

Original article

Ready-to-use introduction schedules for first exposure to allergenic foods in children at home

Background: The vast majority of children will undergo their first exposure to common allergenic foods at home. However, the first exposure may lead to clinical reactions. It has been proposed to introduce allergenic foods gradually into the diets of children at risk for food allergy, but no practical dietary advice has been devised.

Objective: The aim of this study was to devise safe introduction schedules for common allergenic foods for use at home, based on the challenge doses as administered in double-blind, placebo-controlled food challenge (DBPCFCs) in children who were never exposed previously to these foods.

Methods: Seventy-two DBPCFCs were performed in 63 children as a first known exposure. The incrementing challenge doses were converted into equivalent portions of these foods in their usual household form and incorporated in introduction schedules. The feasibility of the introduction scales was tested in parents of the children attending our clinic.

Results: Based on the results of the positive challenges (37) in which severe reactions did not occur, detailed introduction schedules and a reference photograph of the required increasing amounts of food were devised for use at home. Feasibility testing showed that, when using these introduction schedules, parents portioned the initial doses significantly lower than without detailed instructions.

Conclusions: The introduction schedules and reference photograph provide information for parents to introduce the required amounts of allergenic foods in initial low doses at home. This is expected to improve the safety of this procedure.

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The vast majority of children, including those who are at risk for food allergy, will undergo their first exposure to common allergenic foods, such as cow's milk, egg, peanut and tree nuts at home. However, it is known that the first exposure to foods may lead to clinical reactions, both in food challenge studies and uncontrolled conditions (1–5). Severe and potentially life-threatening reactions following such first exposures in uncontrolled conditions have been reported (1). In a study by Sicherer et al. (1) it was shown, that the majority of the initial reactions occurred at home (72%). Similar figures were found in the UK in children developing peanut allergy (6). While ideally all such children should undergo their first exposure to allergenic foods under medical supervision, or undergo skin testing and/or specific IgE determination for further risk stratification, it is clear that such a recommendation is

unachievable. The physician's assessment, taking account of the patient's age, co-existing asthma, and the food to be introduced (peanuts/nuts vs other foods) (7–9), may lead to the recommendation that introduction should either occur under medical supervision, or at home. Current guidelines recommend the introduction of these common allergenic foods gradually and individually into the diets of infants at risk for atopic disease (10), but no practical advice as to how this may be performed safely has been developed so far. Furthermore, little is known about the eliciting dose at first known exposure upon which safe dietary advice may be based. Thus, while medical supervision may be needed for children with the highest risk, providing guidelines with improved safety for home introduction of allergenic foods is equally important.

In general, the lower the dose, the less severe would be the symptoms (11). Therefore, the incremental scales of food challenges, provided that no severe reactions occurred, may serve as the basis for these introduction schedules for children who are eligible to be introduced at home.

The aim of this study was to devise safe introduction schedules for common allergenic foods for use at home, based on the challenge doses as administered in double-blind, placebo-controlled food challenge (DBPCFCs) in children who have never previously been exposed to these foods.

Methods

Study population

All children at high risk for food allergy, who consecutively attended our paediatric allergy clinic between January 2003 and June 2006 for the assessment of possible food allergy, and who had never knowingly ingested the food in question before, were included in this study.

Children at high risk for food allergy were defined as children with manifestations of atopic disease (asthma, allergic rhinitis, eczema, food allergy to foods other than the food in question), and/or with at least one first-degree relative with atopic disease, and/or having sensitization to food as assessed by skin prick tests (SPT) or specific IgE.

Because of dietary preventive measures, the children had been adhering to a diet from birth in which certain known allergenic foods (cow's milk, egg, peanut, hazelnut, soy or walnut) were avoided prior to this study. In some individuals, exposure to allergenic foods was even delayed until teenage. In all children, the dietary restrictions were imposed by other healthcare professionals or were initiated by the parents themselves in the past. Because of the uncertainty as to whether the foods that had been avoided so far would be tolerated, or because of positive SPTs or positive radioallergosorbent test (RAST) results for the avoided foods, introduction was postponed.

Elimination of the food in question was confirmed by an experienced dietician, as described previously (12). Information on sex, age, allergic symptoms, family history (number of first degree family members with atopic dermatitis, asthma, rhinitis or food allergy) was obtained. This study was exempted from medical ethical approval, as DBPCFCs in these children were performed as a routine diagnostic test.

