
REVIEW

Fluorine in medicine

Anna Strunecká¹, Jiří Patočka², Paul Connett³

¹ Department of Physiology and Developmental Physiology, Faculty of Sciences, Charles University, Praha, Czech Republic

² Department of Toxicology, Military Medical Academy, Hradec Králové and Faculty of Health and Social Studies, University of South Bohemia, České Budějovice, Czech Republic

³ St. Lawrence University, Canton, New York, USA

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Summary

Fluoride has long been known to influence the activity of various enzymes *in vitro*. Latterly it has been demonstrated that many effects primarily attributed to fluoride are caused by a synergistic action of fluoride plus aluminum. Fluorinated chemicals are of growing importance, with applications in medicine. Fluorine substitution has profound effects on the properties of organic compounds. The very high electronegativity of fluorine can modify electron distribution in the molecule, affecting its absorption, distribution and metabolism. Fluorine-containing drugs are used in medicine as anesthetics, antibiotics, anti-cancer and anti-inflammatory agents, psychopharmaceuticals, and in many other applications. The potential contribution of fluorinating pharmaceuticals to human fluoride exposure is discussed.

Keywords: fluoride – aluminofluoride complexes – fluorine-containing drugs – health effects

INTRODUCTION

It is noteworthy that fluorine, which is the most abundant halogen and the thirteenth most abundant element in the earth's crust, was not involved in the ancient evolution of life on Earth as a regular component of organic compounds of living organisms (O'Hagan et al. 2002). All the known naturally occurring fluoro-organic compounds are poisonous (Patočka and Cabal 1999). The finding of fluorine in teeth enamel, ash of blood, and the yolk and shell of eggs stimulated the search for its physiological role (McClure 1933, Waldbott et al. 1978). The effects of fluoride were reported in many enzymatic reactions in research conducted by prominent biochemists Embden, Lohman, Lipmann,

Meyerhof, and their coworkers (McClure 1933). The use of sodium fluoride helped in understanding the mechanisms of enzyme catalysis in glycolytic and Krebs-cycle pathways. Laboratory investigations during the last several decades has produced evidence that fluoride in the presence of trace amounts of aluminum ions acts as an analogue of phosphate groups and stimulates G proteins in cell signalling cascades.

In addition to laboratory research using isolated cells/tissues or animal models, many epidemiological, ecological, and clinical studies have shown the effects of fluoride on wildlife, domestic animals, and humans. Most of the ill effects caused by fluoride were first recognized among workers in aluminum factories, where

fluoride and aluminum are present in high concentrations. The levels of fluoride in the serum, urine, and hair of these workers are higher than in the control subjects. Osteoarthritis and related disorders in industrial workers have been reported since the 1930's (McClure 1933, Roholm 1937, Waldbott et al. 1978). Observation of industrial fluorosis led to the use of fluoride in medicine as a treatment to increase bone mass in osteoporosis patients (Franke 1997).

Seventy years ago a dentist H. Trendley Dean, working for the U.S. Public Health Service, examined water from 345 communities in Texas and claimed that there was a lower incidence of dental caries in communities having about 1 ppm (1 milligram per liter) fluoride in the water supply. Dean's famous 21 City Study (Dean 1942) led to the concept that fluoride ingestion will harden the surface of teeth and make them less susceptible to dental caries. In 1950, before any trials had been completed, the US Public Health Service (PHS) endorsed fluoridation of public water supplies. This practice was initiated later also in many countries all over the world as a way of preventing dental caries. Numerous laboratory, clinical, and epidemiological studies dealing with all aspects of the metabolism, biological effects, pharmacology, and toxicology of fluoride have published during the last 50 years. The information already at hand, however, presents a number of reasons for the serious assessment of the risks of fluoride to the human body. Additionally, people now get fluoride from many other sources, including foods and beverages prepared with fluoridated water, pesticide and fertilizer residues, dental treatments and products. The past 50 years have seen a dramatic increase in the volume of man-made industrial fluoride compounds released into the environment, so total fluoride intake has become an issue of particular concern (Bryson 2004).

The development of new fluorinating agents and advancement in organofluorine chemistry has eminently increased the potential for synthesis of novel fluorinated drugs and fluorine-containing compounds with applications in medicine. These include general anesthetics, antibiotics, antiviral and antimalarial agents, anti-inflammatory drugs, antidepressants, antipsychotics, and different biocompatible materials. Many of them release fluoride into body fluids and tissues. Medical schools and university texts seldom share the scientific details of fluoride's physiological and/or toxicological activity. Because of this situation important questions remain unanswered and many research avenues unexplored. The aim of our article is to provide the first foundation for the assessment of the safety, benefits and/or risks of fluorine-containing drugs for human health.

