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Oral rehydration Salts (ORS)

A joint UNICEF/WHO update

Introduction

This document was prepared to inform national authorities on the position of the United Nations Children's Fund (UNICEF) and of the World Health Organization (WHO) with respect to issues such as flavouring, colouring, and rice-based ORS. It is based on a document first published in July 1996 that was revised to take into account results of studies on ORS formulation and zinc supplementation.

Additional ingredients/additives

The four ingredients of ORS (glucose, sodium chloride, potassium chloride and trisodium citrate) in the concentrations described in the document entitled "Oral Rehydration Salts: a new reduced osmolarity formulation" yield an effective solution for rehydration and for the prevention of dehydration. The addition of other ingredients, such as other minerals (especially zinc) or vitamins, has not been shown to improve the solution's efficacy. For this reason neither UNICEF nor WHO approve or provide ORS with additives. If additional ingredients are included, they should be clearly described on the packet. The responsibility for demonstrating their clinical value, safety, and chemical stability rests with the manufacturer.

Additional ingredients may increase the total and individual substance concentration of a solution. They must be considered when the total substance concentration of a new product is calculated for comparison with the criteria mentioned in the above mentioned document.

A clear distinction should be made between products recommended for treating/preventing dehydration caused by diarrhoea and preparations with compositions that are designed for replacing water and salt losses during exercise (sport drinks). In order to avoid confusion among health professionals and the population at large, it is important that manufacturers of the latter limit their commercial promotion strictly to the indication of the product and that no reference is made to their use for treating diarrhoea or cholera.

Flavouring/colouring of ORS

The theoretical advantage of flavoured and coloured ORS is greater acceptability, and consequently increased use. Because this, in turn, might lead to over-consumption, the WHO/CDD Programme conducted a safety/efficacy study in Egypt and an acceptability study in the Philippines of flavoured and coloured ORS solutions. The results of these studies showed neither an advantage nor disadvantage for the

flavoured and coloured ORS when compared to the standard ORS with regard to safety, acceptability and correct use. For this reason, and with the aim of making an essential drug available at low price in the public health system, UNICEF and WHO recommend that governments should use the ORS composition that contains only the four basic ingredients needed to effectively treat dehydration due to diarrhoea.

ORS produced for use in the private sector (commercial sales) and indicated for the prevention and treatment of dehydration due to diarrhoea, may contain flavouring or colouring agents, if this is seen as vital by a manufacturer for promoting the product or to compete with other brands. In practice, two or more types of flavouring are often needed, and saccharine is added to increase their effect. The ingredients used for flavouring ORS must be among those listed as “Generally Recognized as Safe” for their intended use by the US Food and Drug Administration (FDA) or by the US Flavour Extract Manufacturer’s Association (FEMA). The responsibility for demonstrating the clinical efficacy, safety and chemical stability of such products remains with the manufacturer.

Special attention must be given to the type of sweetener used. In 1968, **cyclamic acid** was reported to cause cancer and is therefore banned in the USA; high dose of **saccharine** are suspected to be carcinogenic; **dulcine** is recognized as toxic and carcinogenic; and **aspartame** is known to be unstable at temperatures above 40 degrees Celsius. For all these products, the above mentioned guidelines specify the maximum dose to be consumed per kg of body weight and per day (i.e., aspartame 40 mg/kg body weight/day). The amount of ORS solution consumed per day is extremely variable from child to child. Some children with high purging diarrhoea may consume very large amounts of ORS solution.

Because of difficulties in controlling the amount of ORS solution consumed per kg of body weight and per day, it is almost impossible to determine whether the consumed doses of colouring and/or flavouring agents are within the safe limits. Although not documented, it also seems that certain flavouring agents can cause allergies and other side effects, particularly in infants and small children. Finally, it must be noted that the flavouring of ORS may increase cost of the product by up to 20-30%, especially when the additional ingredients must be imported.

The amino acid- and/or maltodextrin-containing ORS

For more than two decades the CDD Programme of WHO has supported research to develop an improved ORS formulation that could reduce stool output when used to prevent or treat dehydration due to diarrhoea. One approach taken has been to replace some or all of the glucose in ORS with various forms of amino acids (glycine, glycyglycine, alanine, glutamine, etc.). Maltodextrins derived from maize were also evaluated. Regrettably, none of the various formulations tested proved superior to standard ORS in children with non-cholera, it was also observed that some of the mixtures were unstable during storage and that many tested products were very difficult to handle during the manufacturing process. For some, split packing was the only way for assuring the product stability during clinical evaluation.