Determination of sensitization

Sensitization to the allergenic food in question was determined by SPT with commercially available extracts (ALK-Abelló, Hørsholm, Denmark) and CAP-RAST (Phadia AB, Uppsala, Sweden) within 3 months prior to the DBPCFC. Skin prick tests were expressed both in mm and as Histamine Equivalent Prick (HEP) (13). The HEP-index is computed by dividing the size of the wheal of the SPT of the food tested (mm) by the wheal of histamine of the SPT (mm). Radioallergosorbent test-results of ≥ 0.35 kU/l and SPT-scores ≥ 3 mm were considered positive. Children showing either positive SPT or specific IgE or both to the food tested were considered to be sensitized to the food in question.

Food challenges

Double-blind, placebo-controlled food challenges with cow's milk, egg, peanut, soy, hazelnut and walnut were performed. Foods chosen for DBPCFC were those foods, which had been eliminated from birth. Double-blind, placebo-controlled food challenges were performed and assessed as described previously (14). Briefly, placebo and active challenges were administered in a random order, and were administered on separate days with at least a 2-week interval in between. The incremental scale and total challenge doses used are shown in Table 1. At the lowest dosages, doses were doubled, whereas at the higher dosage, the doses were increased four- to fivefold. Time interval between any two challenge doses was 30 min.

The challenge was discontinued when objective allergic symptoms occurred, or subjective allergic symptoms occurred twice on two successive administrations of the challenge material. Immediate symptoms were defined as symptoms that occurred during the challenge or within 2 h after the last challenge dose. Two days after each challenge session late onset reactions were recorded by telephone questionnaire. Late onset symptoms were defined as symptoms that occurred between 2 and 48 h after the last challenge dose. All challenge sessions were assessed according to a standardized algorithm. Forty-eight hours after the second challenge session, the code was broken and the outcome of the DBPCFC was assessed according to a standardized protocol (14).

Design of introduction schedules and feasibility testing

All challenge doses of the incremental scales used in DBPCFCs, as well as two additional higher challenge doses, were converted into equivalent portions of these foods in their usual household form.

Table 1. Incremental scales and challenge doses used in DBPCFCs

	Cow's milk (ml~g)	Soy milk (ml~g)	Egg (mg)	Protein equivalent (mg)	Peanut (mg)	Hazelnut (mg)	Walnut (mg)	Protein equivalent (mg)
Dose 1	0.05	0.05	13	1.75	6	12	12	1.75
Dose 2	0.1	0.1	27	3.50	12	25	23	3.50
Dose 3	0.4	0.4	108	14	48	100	93	14
Dose 4	2.0	2.0	538	70	241	500	470	70
Dose 5	10.0	10.0	2690	350	480	860	870	130
Dose 6	50.0	50.0	13460	1750	1206	2500	2330	350
Total	63.0	63.0	16830	2190	2000	4000	3800	570
			(~1/3egg)*		(~5–7 peanut kernels)†	(~4 small hazel-nuts)	(~1walnut)	

Protein equivalent amounts of allergenic food were administered, except for the highest amounts of peanut, where the high amounts of peanut and nuts could not be validated. The total and maximum challenge doses were determined by the limitations of adequate blinding in sensory testing.

*1 medium egg = 50 g.

†1 peanut kernel = 290–400 g.

We examined foods likely to be frequently used by parents of young children (except for walnut), which are universally available, have standardized recipes, can easily be prepared in a household setting, and are acceptable for young children. We examined cow's milk, soy milk, egg, peanut and nuts, as well as manufactured foods, such as sponge fingers, home-made muffins, peanut butter (15) and Nutella® (Ferrero). Foods in their most appropriate and practical household forms were incorporated in the home introduction schedules, taking into account the young age of most children in whom the introduction schedules are to be applied and the small amounts in which the portions have to be administered. The increasing portions of the introduction schedule were photographed (except for cow's milk or soy milk) to visualize the required amounts (Fig. 1).

Without providing detailed instructions other than a suggestion to introduce these foods gradually in increasing amounts, we then asked 10 parents of children who were attending our clinic for DBPCFC, as to how much and in which form they would administer cow's or soy milk, egg, peanut, hazelnut or walnut as a first known exposure.