MECHANISM OF FLUORIDE EFFECTS IN LIVING ORGANISMS

Fluoride interactions with enzymes

Fluoride has been found to inhibit the activity of many important enzymes such as enolase, lipase, phosphofructokinase, pyruvate kinase, glycogen synthase, succinate dehydrogenase, cytochrome oxidase, various phosphatases, ATP-ases, urease, and cholinesterases, to name a few (Machoy 1981, Strunecká and Patočka 2002, 2003). The Clinical Toxicology of Commercial Products (FCDSW 1984) accounts for the toxic action of fluoride by the fact that fluoride ions act as enzymatic poisons, inhibiting enzyme activities and, ultimately, interrupting metabolic processes. Some enzymes, such as adenylyl cyclase, lactate dehydrogenase, glycogen phosphorylase, and many others, are stimulated by fluoride in millimolar concentrations.

While fluoride in human organism will probably not reach the concentrations used in laboratory experiments with isolated cells/tissues, there may be moments where fluoride ions reach microenvironments where interference may occur, especially at the active sites of certain enzymes.

In some cases the biological effects of fluoride can be realized with the help of any metabolite of fluoride, e.g. fluoroacetate (Arellano et al. 1997). Fluoroacetate as well as some higher ω -fluorocarboxylic acids have been described as the toxic principle of some poisonous plants (Patočka and Cabal 1999). Fluoroacetate is toxic because it is converted in vivo in mitochondria to fluorocitrate, which occurs through condensation of fluoroacetyl-CoA with oxaloacetate by the enzyme citrate synthase, which supplies acetyl-CoA into the citric acid cycle. Fluorocitrate is a strong inhibitor of aconitase. The vital biochemical pathway for energy production in living organisms is thus frozen.

Fluoride synergistic effects with aluminum ions

Another concern is that fluoride forms complex ions with aluminum ions. Fluoride anions, generally introduced as NaF solutions, have long been known to stimulate the activity of adenylyl cyclase and GTP binding proteins (G proteins). It was later demonstrated that the effects primarily attributed to fluoride are caused by synergistic action with aluminum (Sternweis and Gilman 1981). This fact had at first been ignored because aluminum is a normal component of glass from which it is etched by a solution with fluoride.

In water solutions, aluminum forms in the excess of fluoride aluminofluoride complexes (AlF_x),

whose average stoichiometry depends on the fluoride concentration and the pH of the solution (Chabre 1990, Strunecká et al. 2002). The ability of these complexes to simulate phosphate groups in many biochemical reactions has been documented by numerous studies. AlFx can bind to proteins by hydrogen bonds to the fluorine atom, just as to oxygen atoms of a phosphate ion. Analogies between the phosphate group and AlFx consist in atomic and molecular similarities.

The transfer of phosphate groups is the basic mechanism in the regulation of the activity of numerous enzymes, energy metabolism, cell signalling, and regulation of cell growth. In view of the ubiquity of phosphate in cell metabolism, a phosphoryl transfer transition state analog represents a useful tool for laboratory investigations, but also a strong potential danger for living organisms including humans (Strunecká and Patočka 2002).

The low cost and availability of these fluorometallic complexes probably contributed to the fact that their use as a tool in laboratory studies of G proteins is widely spread. Heterotrimeric G proteins mediate the transfer of information from heptahelical receptors in plasma membrane to effector molecules (Gilman 1987, Morris and Malbon 1999). Physiological agonists of G protein-coupled receptors include neurotransmitters and hormones, such as dopamine, epinephrine, norepinephrine, serotonin, acetylcholine, glucagon, vasopressin, melatonin, TSH, neuropeptides, opioids, excitatory amino acids, prostanoids, purines, photons, and odorants. The use of AlFx in G protein studies brought a great deal of knowledge about the role of G proteins in cell signalling (Rodbell 1995). Numerous papers offer evidence that AlFx influence various functions and biochemical reactions of all cells and tissues of the animal or human organisms with powerful pharmacological efficacy. Fluoride in the presence of trace amounts of aluminum affects all blood elements, endothelial cells and blood circulation, the function of lymphocytes and cells of the immune system, bone cells, fibroblasts and lung cells, ion transport in kidneys, calcium homeostasis, processes of neurotransmission, metabolism of the liver, growth and differentiation of cells, protein phosphorylation, and cytoskeletal proteins (Strunecká and Patočka 1999).

