Study of Child-resistant Packaging Technologies to Prevent Children from Accidental Ingestion of Drugs in Japan

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When handling high risk medications, such as anticancer agents, at home, it is necessary to take measures to prevent children from accidentally ingesting these drugs. In this study, we investigated pediatric characteristics such as literacy ability and finger function in Japanese subjects and examined the usefulness of child-resistant (CR) packaging technologies used in the U.S. when given to children in Japan. The survey covered 104 Japanese children aged 37–84 months. The results of the survey revealed that of the five types of CR packaging technologies, that which leveraged the differences in hand size and muscle mass between children and adults was effective against children aged 3–6 years. However, the CR packaging styles that rely on literacy, the ability to use tools, and the ability to perform complex operations are only applicable to children of a certain age. This suggests that the differences in the language, culture, and preschool education between Japan and the U.S. have a significant influence on pediatric characteristics. Based on the results of this study, it is possible to adopt CR packaging for Japanese children, which is expected to decrease the number of cases of accidental drug ingestion by children in Japan.

Key words—accidentally ingesting; child-resistant; packaging

INTRODUCTION

Accidental ingestion of certain drugs by children could exhibit serious symptoms in children and can even be fatal. In particular, when high risk drugs, such as anticancer agents, are stored at home, it is necessary to take measures to prevent children from accidentally ingesting them. The National Poison Prevention Week Council reported the death of 450 children from drug poisoning in the U.S. in 1962. Thus, the Poison Preventive Packaging Act of 1970 mandated the use of child-resistant (CR) packaging for certain drugs in the U.S. CR packaging is technology that makes it impossible for a child to easily access products that may cause accidents when used incorrectly, such as pharmaceuticals and lighters. The Poison Preventive Packaging Act states that CR packaging must prevent at least 85% of infants aged 42–51 months from opening drug packaging within 5 min. At the same time, CR packaging must allow 90% of adults aged 50 or older to open it within the same period. The U.S. Consumer Product Safety Commission conducted a survey in 2009 to characterize the usefulness of CR technology for drugs; the results showed that accidents caused by accidental ingestion of drugs by children decreased by one eighth after the introduction of CR packaging. In light of its proven effectiveness, CR packaging has since been mandated for certain drugs in countries such as the U.S., Canada, the U.K., France, Italy, Germany, Australia, New Zealand, and Korea.1–4 However, as of 2018, the use of CR packaging for pharmaceuticals has not been made mandatory in Japan. Consequently, according to a report released by the Consumer Affairs Agency and the Ministry of Health, Labour and Welfare, the number of reported drug accidents in children has continued to increase since 2006.5,6 In 2015, the ingestion of a drug became the most prominent cause of accidental injuries superseding the cigarette. Despite the warnings issued by the Ministry of Health, Labour and Welfare from 2013 to 2016 regarding accidental ingestion of drugs by children, the number of accidental injuries did not decrease and the issue of drug ingestion by children remains unsolved.

The main barriers preventing the introduction of CR packaging for drugs in Japan are the differences between the children in Japan and those in the U.S. and Europe in terms of the physical constitution, lan-
Table 1. 5 Categories of CR Drug-packaging Technologies That Are Currently Used in the World

| Category       | Characteristics of children | Child-resistant mechanisms                                                                 |
|----------------|-----------------------------|-------------------------------------------------------------------------------------------|
| Type A         | Hand strength               | The blister pack that cannot be pressed the tablet out unless it is strongly pressed.     |
| Type B         | Hand length                 | The carton designed not to be able to pull out the tray unless pressing two hooks at the top of the carton simultaneously. |
| Type C         | Literacy                    | The blister pack laminated with a plastic or paper film. The way to peel off is written on the surface of the package. |
| Type D         | Ability to use tools        | The heat seal pouch that cannot be opened without using scissors.                          |
| Type E         | Ability to perform multiple actions | The bottle that cannot be opened unless the cap is pushed down and turned simultaneously. |