Finally, in these 10 parents, we tested the feasibility of the introduction schedules for the lowest portions (doses 1 and 2 for cow's milk, doses 1–3 for egg, doses 1–4 for peanut, doses 1 and 2 for hazelnut and doses 1–3 for walnut) (Fig. 1 and Appendix A). We

examined whether these parents were able to portion these foods with sufficient accuracy to ensure the safety of the procedure. The feasibility testing was performed in the Food Challenge Unit of our clinic under supervision of one of the staff members. The staff member explained the purpose of the introduction schedules to the parents. Subsequently, she asked the parents to portion the required doses using the written instructions from Appendix A and, for the solid foods, the photograph as shown in Fig. 1. She did not demonstrate the portioning, nor did she train the parents in using the introduction schedules or intervene during the feasibility testing by the parents. The parents were not allowed to practice first. For the portioning of cow's milk and soy milk, we asked the parents to use a medicinal dropper. As indicated in Appendix A, a sharp knife was provided to portion the lowest doses of egg and peanut. For the portioning of Nutella, a type of knife as shown in Fig. 1 was provided for the testing. We ascertained the accuracy of the portioning by weighing.

Statistics

The chi-squared test (SPSS Software, 14th edition, SPSS Inc., Chicago, IL, USA) was used to analyse the differences between the rate of positive results of DBPCFCs performed in sensitized and nonsensitized children.



Figure 1. Incremental portions of egg, peanut, hazelnut and walnut of the introduction schedules for use at home.

The Wilcoxon-signed ranks test was used to analyse the differences between portions of allergenic foods administered by parents both with and without instructions. Differences in mean age between the age of children having positive and negative challenges was determined by the two sample *t* test (two-sided) (normally distributed).

Results

Patients' characteristics

A total number of 72 DBPCFCs were performed in 63 children: nine children underwent more than one DBPCFC with different foods. The characteristics of the patients who underwent the 72 DBPCFCs are shown in Table 2.

Food challenges

A total number of 37/72 challenges (51%) were positive. Positive DBPCFCs were found for cow's milk ($n = 6/10$), egg ($n = 8/19$), peanut ($n = 18/26$), soy ($n = 1/7$), hazelnut ($n = 3/9$) and walnut ($n = 1/1$). There were no significant differences in age between children having a positive and negative DBPCFC. Positive DBPCFCs occurred in 33/57 sensitized cases (58%), and in four of the 15 cases not sensitized to the food in question (27%). These frequencies were significantly different ($P = 0.043$).

Type of symptoms

The type of symptoms observed in positive challenges were dermal (54%), gastro-intestinal (49%), local and upper airway (49%), lower airway symptoms (11%), accompanied by other symptoms, such as drowsiness and irritability in 43% of the challenges.

Table 2. Characteristics of 72 DBPCFCs

Patient characteristics	
Gender, <i>n</i> (%)	
Males	46 (64)
Females	26 (36)
Age (years), median (range)	5.7 (0.7–15.9)
Atopic disease at time of challenge, <i>n</i> (%)	
Atopic dermatitis	48 (67)
Asthma	45 (63)
Allergic rhinitis	28 (39)
None	—
First degree family member with atopy, <i>n</i> (%)	
0	14 (19)
≥1	58 (81)
Degree of sensitization to the food in question, median (range)	
SPT (mm) ($n = 67$)	4 (0 to 19)
SPT (HEP) ($n = 67$)	0.8 (0 to 2.5)
Specific IgE (kU/l) ($n = 65$)	1.71 (0 to >100)
Sensitization rate, <i>n</i> (%)	
Sensitized	57 (79)
Nonsensitized	15 (21)

No severe symptoms or signs of difficulty in swallowing, stridor, hoarseness or anaphylaxis occurred. No adrenaline was administered. In 30/37 positive active food challenge sessions, immediate symptoms occurred (within 2 h after the last challenge dose), whereas in seven of the 37 positive active food challenge sessions, only late onset symptoms were reported by the parents (2–48 h after the last challenge dose).

In cases in which only late onset of symptoms were observed, dermal symptoms were reported in three cases (exacerbation of eczema, rash), gastro-intestinal symptoms in four cases (cramp, diarrhoea) and lower airway symptoms in one case (coughing, wheezing). In two cases, a positive diagnosis could be refuted because of placebo reactions.