Such evidence is not surprising in respect to the role of G proteins in signal transduction. It has been demonstrated that AlFx may clone or potentiate the action of numerous extracellular signals. Moreover, the signal of every AlFx molecule is greatly amplified during the processes of signal transduction inside the cell. AlFx is therefore efficient in extremely low (nM) concentrations. The toxicological potential of fluoride is thus markedly

increased in the presence of trace amounts of aluminum ions (Lubkowska et al. 2002).

FLUORIDE IN THE PREVENTION OF TEETH CARIES AND DENTAL FLUOROSIS

In 1931, it was determined that the cause of mottling tooth enamel, now called “dental fluorosis,” was the presence of fluoride in the water. Because some early researchers reported less tooth decay in children with dental fluorosis (Dean 1942), it was speculated that there might be a level at which fluoride would protect teeth but not cause too much fluorosis. However, the largest US survey and a compilation of studies worldwide (www.fluoridealert.org) indicate that somewhere between 30% and 50% of children in fluoridated communities have dental fluorosis, and not all of it in the very mild and mild categories. Thus, dental fluorosis is now impacting 3–5 times as many children as intended. There are many discussions between proponents and opponents of water fluoridation all over the world. While proponents, including WHO, describe water fluoridation as “one of the top ten public health achievements of the twentieth century” and dismissed any notion of health concerns, many scientists are concerned about the risks of increased fluoride supplementation for human health. Much evidence forces them to consider whether any dental benefits could justify potential health risks to so many people. One of the reasons Dr. Arvid Carlsson (Nobel laureate in medicine, 2000) gave for leading the successful campaign against water fluoridation in Sweden was his concern about what such increased fluoride levels would do to the developing brain of newborn infants (Carlsson 1978). In the light of recent findings concerning fluoride’s potential neurotoxicity, Carlsson’s concerns have gained renewed significance (Strunecká and Patočka 2003).

Today, approximately 60–70% of American people are supplied with fluoridated drinking water. Worldwide, however, the vast majority of countries do not support the practice and only Australia, Columbia, Ireland, New Zealand, and Singapore have more than 50% of their population drinking fluoridated water (www.fluoridealert.org). Nevertheless, the use of fluoride tablets (0.5 mg NaF) as an efficient way for the prevention of dental caries is commonly recommended by official health and dental organizations (WHO, EAPD).

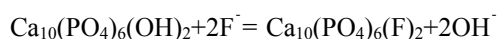
While an analysis of discussions of fluoride supplementation has not been the focus of this review it seems that the reduction in tooth decay attributed to water fluoridation is very small and

appears to be neither clinically nor statistically significant (www.fluoridealert.org). WHO data available online indicate the same declines in tooth decay have occurred worldwide in both fluoridated and non-fluoridated countries over the period from the 1960's to 1990's. Unpurified hexafluorosilicic acid is the primary chemical now used to fluoridate public water supplies in the USA. Being able to convert a hazardous waste material into a saleable product is very attractive for the phosphate industry. It would be extremely expensive to send this material to hazardous waste sites.

Science has already accumulated evidence about the detrimental effects of fluoride on the living organism. Numerous published reports bring us at least strong warnings and a challenge to increased responsibility before prescription and recommendation of endogenous administration of fluoride in various drugs, particularly for children.

BONES AND SKELETAL FLUOROSIS

Caverzasio et al. (1998) have offered a very plausible mechanism for fluoride's ability to stimulate the proliferation of osteoblasts, a phenomenon exploited in the treatment of patients with osteoporosis. When fluoride reaches calcified tissues (like the teeth and bone) it rapidly exchanges with the hydroxide ion on the calcium hydroxy apatite crystals, forming calcium fluorapatite:



Numerous authors have reported deterioration in the mechanical properties of fluoride-containing bone (Bohatyrewicz 1999, www.fluoridealert.org). It seems that the effects of fluoride on bone quality are dependent on the balance between the beneficial effects and deleterious effects, which are influenced by daily doses and the duration of treatment, and actual content of fluoride in the bone. In examining fluoride's impact on bone in more detail, the concern only deepens. Fluoride has different effects on different parts of the bone. It tends to increase the bone mineral density of trabecular bone (the mesh-like interior of the bone, which is important for weight bearing), but decreases the bone mineral density of cortical bone, the outside layer of the bone, which is important for resistance to torsional and sheer stress.

