

abstracts and full texts was performed. Meticulous inspection was done for references of each article for possible candidates. The resulting articles were then subjected to clear inclusion and exclusion criteria by two reviewers.

Literature search

The electronic search was carried out in PubMed, Cochrane Library google scholar databases, Medline, Embase, TOXLINE, and papers dated between march 1945 and may 2013 were selected. The following table search descriptors were used together, based on the objective of the present systematic review

a. Data extraction and assessment of study quality

After reading the abstracts and titles, studies retrieved from the databases were selected, following a calibration exercise with 9% of the studies understand by reviewers to establish interexaminer agreement (Kappa: 0.71 to 0.89). Disagreements were resolved by consensus. Reviews were included.

The following electronic databases were searched Medline, Embase®, The Cochrane Library and Google Scholar®. Two preliminary searches were conducted in June 2011 to obtain an overall idea of findings and to polish searching terms (MeSH words) and limits. No topic related nor relevant finding resulted from both The Cochrane Library and Google Scholar®; these electronic databases were therefore excluded from final Boolean search. Final search was conducted on January 30th, 2013. Reference lists of included and relevant papers were reviewed. Abstract was collected for all findings

Eligibility criteria

Protocol for this review was the PRISMA 2009 checklist (available at www.prismastatement.org). It included prevalence and risk factors as variables investigated in the articles; Measured fluoride toxicity according to standards; Reported dietary, oral hygiene habits and Socio-economic level of the family; Clearly describe objective, methods and results, with no significant discrepancies; Case reports, case series, outbreak investigations and abstracts were excluded. The study population included persons who were above 6 years; The study design was a cohort, cross-sectional, case-control.

b. Data collection method and Method of handling the data

Investigator screened all collected findings and registered title, author and whole reference in two Excel files (one for included and one for excluded findings, according to eligibility criteria) using a screening guide created on eligibility criteria. Kind of source was registered as reason for exclusion. Duplicates from different electronic databases were excluded. The full text of all studies judged potentially eligible in at least one screening were retrieved. Then, investigator screened the full text for inclusion using a screening guide and all findings.

3. Results

A total of 1500 relevant records were found in the eight databases, 145 of which were duplicated. A total of 400 references were excluded based on the abstracts, and 65 were selected for full-text analysis, 14 of which were selected for inclusion.

Mohmoud Trabelsi et al (2001)¹⁰ conducted a study to know the effect of fluoride on murine thyroid function and cerebellar development by administering NaF in drinking water (0.5 g/L) to pregnant and lactating mice, from the 15th day of pregnancy to the 14th day after delivery. Results of the study showed that when compared to a control group, the NaF – treated pups, at age 14 days, showed a 35% decrease in body weight, and 75% decrease in plasma free T4. study conducted by Susheela AK et al in children living in Delhi, India indicate that among 90 sample children 49 (54.4%) had well defined hormonal derangements in high fluoride areas.

Du Y et al (2000)¹¹ conducted a study by measuring the intelligence quotient of 118 children; aged 10-12 years differed in the level of fluoride in drinking water. The IQ of the 60 children in the high fluoride area was significantly lower, mean 92.27 + 20.45, than that of the 58 children in the low fluoride area, mean 103.05+ 13.86.

Akpata ES et al (1997)¹² conducted a study to investigate the relationship between fluoride levels in well drinking water, severity of dental fluorosis and dental caries in the Hail region of Saudi Arabia, 2355 rural children aged 12-15 years were examined. Results of the study showed that 90% of the children had fluorosed teeth.

John A AK et al (1993)¹³ conducted a study to assess the prevalence and severity of non-skeletal manifestations, especially gastrointestinal disturbances, in an area of skeletal and dental fluorosis. Results showed that gastrointestinal complaints accounted for 26% were consuming water with fluoride in the range of 0.25-8.00 ppm.

Teotia M et al (1998)¹⁴ conducted an epidemiological studies during 1963-1997 on 45,725 children exposed to high intake of endemic fluoride in the drinking water since their birth. he toxic effects of fluoride were severe and more complex and the incidence of metabolic bone diseases (rickets, osteoporosis, PTH bone disease) and bone leg deformities (genu valgum, genu varum, bowing, rotational and wind-swept) was greater (>90%) in children with calcium deficiency as compared to <25%. John A Yiamouyiannis (1993)¹⁵ conducted a study to know the association between fluoridation and cancer. Using three different data bases they found that the bone cancer incidence rate was as much as 0.95 cases a year per 10,000 population higher in males under age 20 living in fluoridated areas.