Fig. 1. The Typical Diagrams for Each Type of CR Drug-packaging Technologies
guage use, and educational environment. Thus, CR drug-packaging technologies that are currently used in the U.S. are required to be re-examined and re-designed for their use in Japan. In this study, the CR drug-packaging technologies that are currently used in the U.S. are classified into five types (Table 1). The typical CR packaging diagrams for each type are shown in Fig. 1. These CR drug-packaging technologies take advantage of five infant characteristics to design packaging that can be opened by adults but not by children: hand strength, hand length, literacy, ability to use tools, and ability to perform multiple actions.

However, in Japan, these pediatric characteristics have not yet been studied and the usefulness of the CR drug-packaging technologies based on these characteristics in Japanese children has remained unexplored. Regarding the Type-E CR packaging technology, Hidaka et al. previously examined the usefulness for Japanese children, but the study was aimed at investigating the torque power of the cap, not the ability to perform multiple actions. Therefore, here-in, a survey of Japanese children was conducted to clarify the usefulness of these CR drug-packaging technologies for children in Japan.

METHODS

Participants A survey of pediatric characteristics was conducted for 104 children aged 37–84 months (3–6 years) in six nursery schools and kindergartens located in the Kanagawa Prefecture, Japan. The survey was administered during the period from October 2015 to March 2017. The consent of all subjects and their guardians was obtained.

Measures Survey Type A was conducted to measure the force with which a child pushes an object out of a blister pack. A load-measuring instrument, M875Z29-1 (Shiro Industry Co., Tokyo), was used to measure the pushing forces. While the subject was sitting on a chair, he or she was asked to place the thumb of his or her dominant hand on the load-measuring instrument placed on a desk to measure the maximum pushing force exerted by the thumb. Using a similar procedure, the subject was asked to place the palm of his or her dominant hand on the load-measuring instrument to measure the maximum pushing force exerted by the palm.

Survey Type B was conducted to measure the distance between two points that a child can simultaneously press with the thumb and the index finger. This characteristic is important for CR packaging that is opened by pushing down two points at the same time. A digital caliper, 19975 (Shinwa Rules Co., Ltd., Niigata), was used for the measurement. In this survey, each subject was asked to spread his or her hand to the maximum range. The maximum linear distance from the tip of the thumb to the tip of the index finger was measured.

Survey Type C was conducted to investigate whether each child can read words related to opening a package. In this survey, the following words were written in Hiragana Japanese syllabary characters in a 26-pt font: osu, hiku, mawasu, and hagasu, which mean push, pull, turn, and peel. Each child was shown the paper and instructed to read it aloud. A time limit of 3 min was set to read each word. The subjects who could read all the letters were judged to have literacy ability for that word.

Survey Type D was conducted to determine whether each child possesses the skill of using scissors, which is necessary for opening a heat seal pouch without a slit. The subject was instructed to sit on a chair and use a pair of scissors to cut along a straight line (width = 3 mm; length = 100 mm) marked on a paper. To avoid accidental injury, children’s safety scissors (Sun-Star Stationery Co., Ltd., Tokyo) with plastic blades were used. Each subject was given 5 min to complete the task, and children who were able to cut within a maximum distance of 20 mm from the drawn line were judged to possess this skill.

Survey Type E was conducted to determine whether each child could open a CR package that required complicated operations. Here, bottle-type test packaging was used; this type of packaging is opened by pushing down the cap while turning it down. In the survey, the procedure for opening a bottle-type package was first explained and the subject was then instructed to open the test packaging within a time limit of 5 min. The success rate of opening the packaging within this time frame was investigated.

Data Analysis The results obtained from the male and female subjects in each survey were compared using a chi-squared test with a significance level of $p < 0.05$. The analysis was performed with the SPSS software package (version 17.0; SPSS Inc., Chicago).