Eliciting doses

In Fig. 2, the cumulative eliciting doses as administered in the DBPCFCs are expressed in amounts of food (mg). For egg, peanut and walnut, the lowest eliciting doses were observed (dose 1), while in cow's milk, soy and hazelnut, the most sensitive children reacted to dose 4. In DBPCFCs performed in sensitized children showing positive SPTs and/or positive RAST results to the food in question, the eliciting doses ranged from dose 1 to dose 6, whereas in DBPCFCs performed in nonsensitized children, all reactions occurred to dose 6. All children with late onset of symptoms reacted to dose 6.

Introduction schedules and feasibility testing

In Appendix A the home introduction schedule with selected foods are shown. In Fig. 1, a reference photograph of the increasing amounts of the solid foods of the incremental scales is shown.

From Appendix A and Fig. 1 it becomes clear, that the lowest doses of these introduction schedules consist of very small amounts of allergenic foods. For cow's milk

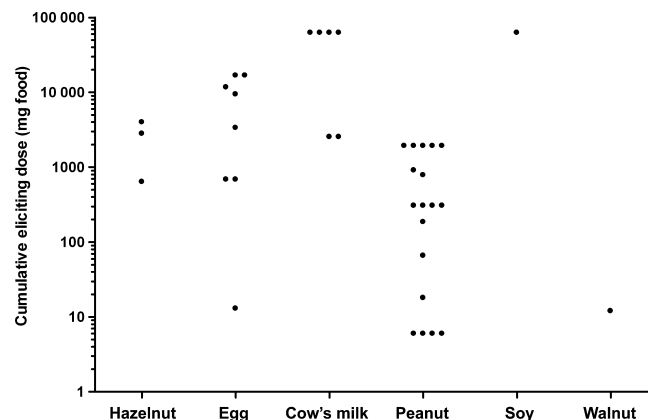


Figure 2. Cumulative eliciting doses (mg) of allergenic foods in positive DBPCFCs.

Table 3. Amounts of allergenic food (mg or ml) administered by parents with and without detailed instructions

Food	Administration without detailed instructions		Administration using instructions from Appendix A and Fig. 1							
	Dose 1		Dose 1		Dose 2		Dose 3		Dose 4	
	Median (range)	Ref.	Median (range)	Ref.	Median (range)	Ref.	Median (range)	Ref.	Median (range)	Ref.
Cow's/soy milk	0.08 (0.05–30)	0.05	0.05	0.05	0.1	0.1	n.a.	n.a.	n.a.	n.a.
Egg	108* (27–2690)	13	11.5* (2–31)	13	15.5 (2–131)	27	35 (26–440)	108	n.a.	n.a.
Peanut	150** (6–2600)	6	6.5** (1–32)	6	8 (1–76)	12	45 (9–107)	50§	175 (3–955)	260¶
Hazelnut	100 (12–520)	12	52 (11–90)	100†	177 (41–230)	200‡	n.a.	n.a.	n.a.	n.a.
Walnut	93*** (12–470)	12	11.5*** (2–41)	12	23 (2–51)	23	48 (20–235)	93	n.a.	n.a.

n.a. = not applicable

* $P = 0.011$; ** $P = 0.021$; *** $P = 0.038$.

†100 mg Nutella is protein equivalent to 12 mg hazelnut.

‡200 mg Nutella is protein equivalent to 25 mg hazelnut.

§50 mg peanut butter is protein equivalent to 48 mg peanut.

¶260 mg peanut butter is protein equivalent to 241 mg peanut butter.

and soy, the lowest doses consist of one drop of cow's milk or one drop of soy milk. For solid foods, the lowest doses consist of crumbs of the allergenic food, equivalent to milligrams of food.

The median portions that the parents would administer as a first exposure without detailed instructions are shown in Table 3 (not normally distributed). These amounts of foods were ascertained by weighing. For cow's milk or soy milk, median portions were similar to the reference (i.e. doses 1 of the introduction schedule). For egg, hazelnut and walnut these median portions were at least approximately eight times higher than the references. For peanut, the median portion was 25 times higher. Especially in the form of peanut butter, parents portioned relatively great amounts.

