching power with each parameter evaluated (Spearman rank correlation coefficient) (n=40)

vs.			**r**	**P**
Age	**Ease of measuring the liquid**	A	0.0069	0.9665
		B	-0.0744	0.6484
		C	-0.1088	0.5041
		D	-0.2837	0.0761
	Ease of cap opening/closing	A	-0.0804	0.6217
		B	-0.2996	0.0604
		C	-0.1088	0.5041
		D	-0.3208	0.0465
	Hygienic design	A	-0.1446	0.3732
		B	-0.0159	0.9234
		C	-0.037	0.8232
		D	-0.2832	0.0806
Pinching power (kg)	**Ease of measuring the liquid**	A	0.1077	0.5083
		B	0.1974	0.222
		C	0.0057	0.972
		D	0.0887	0.586
	Ease of cap opening/closing	A	0.1022	0.5303
		B	0.0515	0.7521
		C	0.0681	0.6844
		D	-0.0275	0.8682
	Hygienic design	A	0.0081	0.9603
		B	0.019	0.9085
		C	0.269	0.0977
		D	0.0085	0.9593

More desirable graduations

When Container A (printed graduations) was compared with Container E (embossed graduations), 90.0% (36 collaborators) selected Container A as more desirable, 7.5% (3 collaborators) selected Container E as more desirable, and 2.5% (1 collaborator) made a neutral answer (both acceptable). Comments given to Container A included "colored graduations are easily visible" (32 collaborators), "visible without relying on illumination" (28 collaborators) and "ease of visualization is unlikely to be affected by the features of the liquid contained" (2 collaborators). Comments to Container E included "graduations likely to be read erroneously when busy" (5 collaborators), "graduations are not visible by elderly people" (5 collaborators), "want to judge the graduations by pressing the surface with nail" (1 collaborator) and "no fear of disappearance of graduations" (1 collaborator).

More desirable spuit

When Container C (with a spuit provided separately) was compared with Container D (with a spuit integrated with the cap), 60.0% (24 collaborators) selected Container D as more desirable and 37.5% (15 collaborators) selected Container C as more desirable. The remaining 2.5% (1 collaborator) made a neutral answer (both acceptable).

Comments given to Container C included "not affected by the drug volume because the spuit can reach the bottom" (6 collaborators), "easy to measure" (6 collaborators), "easy to manipulate" (3 collaborators), "no need of declining the container" (1 collaborator) and "hygienic" (1 collaborator). Comments given to Container D included "no trouble in finding a place for storage after use" (17 collaborators), "hygienic" (17 collaborators), "no need to wash" (3 collaborators), "no fear of losing" (3 collaborators) and "easy to measure" (1 collaborator).

Containers handled before

Collaborators were asked to answer about the containers they had handled before among Containers A through E, allowing them to make multiple answers. Container A were answered by the largest number of collaborators (39/40, 98%), followed by Container C (20/40, 50%), Container B (8/40, 20%), Container E (7/40, 17.5%) and Container D (3/40, 7.5%).

Container handled most frequently by individual collaborators

When asked to answer about the container handled most frequently before among Containers A through E, Container A was answered by the largest number of collaborators (29/40, 72.5%), followed by Container C (8/40, 20%), Container E (2/40, 5.0%), Container D (1/40, 2.5%) and Container B (0/40, 0%).

Factors determining the ease of using liquid medication containers

When rated with NRS, the median score was highest at 7.8 with "1: Graduations on the container," second highest at 7.2 with "5: Ease of cap opening/closing," followed by 6.0 with "3: Presence/absence of inner stopper nozzle," and 5.4 with "2: Shape of the container" and "4: Shape of the cap" (Figure 3). The score did not differ greatly between any two of "2: Shape of the container," "3: Presence/absence of inner stopper nozzle", and "4: Shape of the cap."