Ethics Committee and Informed Consent We conformed to the “Ethical Guidelines for Medical
and Health Research Involving Human Subjects”. This study was approved by the Josai International Education Ethics Committee (approval number: 40). Before conducting the survey, the purpose of this research was comprehensively explained to all subjects and conveyed in writing to their parents/guardians for obtain their consent.

RESULTS

The demographics of the subjects are summarized in Table 2. In total, 104 subjects (50 male (48.1%) and 54 female (51.9%)) surveyed. All subjects were healthy without paralysis of the hands or severe visual impairment.

Table 3 summarizes the results concerning the finger function. In the case of male subjects, the average thumb-pushing force was 8.0 ± 1.1 N for the subjects aged 37–48 months (3 years) and 17.7 ± 2.1 N for the subjects aged 73–84 months (6 years). On the contrary, in the case of female subjects, the average thumb-pushing force was 6.4 ± 0.9 N for the subjects aged 37–48 months (3 years) and 14.1 ± 1.7 N for the subjects aged 73–84 months (6 years). The average maximum linear distance from the tip of the thumb to the tip of the index finger when the hand was spread was 89.2 ± 6.1 mm for the male subjects aged 37–48 months (3 years) and 102.7 ± 9.6 mm for those aged 73–84 months (6 years). In contrast, in the case of female subjects, the same distance was 86.5 ± 5.6 mm for those aged 37–48 months (3 years) and 99.6 ± 8.8 mm for those aged 73–84 months (6 years).

Table 4 summarizes the survey results of the children’s literacy for words related to opening a package. None of the subjects aged 37–48 months (3 years) could read the word “push” and only 66.7% of the subjects aged 49–60 months (4 years) could read the word. Additionally, none of the subjects aged 37–48 months (3 years) could read the word “pull” and only 66.7% of the subjects aged 49–60 months (4 years) could read the word. Furthermore, none of the subjects aged 37–48 months (3 years) could read the word “turn” and only 66.7% of the subjects aged 49–60 months (4 years) were able to

Table 2. Number of Participants Divided by Gender and Age

| Age (month) | Number of boys | Number of girls | Total |
|------------|---------------|----------------|-------|
| 37–48      | 11            | 11             | 22    |
| 49–60      | 14            | 16             | 30    |
| 61–72      | 15            | 17             | 32    |
| 73–84      | 10            | 10             | 20    |
| Total      | 50            | 54             | 104   |

Table 3. Results of the Finger Function Survey

| Age (months) | Boys | Girls |
|--------------|------|-------|
|              | Maximal pushing strength of a thumb (N) | Maximal pushing strength of a hand (N) | Length from the tip of the thumb to the tip of the index finger (mm) |
| 37–48 (n=11) | 8.0 ± 1.1 | 31.9 ± 4.5 | 89.2 ± 6.1 |
| 49–60 (n=14) | 10.2 ± 1.5 | 39.5 ± 4.8 | 93.8 ± 6.9 |
| 61–72 (n=15) | 14.0 ± 1.8 | 48.5 ± 5.3 | 97.3 ± 7.5 |
| 73–84 (n=10) | 17.7 ± 2.1 | 55.9 ± 5.7 | 102.7 ± 9.6 |

Data are presented as mean ± S.D.

Table 4. Results of the Children’s Literacy Survey for Words Related to Opening a Package

| Age (months) | Number of children who can read the word “Osu” meaning “push” (%) | Number of children who can read the word “Hiku” meaning “pull” (%) | Number of children who can read the word “Mawasu” meaning “turn” (%) | Number of children who can read the word “Hagasu” meaning “peel” (%) |
|--------------|---------------------------------------------------------------|---------------------------------------------------------------|---------------------------------------------------------------|---------------------------------------------------------------|
| 37–48 (n=22) | 0 (0)                                                         | 0 (0)                                                         | 0 (0)                                                         | 0 (0)                                                         |
| 49–60 (n=30) | 20 (66.7)                                                     | 20 (66.7)                                                     | 20 (66.7)                                                     | 16 (53.3)                                                     |
| 61–72 (n=32) | 30 (93.8)                                                     | 32 (100)                                                     | 30 (93.8)                                                     | 28 (87.5)                                                     |
| 73–84 (n=20) | 20 (100)                                                      | 20 (100)                                                     | 20 (100)                                                      | 20 (100)                                                      |

