ISDB WHO Single Medicine Review

Sodium Fluoride

Introduction

Sodium fluoride as mouth wash agent has been listed in the WHO essential model list for prevention of dental caries not for areas where drinking water is fluoridated or where fluorine content is naturally high. However, the public health relevance and/or safety of this item has been questioned and its continued inclusion on the list will be reviewed at the next meeting of the Expert Committee.

Product and dosage

For mouth wash, sodium fluoride 0.05%, 0.2% is listed in the 13th WHO Model List of Essential Medicines as a representative of fluoride among various alternative fluorides.

Dosage: Prevention of dental caries, as oral rinse, CHILD over 6 years, 10 ml 0.05% solution daily or 10 ml 0.2% solution weekly. The WHO Model Formulary notes that fluoridated toothpastes are also a convenient source of fluoride for prophylaxis of dental caries.

Evidence of value

Average number of dental caries experience (DMFT) among 12-year-olds in developing countries has not been changed (around 2.0) during about two decades until 1998 and declined below 3.0 in developed countries (about 4.5 in 1980 to 2.5 in 1998)\(^1\)

A main goal for dental caries to be achieved by the year 2000 that WHO and the FDI world Dental Federation jointly formulated in 1981 was the global average to be no more than 3 DMFT at 12 years of age. It was accomplished in 1994 as the result of a number of public health measures\(^1\).

It is noteworthy that the decline is observed not only in the developed countries where the water is fluoridated but also in the non-fluoridated countries in the same extent\(^1\).

The relative risk reduction (RRR) of mouth rinses for preventing dental caries expressed as prevented fraction (PF) of DMFS was calculated by the meta-analyses of 34 RCTs and quasi RCTs (with no treatment group as controls)\(^2\) (PF is the difference in mean caries increments between the treatment and control groups expressed as a percentage of the mean increment in the control group).

Overall RRR(PF) was 26 % (p<0.0001) but 20 to 60 % of participants were withdrawn within the trial periods (1-3 years) and the heterogeneity was statistically significant (p=0.008) meaning these studies of low quality. RRR(PF) was about 11% (0.4 surface) and 20% (0.8 surface) when DMFS of...
control group was less than 2 and 4 surfaces respectively\(^2\). Only three studies was published after 1990 among 34 studies analysed\(^2\). Most of the studies analysed were published before 1980. Using these three studies published after 1990, overall RRR(PF) was estimated about 8% (probably of no significance)\(^2\). Effectiveness of the mouthrinse could not be expected in these days when dental caries rapidly decreasing globally.

Cochrane systematic review of combination of topical fluoride (tooth paste, mouthrinse, gels, vanishes) versus single topical fluoride for preventing dental caries in children and adolescents analyzing five studies that were all published before 1987 revealed no combination was significantly superior to single topical fluoride except one combination\(^3\). RRR(PF) of combination of mouthrinse with tooth paste and tooth paste alone was not statistically significant (7%; \(p=0.06\)). RRR(PF) for combination of mouthrinse with tooth paste compared with mouthrinse alone was 4% (\(p=0.33\))\(^3\).

This means that moutherine is not necessary for preventing dental caries. Tooth paste may be more convenient and safe at least concerning with acute effects, if one dare to take it.

**Adverse effects**

The latest version of WHO Model Formulary says that toxicity of sodium fluoride is unlikely in recommended doses. But if one drank all of fluoride in mouth rinse, symptoms such as abdominal cramp and/or nausea and vomiting of acute toxicity might be seen. Occasional white flecks on teeth at recommended doses; rarely yellowish-brown discoloration (dental fluorosis) if recommended doses are exceeded may be seen (WHO Model Formulary).

A Cochrane systematic reviews\(^2\) stated “The few trials that report on adverse effects give no useable or incomplete data for analysis.” And data for unacceptability of treatment (as measured by drop outs) were reported in only two among 34 studies. Proportion of dropout in the mouth rinse group of the two studies were relatively low (9% and 37%).