The amounts of the foods the parents portioned when using the written instructions of the introduction schedules (Appendix A) and the photograph in Fig. 1, with use of a medicinal dropper for cow's milk or soy milk, are also shown in Table 3 (not normally distributed). These amounts of foods were also ascertained by weighing. For all 140 portions, the median amounts were similar to or smaller than the reference amounts of foods. The median of doses 1 of egg, peanut and walnut when portioned using the introduction schedules were significantly lower than that when portioned without detailed instructions ($P = 0.011$, 0.021 and 0.038 respectively).

In 105/140 (75%) portions, the absolute weighed amounts were similar to or lower than the reference amounts of food, i.e. the required amounts of foods used in the introduction schedules (data not shown). In the remaining 35/140 (25%) portions, the absolute weights exceeded the reference amounts, but not for cow's milk and soy. These greater amounts exceeded the required amounts of food by not more than one dose of the incremental scale used in DBPCFCs.

Discussion

In our study, we devised ready-to-use home introduction schedules for common allergenic foods in young children designed to avoid severe reactions at first exposure. Although it may be a matter of debate over the determination criteria as to which children these guidelines are to be used upon, they could be recommended for any child at risk who does not warrant first exposure under medical supervision. As there is no consensus about the clinical characteristics of children who should be introduced to allergenic foods at home, and assigning children who should be challenged under medical supervision because of a significant risk for (severe) allergic reactions, additional studies are needed to answer this question. Although increasingly higher values of food-specific IgE are strongly associated with an increasing probability of clinical reactivity to food IgE (16), they are not associated with the severity of a reaction. In only one study, an association was found between specific IgE to peanut and the severity of reaction in DBPCFCs (17). It is noteworthy that in this study the dose of allergen in DBPCFCs was considered and incorporated into the statistical model. However, several risk factors are known to be associated with severe reactions, such as the coexistence of asthma, adolescence or young adult age, reacting to trace amounts of the offending food, (suspected) allergy to peanuts or tree nuts and distance to emergency medical care (7–9). The physician's assessment of the individual child will decide whether the child should be referred for introduction under medical supervision or at home. The latter population will generally consist of children in whom there is an increased risk for food allergy, but in whom there is little suspicion for the specific food in question. These children may be found for example in primary or secondary care centres, or may have older siblings with food allergy or atopic parents. They may have atopic

dermatitis, or may be known with allergy to foods unrelated to the foods in question, such as cow's milk.

Little is known about the eliciting dose at first-known exposure to allergenic foods. Our study shows that the eliciting dose may vary from very low doses in the most sensitive individuals, to the maximum challenge dose in less sensitive children. The lowest eliciting doses were found for egg, peanut and walnut (dose 1, which contained 13 mg of egg, 6 mg of peanut or 12 mg of walnut). Although we did not observe reactions to the lowest doses of cow's milk, soy and hazelnut, we cannot exclude that some sensitive children might react to lower doses.

We thus converted all challenge doses of all foods into home introduction schedules. Caffarelli et al. (4) also reported low eliciting doses to freeze dried (raw) egg on first exposure in DBPCFC, ranging from 0.5 to 20 mg, presumably equivalent to 2–80 mg of fresh egg. Similarly, Lack et al. (5) described eliciting doses ranging from 50 mg to 8 g of peanut, but it is not clear in the latter study if 50 mg was the lowest challenge dose used.

Although we observed a large spectrum of symptoms, no severe symptoms occurred. Most symptoms occurred immediately (30/37 positive challenges). Anaphylaxis did not occur, and no patient required adrenaline. The most severe reactions seen in our study consisted of lower airway symptoms seen in a small number of children (4/37). These were easily controlled by using bronchodilator therapy. Thus, using these introduction schedules is likely to contribute to avoiding severe reactions at home. Importantly, the parents of the children using the introduction schedules are instructed to terminate the introduction, as soon as allergic symptoms occur. Additionally, ensuring reasonable, long-time intervals between doses are important to avoid severe reactions. Consequently, we propose that a maximum of one to three doses should be administered on 1 day, with a time interval of at least 1 h in between the doses when using the introduction schedules (Appendix A). However, the improved safety of these introduction schedules needs to be validated in further studies.

Without instructions, doses administered at home are likely to be much higher than the low doses we administered in DBPCFCs. From our data it becomes clear, that for egg, hazelnut and walnut, when performed without detailed instructions, parents would administer median doses which are approximately at least eight times higher than the first doses of the introduction schedules, and for peanut a median of dose value that is 25 times higher.

