E-mail submission received from

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Subject: SUBMISSION of COMMENTS on Proposed Deletion of Drug from WHO Essential Medicines:

I am writing in regards to the recent proposal to remove sodium fluoride from the list of WHO's essential medicines.

Safety Concerns

1) About adverse effects in the Cochrane systematic review on “Topical fluoride (toothpastes, mouth rinses, gels or varnishes)” of 2004, reviewer concluded that (1):

We were unable to reach definite conclusions about any adverse effects that might result from the use of topical fluorides, because data reported in the trials are scarce.

Because the review did not identify specific adverse effects, it should not be interpreted that adverse effect doesn't exist.

2) As topical fluoride therapies generally employ relatively high concentration of fluoride, risk of acute toxicity must be considered. On what bases are fluorides “safe” in terms of acute toxicity? In many publications, “Probably Toxic Dose” (PTD), 5.0mg F/kg, is referred to for safety concern in use of fluoride (gels, mouth-rinses etc.). According to Whitford (2):

The PTD, 5.0 mg F/kg, is defined as the dose of ingested fluoride that should trigger immediate therapeutic intervention and hospitalization because of the likelihood of serious toxic consequences.

He also states in his review that (2):

From the foregoing, is reasonable to conclude that if a child ingests a fluoride dose in excess of 15 mg F/kg, then death is likely to occur. Based on the report by Dukes (1980), a dose of between 3 and 4.5 mg F/kg can be fatal for a young child. The rather difficult problem which must be addressed is to estimate the safety tolerated dose or, from the other point of view, the “probably toxic dose” or PTD. The latter would be the minimum dose that could cause toxic sign and symptoms, including death, and that should trigger immediate therapeutic intervention and hospitalization. It could be argued that such a dose should be called the “possibly toxic dose”. However, probably is preferable because it conveys a more appropriate level of urgency.

Since PTD is nearly equivalent to minimum lethal dose for a child, it is not an
appropriate criterion for judging safety. It should be based on TDL (Toxic Dose Low) or “minimum acute toxic dose”. The Medwatcher Japan cites estimated range between 0.1 to 0.5 or 0.8 mg F/kg for “minimum acute toxic dose”, which are based on appearance of adverse effects such as stomachache, nausea, vomiting, etc. (3)

Some fluoride therapies have potential toxic effect when ingested accidentally.

3) However, there is another mechanism of initial symptoms that we should take into consideration. That is the concentration of fluoride in the solution in contact with the stomach mucosa. According to “Effects of fluoride on structure and function of canine gastric mucosa.” by Whitford et al (4):

Minor effects were caused by exposure to 1 mmol/liter F. Both 5 and 10 mmol/liter F caused marked increases in the fluxes of water and Na, K, and H ions; mucus secretion; and tissue swelling and redness. The extent of these changes did not increase appreciably upon exposure to 50 or 100 mmol/liter F. Histological findings included marked thinning of the surface cell layer, reduced uptake of PAS stain, localized exfoliation and necrosis of surface cells, acute gastritis, and edema. It was concluded that: (1) the threshold F concentration for effects on the structure and function of the gastric mucosa was approximately 1 mmol/liter; (2) the maximum or near-maximum effects were caused by 10 mmol/liter F; (3) the effects persisted for at least 6 hr after the exposure.

The concentration used in 0.2% sodium fluoride rinse (930ppmF) is approximately 49 mmol/litter F. This concentration is sufficient to cause effects on the structure and function of the gastric mucosa.

As for the fluoride tablets, according to Muller et al (5):

In a randomized double-blind study with two parallel groups of 10 male healthy volunteers each the response of gastric mucosa after a 7 days ingestion of sodium fluoride tablets (NaF) or sodium monofluorophosphate tablets (MFP) was compared. Gastroscopic evaluations were performed before treatment, day 1 and day 7. Simultaneously blood samples were collected for determination of laboratory data and serum fluoride values. In the MFP-group no severe gastric lesions were observed, whereas in the NaF-group in 7 of the 10 subjects significant gastric mucosal lesions including acute hemorrhages and free blood in the gastric lumen were found. The differences of the lesions scores in both groups were statistically significant (p = 0.0015). The serum fluoride content was comparable in both treatment groups. Possible adverse drug reactions were reported in 4 subjects with NaF and in 1 subject with MFP.

In my opinion, I must say; question of safety has not been fully answered.

**Dubious genesis of “optimal” dose of fluoride**

For your information, description of “Health Effect of Ingested Fluoride” (1993) by US National Academy of Sciences about “optimal” dose are as follows (6):
The concept of an optimal dose goes back to the early days of fluoride research in dentistry. In 1943, the normal daily fluoride intake of children 1-12 years old was estimated to be 0.4-1.7 mg, which provided an average intake of fluoride at 0.05 mg/kg of body weight per day (McClure, 1943). Actual fluoride intake for an individual depended on age, diet, and fluoride content of water. That estimate somehow evolved into a recommendation (Farkas and Farkas, 1974) and then to apparent acceptance of 0.05-0.07 mg/kg per day as an optimal dose (Ophaug et al., 1980a).

Despite its dubious genesis, that dose might be a fair estimate, based on empirical evidence, of the upper limit for fluoride intake in children to minimize fluorosis (Burt, 1992). If all fluoride intake comes from drinking water, that dose for a child weighing 10 kg (an average 1-year-old) would be ingested in 0.5-0.7 L of water fluoridated at 1.0 mg/L. For a child weighing 22 kg (an average 6-year-old), it would be ingested in 1.1-1.5 L of water. Because the scientific base is weak, however, the range of 0.05-0.07 mg/kg should not be referred to as an optimal dose, and it should not be considered more than a guide to the upper limit of intake for minimizing fluorosis.

For the reason listed above, the proposal to eliminate sodium fluoride in forms of rinses and tablets from WHO’s list of essential medicines is justified.

Sincerely,

REFERENCES:


3) Comment on school based fluoride mouth-rinsing program. Medwather Japan, 4 August 2003. (in Japanese)