The rice-based ORS

a) Clinical evaluation

Studies to evaluate cooked rice as a replacement for glucose in ORS solution began in 1980. Initially, solutions were prepared by cooking rice powder (50-80g/l) for at least 10 minutes and then adding salts in concentrations identical to those of the ORS recommended by WHO. Some studies used “popped” rice in place of cooked rice. An instant, pre-cooked ORS was used in later studies. This was specially developed in close collaboration with a private company in Switzerland.

Other cooked cereal powders have also been evaluated in ORS formulations, including wheat, maize, sorghum and millet. Although fewer studies have been done, results have been similar to those obtained with rice-base ORS. Conclusions for rice-based ORS can, therefore, be applied to these other cereal-base ORS solutions.

A total of 22 randomized clinical trials comparing the safety and efficacy of rice-based ORS solution with that of standard ORS solution have been conducted in adults and children with cholera (seven trials) or in children with acute non-cholera diarrhoea (15 trials). A joint WHO/ICDDR, B Consultative Meeting on ORS Formulation, held in Dhaka from 10 to 12 December 1994, reviewed the results of these trials. On the basis of that review, it was concluded that:

- rice-based ORS is superior to standard ORS for adults and children with cholera, and may be used to treat such patients wherever its preparation is convenient;
- rice-based ORS is not superior to standard ORS in the treatment of children with acute non-cholera diarrhoea, especially when food is given shortly, after rehydration, as is recommended to prevent malnutrition.

b) The development of a pre-packaged rice-based ORS

Solutions of rice-based ORS evaluated in Bangladesh and India were made with local rice flour. This entails cooking of the solution, which must be used promptly after it is prepared. For clinical trials, however, a product was needed that did not require cooking and could be produced industrially in sachets, similar to standard ORS. As rice-based products are traditionally produced by baby-food manufacturers, contacts were established with a number of such companies. In 1989, a Swiss company working closely with the CDD Programme of WHO, developed a product that dissolved readily in cold water and remained in suspension over 24 hours without sedimentation of rice particles.

c) The manufacturing process

Manufacture of this product consists of three steps, i) dissolving the salts and rice powder in water, ii) heating of the solution, and iii) drying of the product. Drying can be done in a fluid bed drier or on a rotating cylinder. The test product was produced with the latter system, a technology commonly used for cereals that provides good homogeneity, gelatinisation (and hence good digestibility), and chemical and

bacteriological stability. Other technologies exist and it remains with the manufacturer to select the most appropriate one.

d) The production facility

The various technologies suitable for manufacture of rice-based ORS are all commonly used by the food processing industries. Therefore, pharmaceutical companies that currently produce ORS and wish to manufacture rice-based ORS, will most likely need to adapt their production facility and install the required equipment. As this will involve substantial investment, it may be justified only where regular production is guaranteed.

e) The manufacturing conditions

Pharmaceutical products, such as ORS, should be manufactured only by licensed manufacturers. The production facility and manufacturing process should meet "Good manufacturing practices for pharmaceutical products" (GMP), established by WHO. If rice-based ORS is classified as a drug, its production would be limited to manufacturers who follow such standards.

Manufacturing conditions in the food industry, including quality assurance and control, do not normally meet GMP standards. Even if rice-based ORS were not classified as a drug, it would be important to set minimal production standards, based on GMP; for example, the allocation of a separate room for at least the filling/dosing/sealing process. Moreover, the individual and total substance concentrations of rice-based ORS should be strictly within the limits given in the monograph for ORS (B.P., USP, IP, etc.), regardless of whether a wider range is commonly applied in this sector of industry. In addition, it would be important to ensure strict controls for microbial contamination of the rice and the water used in the manufacturing process.

Specific guidelines for the manufacture of rice-based ORS are not yet available, but most of the necessary information can be found in the document "*Oral Rehydration Salts, Planning, establishment and operation of production facilities*" (WHO/CDD/SER/85.8).

f) The classification of rice-based ORS

The ORS formulation recommended by UNICEF and WHO is classified as a drug and considered as such by local drug administrations worldwide, except in the USA, where it is classified as a "medical-food". Given that the formulation of rice-based ORS contains the same individual and total substance concentrations for the various salts (in mmol/l), it would seem appropriate to accept it as an alternative formulation. So far, however, neither UNICEF nor WHO has taken a formal decision on this point. Some of the reasons are given below.