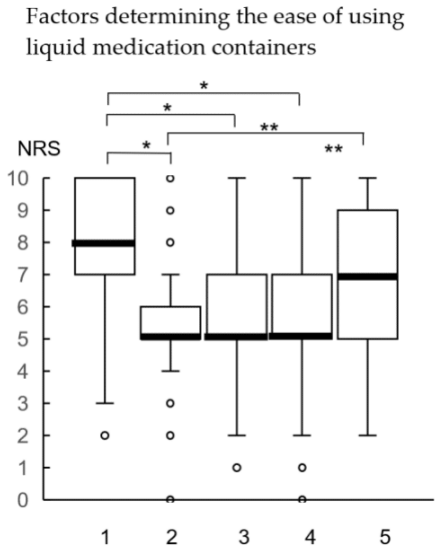

Figure 3 Factors determining the ease of using liquid medication containers (n=40, Steel-Dwass test **P<0.001, * P<0.01).

CR caps

Recognition of CR caps

To the question "Do you know what a CR cap is?" (n=40), 22.5% (9/40) answered "Yes, I do." The answer to this question was "Yes" by 7 of the 30 collaborators aged 40-49 (these 7 collaborators accounting for 18.0% of the entire study population) and 2 of the 5 collaborators aged 30-39 (accounting for 5.0%). All collaborators at age 20-29 (1 collaborator) and 50-59 (4 collaborators) answered "I don't know." Thus, the extent of knowledge about the CR cap was low.

After the CR cap was presented, each collaborator was asked "Have you used any CR cap before?" (n=40). To this question, 30.0% (12 collaborators) answered "I have used it." The answer to this question was "Yes" by 9 of the 30 collaborators aged 40-49 (these 9 collaborators accounting for 22.5% of the entire study population) and 3 of the 5 collaborators aged 30-39 (accounting for 7.5%). All collaborators at age 20-29 (1 collaborator) and 50-59 (4 collaborators) answered "I have never used it."

Time taken to open the CR cap

Without given any particular explanation in advance, individual collaborators were asked to open the CR cap, and the time taken for opening was measured. Of the 40 collab-orators, 29 were able to open the cap in 30 seconds and 11 were unable to open it in 30 seconds. The median time taken for opening the cap was 8 seconds (IQR: 6.5-15) among the 29 collaborators who were able to open the cap in 30 seconds. Between the group having successfully opened the cap in 30 seconds and the group having failed to do so, there was no significant difference in the pinching power, but there was a significant difference in age (Wilcoxon rank sum test, p=0.0494).

The 11 collaborators having failed to open the cap in 30 seconds were asked to open the cap again after a leaflet was presented to them. In the second attempt, 10 out of these 11 collaborators were able to open the cap in 30 seconds. The median time taken for opening the

Citation: Murata M, Yoshida Y, Hamada M, et al. Evaluation of easy-to-use containers for liquid medication. *Pharm Pharmacol Int J.* 2024;12(2):50–60. DOI: 10.15406/ppij.2024.12.00432

cap was 8 seconds (IQR: 6.75-11.25). One collaborator (age 40-49, pinching power 10.0 kg) took 58 seconds to open the cap.

About CR caps

To the question "Do you want to use the CR cap from now on?" (n=40), 55.0% (22 collaborators) answered "Yes, I want to use it" and 42.5% (17 collaborators) answered "No, I don't want to use it." The remaining 2.5% (1 collaborator) gave no answer. The answer to this question was "Yes" by 17 of the 30 collaborators aged 40-49 (these 17 collaborators accounting for 42.5% of the entire study population), 3 of the 5 collaborators aged 30-39 (accounting for 7.5%), 2 of the 4 collaborators aged 50-59 (accounting for 5.0%) and none of the 1 collaborator aged 20-29 (accounting for 0.0%).

Table 7 shows the free comments given to the CR cap.