The lowest challenge doses of our incremental scales represent very small amounts of foods in their normal household form. Therefore, to achieve very low initial doses, the gradual introduction of allergenic foods in the household setting, as has been proposed previously (10), should be accompanied by detailed instructions on administering these very small amounts of allergenic foods, as have been devised in this study.

We tested the feasibility of these introduction schedules in parents of allergic children. Our results showed that for all doses parents seemed capable of portioning the required median amounts of foods with great accuracy. They were all similar to or lower than the reference amounts. Furthermore, the median doses of egg, peanut and walnut when portioned using the introduction schedules were significantly lower ($P = 0.011$, 0.021 and 0.038 respectively) than that when portioned without detailed instructions. We did not train the parents before using the introduction schedules, because the introduction schedules were meant to be usable for a large majority of parents without specific instructions. The types of knives we used for the portioning are commonly used in the households. With regard to the absolute required amounts, for cow's milk and soy milk it seemed feasible to portion the smallest amounts using medicinal droppers, which are widely available. For the solid foods, in 75% of the portions it seemed feasible for the parents to estimate the required amounts of the incremental scale quite accurately. In 35/140 (25%) portions, the absolute weights exceeded the reference amounts, but the maximum doses administered by some of the parents were much lower than the maximum amounts administered without use of the introduction schedule, often by a factor of 10- to 100-fold. Altogether, introducing common allergenic foods at home for children, using the introduction schedules provide instructions for parents, which may be expected to improve the safety of this procedure by allowing the administration of the required amounts of allergenic foods in low doses initially.

Conclusions

Children may react to very small amounts of foods on first exposure. Consequently, the gradual introduction of common allergenic foods at home should start at very low initial doses. In this study, introduction schedules and a reference photograph of the incrementally increasing amounts of allergenic foods for use at home are described. These schedules provide instructions for parents to introduce the required amounts of allergenic foods in low initial doses at home with improved accuracy. This may be expected to improve the safety of this procedure.

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Appendix A

Introduction schedules for common allergenic foods for introduction at home (see also Fig. 1).

	Day 1			Day 2		Day 3		Day 4
	Dose 1	Dose 2	Dose 3	Dose 4	Dose 5	Dose 6	Dose 7	Dose 8
Cow's milk or soy milk	1 drop*	2 drops*	8 drops*	teaspoon‡	2 teaspoons‡	1/3 serving (50 ml)	2/3 serving (100 ml)	1 serving (150 ml)
Hard boiled egg	1 very small crumb† of egg white	1 small crumb† of egg white	1 crumb† of egg white	1/8 teaspoon‡ of crumbs of hard boiled egg	1/2 teaspoon‡ of crumbs of hard boiled egg	medium hard boiled egg (12.5 g)	medium hard boiled egg (25 g)	1 medium hard boiled egg (50 g)
Peanut and peanut butter	1 very small crumb† of peanut	1 small crumb† of peanut	1 small knife-point§ of peanut butter	1 knife-point§ of peanut butter	Almost 1/8 teaspoon‡ of peanut butter	Almost teaspoon‡ of peanut butter	Almost teaspoon‡ of peanut butter	Almost 1 teaspoon‡ of peanut butter
Nutella® and hazelnuts	1 small knife-point§ of Nutella	1 knife-point§ of Nutella	1/8 teaspoon‡ of Nutella	teaspoon‡ of Nutella	1 teaspoon‡ of Nutella	2 large hazelnuts	3 large hazelnuts	7 large hazelnuts
Walnut	1 very small crumb† of walnut	1 small crumb† of walnut	1 crumb† of walnut	1/10 walnut	1/5 walnut	walnut	1 walnut	2 walnuts

For optimal safety, one to three doses may be administered on 1 day, with a time interval of at least 1 h in between the doses. When allergic symptoms occur, the introduction should be terminated, and a physician should be contacted. *To be administered by a medicinal dropper. †Crumbs of egg, peanut and walnut can be obtained by using a sharp and pointed knife. ‡To be administered using a measuring spoon set: 1/8 teaspoon = 0.625 ml; teaspoon = 1.25 ml; teaspoon = 2.5 ml; 1 teaspoon = 5 ml. §To be administered by a kind of knife as shown on the photograph.