The ability of fluoride to damage children's bones, even at low levels of water fluoridation (1 ppm), was first observed in the 1945–55 fluoridation trial in the USA (Schlesinger et al. 1956). A higher incidence of cortical bone defects

was observed in the children in fluoridated Newburgh (13.5%) than in non-fluoridated Kingston (6.5%). In a survey of an area in Mexico, which had naturally high levels of fluoride in the water, the incidence of bone fractures in both children and adults increased in a linear fashion with the severity of dental fluorosis.

Since 1990, there have been at least seventeen epidemiological studies that have examined whether fluoridation influences the rate of hip fracture. Of these, 10 have found a positive relationship and 7 have not (www.fluoridealert.org). Since the Roholm's classic study of cryolite workers in Denmark (Roholm 1937), it has become apparent that skeletal fluorosis impacts millions of people in countries with regions of high endemic levels of fluoride, like India and China. WHO (2002) estimates indicate that for a total intake of 14 mg F/day, there is a clear risk of skeletal adverse effects. There is suggestive evidence of an increased risk of effects on the skeleton at total fluoride intakes above about 6 mg/day.

FLUORINE-CONTAINING DRUGS

Artificial fluorine substitution of biologically active molecules exercise an influence on their properties and activities. The replacement of a hydrogen atom and/or a hydroxyl group by a fluorine atom are common strategies in drug development (Alkorta et al. 2000). Fluorine substitution in a drug molecule can influence not only pharmacokinetic properties, such as absorption, tissue distribution, secretion, and the route and rate of biotransformation but also its pharmacodynamics and toxicology (Wakselman 1999). At present more than two hundred fluorinated pharmaceuticals are available and others are appearing. The benefit of fluorinated drugs for human medicine is very well known; much less is known about the danger of these compounds for human health. The mechanism of fluorine participation in their different undesirable effects has not been fully explained. Defluorination of fluorinated drugs can readily occur during biotransformation, or may also occur spontaneously, if a molecule is sufficiently electrophilic to undergo direct reaction with a nucleophilic group present in proteins and amino acids, such as the amino group in lysine, the sulphydryl group in cysteine or the hydroxyl group in serine (Park et al. 2001). Such defluorination was observed for example in the case of an antimalarial drug 5-fluoro-amodiaquine (Harrison et al. 1992) or hormone 2-fluoroethynilestradiol (Morgan et al. 1992). In rare instances, even the trifluoromethyl group may undergo defluorination (Thompson et al. 2000).

Fluorine-containing volatile anesthetics

The first inhalation anesthetic, methoxyflurane, was widely used in clinical anesthesia until its association with nephrotoxicity was reported (Crandell et al. 1966). In some cases fatal renal failure was described (Panner et al. 1970). A high urine output syndrome leading to dehydration was related to the extensive metabolism of methoxyflurane joined with high serum concentrations of inorganic fluoride, since methoxyflurane is metabolized to oxalic acid and free fluoride. The increased intrarenal fluoride concentration has been suggested as the most important factor in methoxyflurane nephrotoxicity (Kusume 1999).

Further volatile fluorine-containing anesthetics such as halothane, isoflurane, sevoflurane, enflurane, and desflurane were synthesized later. A concern about the potential nephrotoxicity and/or hepatotoxicity of new anesthetics have led to numerous clinical studies during the last two decades. The toxicity of these anesthetics might be caused by their biotransformation to toxic metabolites. Flurane anesthetics are metabolized to hexa-fluoro-isopropanol and inorganic fluoride by the human liver (Kharasch 1996). In vitro investigations have identified a role for human cytochrome P450 (CYP 2E1 and 2A6) in oxidation and CYPs 2A6 and 3A4 in reduction. Kharasch and Thummel (1993) demonstrated that CYP2E1 is the principal, if not sole human liver microsomal enzyme catalyzing the defluorination of the fluorinated ether anesthetics in vivo. The rank order of anesthetic metabolism, assessed by fluoride production at saturating substrate concentrations, was methoxyflurane > sevoflurane > enflurane > isoflurane > desflurane > 0. Until recently, inorganic fluoride has been thought to be the main etiological agent responsible for fluorinated anesthetic nephrotoxicity, with a toxic concentration threshold of 50 $\mu\text{mol/L}$ in serum (Gentz and Malan 2001), exceeded the reported basal values (about 3 $\mu\text{mol/L}$) 5–20 times. However, numerous studies including hundreds of patients have not shown evidence of their nephrotoxicity based on the biochemical parameters for kidney functions examined after the termination of anesthetic administration (Gentz and Malan 2001, Conzen et al. 2002). It seems that the human body has an efficient homeostatic mechanism to respond to a short time peak in the serum fluoride level.