All words are written in hiragana that are Japanese syllabary characters.
read the word. Moreover, none of the subjects aged 37–48 months (3 years) could read the word “peel” and only 53.3% of the subjects aged 49–60 months (4 years) were able to read the word.

Figure 2 shows the results of the survey on scissor skills. The success rate of straight cutting with scissors was 59.1% for the subjects aged 37–48 months (3 years), 86.7% for those aged 49–60 months (4 years), 100% for those aged 61–72 months (5 years), and 100% for those aged 73–84 months (6 years). Furthermore, no significant differences were identified between males and females of any age.

Figure 3 shows the results of the survey conducted to investigate the ability of the subjects to perform multiple actions simultaneously, i.e., a bottle-type test packaging that must be opened by turning the cap while pushing it down. The results show that 9.1% of the subjects aged 37–48 months (3 years), 66.7% of those aged 49–60 months (4 years), 87.5% of those aged 61–72 months (5 years), and 100% of those aged 73–84 months (6 years) could open the package within the allotted time. Furthermore, there were no significant differences between the male and female subjects of any age.

**DISCUSSION**

In this study, to investigate the types of CR packaging suitable for Japanese children, we conducted a survey of five pediatric characteristics in Japanese subjects. The results showed that the thumb-pushing force, which is used in Type-A CR packaging, generated by children was lower than that generated by adults. Normally, the operation of pushing a tablet out of a blister pack was mainly performed using the thumbs of both hands. Therefore, if the blister pack is designed such that the pressure necessary to remove the tablet from the packaging is twice as high or more than the force generated by the thumb of a child, it is considered to be difficult for the child to access the tablet. In this survey, for all age groups, the thumb-pushing force generated by male subjects was higher than that generated by female subjects. Thus, the value obtained by doubling the maximum value (including the S.D.) of the thumb-pushing force generated by male subjects should be used as the maximum extrusion pressure: ~19 N for children aged 37–48 months (3 years), ~24 N for children aged 49–60 months (4 years), ~32 N for children aged 61–72 months (5 years), and 40 N for children aged 73–84 months (6 years). The thickness of the aluminum foil in the design of Type-A CR packaging should be adjusted such that the force required to extrude the tablet is greater than or equal to this value depending on the target age. However, since the necessary extrusion pressure varies depending on the deformation of the blister pack at the time of extrusion and on the shape of the tablet, a CR package must be specifically designed for each blister pack product to have an appropriate extrusion pressure.

Next, we examined the effectiveness of Type-B CR packaging technology, which functions based on the distance between the outspread thumb and the index finger being shorter in children than in adults. In a Type-B carton package, a tray containing a blister package must be pulled out from a carton; however, it cannot be pulled out unless two hooks at the top of the carton are pressed simultaneously with the thumb and the index finger. Therefore, if the carton is
designed such that the distance between the two hooks is greater than the distance between the tips of a child’s thumb and index finger, it would be difficult for a child to open the package. In this survey, for all age groups, since the maximum linear distance between the thumb and index finger was greater in male subjects than in female subjects, the results from the male subjects (including the S.D.) were considered to represent the maximum linear distance between the thumb and index finger for each age group: around 96 mm in children aged 37–48 months (3 years), around 101 mm in those aged 49–60 months (4 years), around 105 mm in those aged 61–72 months (5 years), and around 113 mm in children aged 73–84 months (6 years). It is difficult to directly compare this characteristic in adults and children because no similar investigation of adults in Japan has been reported. However, as a reference, a study conducted by the Ministry of Economy, Trade and Industry reported that the average hand length (the distance of the line connecting the radius and the distal end of the styloid process of the ulna to the tip of the middle finger) is approximately 116 mm in children aged 49–60 months (4 years) and 170–200 mm in adults aged 20–64 years; this finding represents a difference of at least 50 mm between adults and children. Based on these findings, in the design of Type-B CR packaging, the linear distance between the two hooks should be larger than the maximum linear distance between the thumb and index finger in children of the target age.