4. Discussion

During the latter half of the 19th century and the first half of 20th century, sodium fluoride was commonly used as a pesticide in US homes and institutions. It was often stored in

kitchen or other places where residents had access to the compound; because of this many cases of accidental or unintentional acute fluoride poisoning occurred.

One of the major incident of acute fluoride toxicity occurred at the Oregon state hospital, a meal of scrambled eggs was prepared with sodium fluoride which had been mistaken for powdered milk. Approximately 17 pounds of sodium fluoride were added to 10 gallons of eggs. There were 263 cases of acute poisoning of which 47 terminated fatally. With major exception of dental products fluoride compound are rarely found in the home today.

4.1 Acute Oral Toxic Dose

The literature contains a wide range of estimates for the acute toxic dose of fluoride. Driesbach (1980) stated that it was 6-9mg F/ kg, while Lidbeck et al (1943) suggested that it was over 100mg F/ kg.

Based on their review of literature Hodge and Smith (1965) concluded that "certainly lethal dose" of Naf for 70kg person was 5-10 g when taken orally. This corresponds to a fluoride dose of 32-64 mg F/ kg. This dose is equalent to an LD₁₀₀ i.e., any adult who ingested that much fluoride would be expected to die and it is of more practical value to dentist or physicians whose patients may experience fluoride overdoses, or to manufacturers who must decide how much fluoride to put into their products. The "safely tolerated dose" the LD₁₀ or LD₃₃.

Whitford (1987, 1990) concluded that the "probably toxic dose" (PTD) of fluoride is 5mg F/kg of body weight. The PTD was defined as the "minimum dose that could cause toxic signs and symptoms," dose that could cause toxic signs and symptoms including death, and that should trigger immediate therapeutic intervention and hospitalization.¹⁶

When sufficient large amount of fluoride are ingested as a single dose, a catastrophic chain of event rapidly develops. The first effects experienced by the victim usually include nausea, vomiting, and burning or cramp like abdominal pains. There may be excessive salivation and tearing, mucous discharges from the nose and mouth, a generalized weakness, paralysis of muscles of swallowing, crapo-pedal spasm or spasm of the extremities, tetany, and generalized convulsions. The pulse may be thready or not detectable. Blood pressure often falls to dangerously low levels at some point during the course of the toxic episode. As respiration is depressed a respiratory acidosis develops.

The different chemical forms of fluoride vary in their toxic potentials as well, chiefly because of differences in the rate or degree of absorption from GI tract. Thus fluoride from sodium or potassium fluoride, compounds which are relatively soluble is more toxic than that from compounds which contains di-or trivalent cations such as calcium, magnesium, or aluminum. Studies have shown that younger animals are more resistant to the lethal effects of fluoride.

4.2 Fluoride in Dental Products

The concentrations of fluoride in dental products should be known by the user. The commonly used products containing fluoride include mouth rinses, dentifrices, topical fluorides, tablets and varnishes. The 0.2% sodium fluoride rinses and the 0.4% stannous fluoride rinses contain 1.0 mg of fluoride per ml. The largest containers of the 0.05% sodium fluoride rinses which are sold OTC contain up to 18 ounces pr 530 ml. Fluoridated dentifrices contain fluoride at approximately 1000ppm, i.e., 1.0 mgF/g. Among the major brand, the fluoride is added as MFP (Monofluorophosphate).

Topical fluoride, which in most cases are acidified with phosphoric acid to a Ph of about 3.5 and contain fluoride at concentration of 1.23% or 12,300ppm thus each ml contain 12.3mg of fluoride. Several variables can affect the susceptibility to the acute toxic effect of fluoride including acid-base status (Reynolds et al., 1978; Whitford et al., 1979), age (Mornstad, 1975) and possibly sex.

"Fluoride tablets or drops are designed to supplement dietary fluoride intake by children from birth to 13 years of age. The ADA council recommends that "as a precautionary measure no more than 264 mg of Naf (120mg F) be dispensed at one time".