Table 7 Comments on the CR cap

Positive comments (number of respondents)	Negative comments (number of respondents)	Correction-requesting comments (number of respondents)
• Safe as it can prevent erroneous drug intake (32) • Cannot be opened without an adult's power (3) • Cap is large and easy to open (3) • No fear of spilling (2) • Very good as the cap cannot be opened if fastened tight (1) • Easily understandable as explanation is given on the cap surface (1) • Cap is large and its erroneous intake can be prevented (1) • Looks easy to carry (1)	• Difficult to open even after reading the explanation (10) • Occasionally difficult to open depending on the way of closing or power application (6) • Irritating when busy (6) • Cannot be opened unless getting a hang of it (6) • Clock sound is loud (6) • Unnecessary if it is not free of charge (4) • Looks difficult to open by elderly people (3) • Difficult to understand how to open it (3) • Even a child can open it if having got a hang of it (2) • Difficult to use because of idling (2) • Spilling likely (2) • Looks expensive (2) • Cap is likely to become broken if opened in a wrong way (1) • Power applied to the cap is likely to reach the container, possibly resulting in spilling (1)	• Correction needed to enable easier opening by elderly people and individuals with less power (8) • Easier to understand is the letters printed on the cap are colored (6) • Explanation at pharmacy using a vacant container is desirable (1) • The printed information on how to use should be given in an easily understandable manner (1) • No need of this kind of cap if the user can take care of drug handling manner (5) • Unnecessary because child cannot reach this container if placed on the upper shelf of refrigerator (5) • A container unfamiliar in Japan (5) • The extra effort needed for this cap may be a stress to the user during busy time (4) • Its use desirable for containers of liquid dangerous if orally taken (4) • Nice for use in containers of powerful or dangerous drugs (4) • This kind of cap for prevention of accidents is desirable also for powered drugs (4) • Desirable if this kind of cap is generally accepted for various objects not confined to drugs (4) • More friendly if explanation on how to open is given sufficiently at pharmacy (1)

Discussion

Regarding the containers used for dispensing oral-dose liquid medication in Japan, the present study was undertaken to evaluate the time taken for measuring the liquid from containers and the ease of using the containers, with the goals of exploring a desirable form of this kind of container and investigating the degree of recognition about the CR cap among general users and the ease/problems of opening the cap by such users.

According to a survey conducted at a national pediatric hospital in Japan about intake of oral-dose pediatric medication, powder was the most frequently used form of medication for patients less than age 6 years, and liquid (including syrup and suspension) was the second most frequent form of medication prescribed for such patients.[7] If a similar survey were conducted at general hospitals or clinics across the country, different results may be obtained. In Japan, for management of fever due to infections (cold, influenza) in pre-school age children, acetaminophen syrup is frequently prescribed, accompanied by other agents for symptomatic therapy such as carbocysteine syrup and tipepidine hibenzate syrup.

The present survey used simple syrup as a phantom drug solution, assuming the use of syrup preparations in clinical practice. The time taken by the collaborators for measuring this test liquid was shortest from Container A and second shortest from Container B. Containers A and B were designed to enable directly measuring the liquid from the container into the cup without using a spuit, thus simplifying the measuring procedure and shortening the time taken. Spilling of the liquid occurred only from Container C and D. As suggested in the free comments given by collaborators, liquid spilling from these two containers was probably attributable to dripping from the spuit, and the spuit's design (the ball is hard and does not resume its original form soon after compression). The trouble of measuring an excess volume of the liquid and returning the excess liquid into the container occurred much more frequently with Container C and D. This seems to be attributable to dripping of the liquid during aspiration with a spuit from the container. The spuit used for Container C and D was of a simple design for which high accuracy in measuring could not be expected. This kind of spuit was shown in this survey to be unsatisfactory in terms of basic functions (tending to cause dripping, and slow in resumption of the original form after compression due to the hard ball). As a result, accurate measuring in short time was difficult with this kind of spuit.

In evaluation by NRS of usability of liquid medication containers, the "ease of measuring the liquid" was higher with Containers B,

C and D than with Container A. The "ease of cap opening/closing" did not differ significantly between any two of the containers. The "hygienic design" score was high with Containers D and B. In the present survey, evaluation was not affected by the graduations marked on individual containers because the test was conducted under the same setting of graduations for all of Containers A through D. The shape of cap was the same for all containers except for Container B.