Moreover no long term harm was assessed by the Cochrane systematic review, while fluoride are suspected to be related to topical and systemic harm such as dental fluorosis\(^4\), bone fluorosis\(^4,5\), increase of malignancies (all sites\(^6-8\), osteosarcomas\(^9,10\), cancers of oral cavity and pharynx\(^7\), Down’s syndrome\(^11-14\), neurotoxicities\(^15\) including mental diseases\(^16\) and hormonal diseases including thyroid\(^17\). These characteristics are supported by many laboratory studies. Fluoride is a potent modulator of various enzymes\(^16,17\), is mutagenic (with transformation) and clastogenic\(^3,19\). Fluoride appears to act as phosphate analogs influencing the G-protein activated effector enzymes producing second messenger molecules such as c-AMP, inositol phosphates and cytosolic calcium level by forming as Alminofluoride complex (AlFx)\(^16\).

NTP revealed the carcinogenicity of sodium fluoride by 2 year
carcinogenicity studies using rats and mice\textsuperscript{9}).

In the large scale epidemiological study\textsuperscript{7}, increase of malignancies (cancer of all sites) was clearly demonstrated by my reanalysis (see figure for example). Increase of cancers of oral cavity and pharynx was also demonstrated (O/E ratio by about 1.5)\textsuperscript{7}.

![Figure: Correlation between duration of fluoridation and O/E ratio of cancer incidence (all sites)](image)

Individual points, for example 1.15 (Iowa male more than 20 years) and 1.12 (Iowa, female more than 20 years) indicate that the cancer incidence of all site increased by 15% and 12% in water fluoridated county for male and for female respectively (p<10\textsuperscript{-8}). O/E ratio of 14 among 18 points (by area and by years after fluoridation) were significantly higher than 1 (p<0.05, p<0.0001 in 8 among 14) according to the reanalysis using the method reported by Bailar\textsuperscript{20}.

**Recommendations**

Sodium fluoride should be deleted from the model list of Essential Medicines as the agent used for mouth rinse for prophylaxis of dental caries, because it has no place for prevention of dental caries even not for areas where drinking water is fluoridated or where fluorine content is naturally high.

A main goal for dental caries “no more than 3 DMFT at 12 years of age” has already been accomplished globally in 1994 as the result of a number of
public health measures. Relative Risk reduction by fluoride mouthrinse is estimated less than 20% where the average DMFT is less than two. It is also estimated less than 10% if used as the combination with other topical fluoride such as tooth paste.

It is also recommended that the safety of fluoride should be critically reassessed because fluoride is a potent chemical that modulates many key enzymes for life, is considered as mutagen and clastogen and appears carcinogenic in animals and in humans as shown in the animal and epidemiological studies.

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References
1) World Oral Health Report 2003:
7) Hoover RN. Fluoridation of Drinking Water and Subsequent Cancer Incidence and Mortality (Appendix E in the reference 5)
8) Hoover RN. Time Trends for Bone and joint Cancers and Osteosarcomas in the Surveillance, Epidemiology and End Results (SEER) Program National Cancer Institute August, 1990 (Appendix F in the reference 5)
9) National Toxicology Program. NTP Technical Report on the Toxicology and Carcinogenesis Studies of sodium Fluoride (CAS No. 7681-49-4) in F344/N Rats and B6C3F1 Mice (Drinking Water Studies) December 1990


14) Erickson JD, Down syndrome, water fluoridation, and maternal age. Teratology 21: 177-180, 1980


18) World Health Organization: "Fluorides and Human Health" 1970


20) Bailar JC and Ederer F. Significant factors for the ratio of a poisson variable to its expectation. Biometrics 1964 Sept. 639-643

Search Strategy

Medical literatures and other documents was searched to identify clinical trials, systematic reviews, meta analyses or guidelines, laboratory studies, toxicity or toxicological studies, epidemiological studies related to use of sodium fluoride as mouthrinse or water fluoridation.

Major publications, electronic databases, websites and journals searched during since Oct 2001 to Oct 2004 are as follows:

WHO Technical Report Series
WHO publications searched at the WHO website http://www.who.int/en/
Cochrane library (issue 4 of 2004)
NHS Centre for Review and Dissemination: http://www.york.ac.uk/inst/crd/fluodid/htm
DHHS: Review of Fluoride "Benefits and Risk"
NTP Technical Report on the Toxicology and Carcinogenesis Studies
PubMed search for fluoride
Google search for fluoride (many websites were found either pro or con of fluoride)
Second hand references of the searched literatures and documents.