The two of the three deaths of children that were attributed to fluoride in dental products occur because of ingestion of fluoride tablets.¹⁷

Children younger than 6 years of age accounted for more than 80% of reports of suspected over ingestion this was shown by study conducted by Shulman J.D (1997).¹⁸

The ADA recommends that no more than 120mg of tablets be prescribed to a patient. But the 120mg limit was set to prevent fatalities or sever toxic reactions, not to prevent mild to moderate toxicity. Dose rate for 3year old child at the 50th percentile (14.69kg) would still be 8.2 kg almost 70% higher than the presumptive PTD. So the data from the study conducted by Shulman J.D (1997) shows young children ingesting relatively small volumes of home use products can reach the PTD.¹⁸

Fatalities due to acute toxic effects of fluoride were independent of the chemical form in which it was given independent of the vehicle and not predictable in terms of a well defined threshold range of peak plasma fluoride concentration as shown by Whitford G.M (1990)¹⁹

Dybing and Loe (1956) and Gruninger et al (1988) reported that female rats were some what more sensitive than males, but Mornstad (1975) concluded that there were no differences between sexes.¹⁹

An important site of a toxic reaction is the stomach. When fluoride is swallowed and react with the HCL of gastric juice, it is converted into the highly irritant HF. Concentration of 10mmol / liter (190ppm) have shown in dogs and rats to produce effects varying from patchy loss of mucous membrane to erosion sufficiently severe to expose the underlying lamina propria. The threshold for changes in

gastric function is between 1 and 5mmol/liter (19-95ppm), concentrations that could be reached by swallowing several dental products in small amounts like about 2.0ml of APF gel (Whitford, 1990).¹⁹

Chronic fluoride toxicity results from long term ingestion of small amount of fluoride. The problems however are not common and are usually associated with a very high level of fluoride intake over a long period.²⁰

Available evidence shows that fluoride-related risks fall generally into two areas: effects on the dentition and other systemic effects. The chronic fluoride toxicity on enamel is dental fluorosis. There is some evidence to link exposure to the high doses of fluoride and skeletal fluorosis and bone fracture. There are concerns about the possible link between the fluoride and cancer or carcinogenicity, chronic low level fluoride exposure and its effects on thyroid, GI system, kidney, brain, fluoride and birth defects, mutagenicity and its effect on reproductive system.²¹

The study conducted by Bohatyrewicz A (1999) showed that Fluoride intake (60mg f/l in drinking water) decreases bone quality in the femoral shaft and femoral neck of young growing rates.²²

4.3 Fluoride toxicity and teeth

Epidemiological studies conducted around the 1940's by Dean and coworkers demonstrated a positive association between the fluorides, prevalence and severity of dental fluorosis. Since then, numerous studies have established that the more fluoride which is ingested during the period of tooth formation and mineralization; the greater the risk of severe manifestation of dental fluorosis at the time of tooth eruption. Dental fluorosis is the undesirable effect of fluoride ingestion. Early manifestation of dental fluorosis as being the undesirable but unavoidable effects of systemic ingestion of fluoride.³

The factors which govern the incorporation of fluoride into dental structures are essentially similar to those pertinent to bone. Fluoride is taken up most rapidly during the phase of growth and development. The overall uptake of fluoride in dentine and enamel is therefore, maximal during their periods of formation and calcification.

Three phases of dental fluoride uptake can be visualized: that occurring in the phase of formation, that occurring during the subsequent period of mineralization and that occurring after mineralization is complete. In the first phase the element is probably taken up uniformly throughout the tissue; in the second, uptake will be largest in areas where mineralization occur; in the third, when the teeth have fully formed and achieved complete mineralization, uptake will be almost entirely limited to the marginal regions of both enamel and dentin.

The toxic effects of large doses of fluoride are predominantly confined to the teeth and skeletal system, with secondary involvement of the nervous system in advance and crippling fluorosis.

5. Conclusion

The effect of fluoride is dose dependent and is not confined to increased caries resistance, that's why fluoride is known as double-edged-sword. Above certain levels in water supply, visible changes or ill effects to the teeth particularly on enamel, bone and other soft tissues become evident.

There is experimental evidence of the toxic effects of fluoride in large concentration on the thyroid, kidney, and other organs but overt clinical disturbances in the function of these organs have not been described in endemic fluorosis. Fluoride poisoning and the biological response leading to ill effects depends on many factors, concentration of fluoride in drinking water, low calcium and high alkalinity of drinking water, total daily intake of fluorides, duration of exposure to fluorides, age of individual, nutritional deficiency also aggravates fluorosis.

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