The time taken for measuring the liquid from each container did not correlate with age or pinching power of the collaborators. In analysis of the correlation of age and pinching power with the other parameters of container usability, the only correlation observed was a weak negative correlation between age and "ease of cap opening/closing" of Container D. The cap for Container D was the same as the cap for Containers A and C, but it has a built-in spuit at the center of the cap. As a result, the cap-opening procedure for Container D differs from that for Containers A and C. This difference and the lack of past experience of using this type of container may be associated with the finding obtained about Container D mentioned above.

When asked about "the most easily usable container (comprehensive evaluation)," the score was highest with Container B, followed by Container D. This result is not fully consistent with the findings about the median time taken for measuring and the other parameters of usability (ease of measuring the liquid, ease of cap opening/closing, hygienic design). Container B has a small diameter nozzle, while Container D has a spuit integrated with the container. Free comments given by the collaborators who selected Container B as the most easily usable container included "easy to make fine adjustments," "spilling unlikely," "simple nozzle design allowing easier measuring" and "large cap easy to grip." Free comments about Container D included "possible to store the spuit together with the container," "hygienic design" and "dripping less likely than Container C." These comments indicate that the collaborators attached importance to hygienic, accurate and careful measurement, i.e., to the features such as the availability of an auxiliary device (small diameter nozzle or integrated spuit) attached to the container for accurate liquid measurement, the ease of making minor adjustments for accurate liquid measurement, and the spuit's basic function associated with prevention of dripping. On the other hand, Container A was probably appraised low because of unavailability of an auxiliary device attached to the container for accurate liquid measuring. Collaborators found problems with Container A because the opening of this container is too wide to enable easy minor adjustments at the time of measuring the liquid although this container allows the most rapid measurement. Container B was found to have a problem in that the spuit used for this container was difficult to store in a hygienic manner. With Containers A and B, the liquid is placed into the cup directly from the container. Thus, the container is first put upside down to pour some volume of the liquid into the cup. The container is then put upright, and the volume in the cup is checked by reading the decrease in volume level on the graduations. By repeating this sequence of steps, the volume for a single dose (equivalent to one scale of graduations marked on the container) is measured. With Containers C and D, on the other hand, the container is kept upright and a spuit is placed into the container to measure the liquid. A free comment given by the collaborator who selected Container B says that it is desirable if Container B has graduations possible to read when the container is put upside side. When asked about the past experience of use, Container A had been used by the largest number of collaborators before (39 out of the 40 collaborators). The frequency of past use was also highest with Container A (29 collaborators). However, the containers used frequently were not necessarily the containers easy to use.

To the question "Which of Container A or E is more desirable in terms of graduations?", an overwhelming majority of the collaborators answered the print type graduations to be easier to read. To the question "Which of Container C or D is more desirable in terms of spuit design?", 60% of the collaborators selected Container D and 37.5% selected Container C. Regarding Container D, there was a comment that this container integrated with the spuit is hygienic and is easy to store. Regarding Container C, on the other hand, there was a comment that the spuit attached to this container can reach the bottom, thus allowing easy measuring without being affected by the volume of liquid contained. However, as mentioned above, the troubles of liquid spilling or the need of returning the excess measured liquid into the container occurred mostly with Containers C and D, and there were many comments pointing out the likelihood of dripping from the spuit tip or inability of aspirating the liquid from the container bottom. These comments seem to reflect the demand to a spuit design which is less likely to cause dripping and allows the tip to reach the bottom of the container.

In analysis of factors making the liquid medication containers easy to use, the NRS score was highest with "graduations on the container" (median: 8) and second highest with "ease of cap opening/closing." After these factors, "shape of the container," "presence/absence of inner stopper nozzle" and "shape of the cap" had similar scores (median: 5 each). These results suggest that greater importance was attached by the collaborators to the design of graduations needed for accurate measurement of the liquid to be administered, rather than to the functionality of the container itself.

Taken together, users in general are demanding liquid medication containers with printed graduations enabling more accurate measurement, being hygienic and easy to store.