Next, we examined the limited ability of children to use tools, such as scissors, as leveraged by Type-D CR technology. Usually, a heat-sealed package is made of plastic or aluminum foil and a tear notch is made to allow the package to be opened by hand. However, Type-D CR packages do not have such tear notches, so they cannot be opened without using scissors. In this study, we aimed to identify the age at which 85% or more of children cannot open a package using scissors. In this study, we found that Type-D CR packages can be opened by children of all ages (37–84 months or 3–6 years). Therefore, it is considered that Type-D CR packaging is not suitable to prevent drug ingestion by children in Japan. With regard to the scissors skills of children, the Nursery School Childcare Guidance Manual formulated by the Ministry of Education, Culture, and Sports indicates that children develop manual dexterity and can deal with scissors from around the age of 4 years. This is consistent with the results of the present study. Further, in Japanese nursery schools and kindergarten classes, it is common to teach children how to use scissors from the age of 3 years to prevent accidents caused by misusing children’s scissors. Therefore, it is presumed that a high percentage of children, even those aged 3 years, can use scissors.

Finally, we considered that children have a reduced capacity to accomplish two simultaneous actions, such as pushing and turning. This characteristic is used in Type-E CR packaging wherein a plastic bottle designed such that it cannot be opened unless the cap is rotated while being pushed downward. These two simultaneous actions cannot be easily performed by children, so they cannot open the bottle. According to
the results of this survey, more than 90% of children aged 37–48 months (3 years) were unable to open Type-E test packaging; however, more than half of those aged 49 months or older were able to open the package. Therefore, in Japan, Type-E CR packaging is considered to be effective only for children under the age of 48 months. Generally, it is believed that children acquire the ability to conduct coordinated movement with each finger around at the age of 48 months. Therefore, when designing CR packaging, it is necessary to select a CR technology that is appropriate to not only the target age group but also the dosage form.

Moreover, when designing CR packages, it is important to ensure that children cannot open them as well necessary to design such that they to be easily opened by elderly and handicapped people. It has been reported that blister-pack CR packaging, which requires a film to be peeled off before pushing the drug out (Type-C CR packaging), and bottle-type CR packaging, which opened by turning the cap while pushing it downward (Type-E CR packaging), cannot be easily opened by elderly and handicapped people.7, 10–15) For this reason, it is desirable to establish a universal CR design that can be easily opened, even by handicapped people, by offering an alternative opening method. Considering the elderly users, there is a standard for CR packaging testing in the U.S. that specifies that at least 90% of adults older than 50 years must be able to open the packaging within 5 min. However, in Japan, people are considered elderly at an age equal to or greater than 65 years. Thus, it is considered inappropriate to set a target age of over 50 years as a criterion for judging whether packaging can be easily opened by elderly people. Therefore, when introducing CR packaging technologies in Japan, it is considered that a specialized opening test is required for elderly people aged 65 years or higher and for handicapped people.

Herein, we investigated the pediatric characteristics relevant to the introduction of CR drug-packaging technologies in Japan. Based on the results of this study, it is possible to re-design CR packaging to be suitable for children in Japan. It is expected that this will lead to a decrease in the number of accidental drug ingestion accidents in children.

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Conflict of Interest  The authors declare no conflicts of interest associated with this manuscript.

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