As rice is a natural organic product, it is normal to find varying compositions, the presence of impurities, and infestations with insect larvae. It is likely that microbial growth may develop if the rice or the rice flour is stored, particularly in hot and humid ambient conditions. It is also possible that the rice has been exposed to

pollutants in air or chemicals and therefore contains undesired heavy metals, pesticides, etc. (the maximum pesticide residue limits are given in the CODEX ALIMENTARIUS, Supplement 1 of Volume 2). Moreover, rice often is chemically treated against oxidation after harvest in order to prevent its becoming rancid. The undesired residues are neither removed nor eliminated during the process of milling, except in cases where rice or rice flour is specially treated or purified (by heat, gas, radiation, etc.)

Rice or rice flower in its natural form is not normally used in pharmaceutical preparations and relevant quality standards are, therefore, not available. It is used, however, in the form of starch, for which applicable quality criteria are established. The quality of rice used in food specialities must comply with specifications or standards established by the national Food and Drug Administration (FDA). These are normally based on guidelines prepared by the Food and Agriculture Organization of the United Nations (FAO). A draft codex standard for rice is included in ALIFORM 95/29, Appendix III.

g) The stability of rice-based ORS

After some time and under certain conditions, rice with a high content of fat can become rancid. For this reason, the theoretical shelf life of rice-based ORS is estimated at around one year, similar to infant/baby food products containing rice. A crucial condition, however, is hermetic packing. In order to ensure absolute protection against humidity and contamination, an appropriate quality of aluminium laminate must be selected. Polyethylene bags should be considered only when the product is prepared for immediate use.

h) The packing of rice-based ORS

Rice-based ORS has a rather low density (high voluminosity) and therefore requires a much larger sachet than standard ORS. The size of sachet to pack a dose for one litre cannot normally be handled on automatic packing machines in food industries. For this reason rice-based ORS used by WHO in clinical trials was packed in doses for 500 ml only. This quantity still required a pouch size of 125x165 mm, or four times more packaging material than for standard ORS. The need for more packaging material is an important factor in the increased cost of the final product.

An adaptation/change of a national dose of ORS (e.g. from a one-litre dose to a dose for 500 ml) would have major operational and programmatic implications. Prior to any change in package size, it is therefore important to discuss such a step carefully with the local authorities or the national CDD Programme manager.

i) The cost of rice-based ORS

The price of rice-based ORS, supplied in 30 kg lots for the WHO's clinical trials, was US\$2.10 per kg, or approximately US\$0.13 for a dose of 57.9 g, sufficient for a one-litre solution. Produced on a larger scale, a packet for 500 ml would cost around US\$ 0.10, or about US\$ 0.20 for one litre of solution. This is three times the price of standard ORS (US\$ 0.07 for one litre).

The ORS in liquid and tablet form

In view of the overriding need to make essential drugs available through the simplest and most appropriate technology at an affordable price, UNICEF and WHO primarily concentrated their effort during the last decade on ORS in powder form. It was considered important, however, to evaluate other ORS presentations.

In 1980 TETRA PAK International AB, in collaboration with the Department of Paediatrics of the University of Lund, Sweden, offered to evaluate the production of liquid ORS in aseptic packages and to develop a method to sterilize liquid ORS. The objective was to make liquid ORS available in locations where water supply was problematic, for example after a natural disaster. While this alternative has not been applied in the field so far, the standard procedure is available and can be obtained from Tetra Laval Marketing Services AB, Ruben Rausing gata, S-221 86 Lund, Sweden.

With the support of the CDD Programme, the Programme for Appropriate Technology in Health (PATH) developed ORS in tablet form. The manufacturing guidelines became available in 1983. Since then PATH has offered a licensing agreement to transfer the technology to manufacturers in developing countries. The formulation of the tablet complies with that recommended by WHO/UNICEF, but contains excipients that are needed to compress the product. It has a size of 15/16” and will make 150 ml of solution. It disintegrates in less than 90 seconds. Later, CIBA-GEIGY, Basle, Switzerland developed an effervescent tablet for 120 ml of solution, that is now marketed worldwide. Other products in tablet form, most with a composition that is different than that recommended by WHO/UNICEF, have since become available.

Because ORS in tablet form increases the cost of ORT and may have programmatic implications, both Organizations have so far refrained from recommending its use in the public health system. However, provided that clear instructions for its preparation and use are given, ORS tablets are seen as an acceptable alternative in the private sector.