According to the "Report on Monitoring of Hospitals about Health Hazards Related to Household Products in 2018" by the Ministry of Health, Labour and Welfare (MHLW),[11] the reports on erroneous oral intake by children (total 626 cases) most frequently pertained to cigarette (20.8%), followed by drugs/quasi drugs (17.4%). MHLW has informed medial facilities and pharmacies about the need of ensuring measures for prevention of erroneous intake of drugs by children,[12,13] accompanied by disseminating the relevant precautions to guardians by local communities and issuance of a proposal for promotion of CR container use.[13] At present, however, CR packages for pharmaceutical products have not been actively introduced in Japan. Also at insurance-covered medical facilities and pharmacies, CR packages/containers have not yet been actively used when providing the dispensed drugs in multi-divided portions in the forms of tablet, powder or liquid. The Japanese Pharmacopeia also has no provision about the testing method. concerning CR packages. To take an example of prescription drugs in the form of tablets, the press-through-pack (PTP) packages are now being used most frequently, and the form of bottle is very rare. There is no standard about PTP in the Japanese Pharmacopeia and this also serve as a hurdle against extensive adoption of CR packages/containers. Also for household products, CR packages/containers have been adopted only in limited products (e.g., disposable lighters) and have not yet been used for cleansers and other products used during daily living, except for a limited range of products such as imported products. Thus, from the viewpoint of consumers in Japan, there are few chances for them to handle CR packages/containers in their daily life.

To the question "Do you know what the CR cap is?", only 22.5% (9 collaborators) answered they knew about it. This result suggests that the term "CR (Child Resistance)" has not spread widely. When

no explanation was given in advance, opening the CR cap in 30 seconds was possible in 11 collaborators. The pinching power did not differ significantly between the group having successfully opened the CR cap and the group having failed to do so. However, age differed significantly between these two groups, suggesting that the older collaborators were less familiar with the CR cap. The results additionally suggest that the action of opening the cap by rotating while pushing has not become familiar in their daily life.

To the question "Do you want to use the CR cap from now on?", 55.0% of the collaborators answered "Yes, I want to use it" and 42.5% answered "No, I don't want to use it." Many of the collaborators having answered "Yes, I want to use it" gave a comment that this cap is safe because it can prevent erroneous intake, while the collaborators having answered "No, I don't want to use it" gave comments such as "difficult to open it even after reading the leaflet," "sometimes cannot be opened depending on the state of closure or the way of force application" and "making me irritated when busy." There was also a comment indicating the necessity of modifying the current design so that it can be opened easily even by elderly people or individuals with low physical power. What is functionally required to open the push-and-rotate type CR cap includes the pushing power and the rotating power. It seems necessary to review the current CR cap design, taking into account the physical characteristics of Japanese people.

Conclusion

The results of the present study indicate that the collaborators to this study attached importance to the accuracy in measuring the liquid, the ease of reading the graduations and the design allowing hygienic handling as the factors determining the most easily usable liquid medication containers. The results additionally show that the recognition of the CR cap among people is not high at present. Pharmacists and other healthcare professionals in Japan should pay attention to these findings and endeavor to facilitate extensive adoption of containers designed to enable accurate measurement of the liquid and to prevent erroneous drug intake by children from the viewpoint of safety management. Discussions are needed also about how to resolve the increased burdens on healthcare providers such as increase in the container-related expenses at medical facilities/pharmacies, and increase in the time needed for medication-related guidance such as guidance about how to use the container. At present, education for appropriate use of drugs and prevention of drug abuse is provided within the framework of compulsory education programs. In addition to these programs, educational campaigns are needed from now on also for prevention of erroneous intake of drugs and household products by infants and young children. In Japan, the tendency for population ageing and low birth rate has been increasing, with the percentage of elderly population to reach 35.3% in 2040 according to an estimate.[14] Now, active discussions are needed about packages and containers functioning as CRSF (Child Resistant & Senior Friendly) Packaging.

Acknowledgments

The authors would like to express their gratitude to all collaborators who participated in the survey. This work was supported by JSPS KAKENHI Grant Number JP21K02339.

Conflicts of interest

The authors declare no conflicts of interest.

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