However, the wide scale of variations in the serum fluoride level and case reports of the individual adverse effects indicate caution in using flurane anesthetics particularly when prolonged anesthesia and surgery are planned. It has been reported that AlF_x can affect the activity of many

ion channels and enzymes in the kidney (Strunecká and Patočka 1999). When AlF_3 or NaF at various concentrations were given to rats in drinking water for 45 weeks (Varner et al. 1998), pathological changes were found in the kidneys of all groups. The kidneys from rats drinking the NaF water exhibited glomerular hypercellularity, renal mesangial proliferation, and the deposition of proteins in the renal tubules. Histological evidence of glomerular distortions was present in both the AlF_3 and NaF groups.

Formation of nephrotoxic halogenated alkenes during alkaline degradation in carbon dioxide absorbers, such as 1-chloro-1,2-difluorovinyl difluoromethyl ether or fluoromethyl-2,2-difluoro-1-(trifluoromethyl)vinyl ether (compound A) were suggested as an alternative mechanism for renal toxicity (Orhan et al. 2001). The mechanism of compound A renal toxicity is controversial, with the debate focused on the role of the renal cysteine conjugate β -lyase pathway in the biotransformation of compound A.

Fluorine-containing antiviral and antibacterial compounds

Some new fluorine containing substituted 3-thioxo-1, 2, 4-triazin-5-ones have been synthesized and many of them have retained a significant antiviral activity (Abdel-Rahman 1991). Also some fluorinated purine nucleotides and nucleosides show significant antiviral (anti-HIV) activity (Marquez et al. 1990). Fluorine has been introduced into both the base and the sugar residue. Fluorine-containing antimetabolites are of interest in the development of anti-HIV drugs, such as alovudine, the direct fluorine analogue of zidovudine (3-azidothymidine, AZT). Alovudine is phosphorylated in cells to the 5-triphosphate, which is the active inhibitor of HIV-associated reverse transcriptase (Matthes et al. 1988). Recently, emtricitabine [(-)-beta-L-2',3'-dideoxy-5-fluoro-3'-thiacytidine] has been approved by the Food and Drug Administration for the treatment of human immunodeficiency virus (HIV) (Anonymous 2003).

5-fluorouracil is a major antimetabolite used in the treatment of solid cancers. This compound is converted into a pharmacologically active metabolite 5-fluoro-deoxyuridine monophosphate, which inhibits the enzyme thymidylate synthetase, which then results in diminished formation of one of DNA wall stone – thymidine (Thomas and Zalberg 1998, Feng et al. 2004). Because 5-fluorouracil and its metabolites are concentrated in cancer cells, the enzymatic blockade inhibits tumor growth. 5-fluorouracil is also metabolised into the highly

toxic fluoroacetate, by scission of the pyrimidine ring (Arellano et al. 1998). The toxicity of fluoroacetate is evoked by its entry into the tricarboxylic acid cycle in mammalian cells and its conversion into fluorocitric acid (Patočka and Cabal 1999). In addition, a catabolite of 5-fluorouracil after fluorinated pyrimidine degradation induces cytotoxicity in tumors (Kubota 2003). Anthracycline derivatives with fluorine atom in different position of the molecules have also found use in modern oncology.

The most known and very much used fluorine-containing antibacterial compounds are fluoroquinolone antibiotics. A fluorine substituent strongly enhances the antibacterial potential of the drug. Fluoroquinolones features a broad antimicrobial spectrum. In general, fluoroquinolones were considered to be remarkably safe. Nevertheless, several side-effect were reported, including hepatic reactions, neurotoxicity, phototoxicity, cardiotoxicity, tendinopathy, and chondrotoxicity (Stahlmann 2002). In premarketing trials with 7000 patients, trovafloxacin was associated with no cases of liver failure and about 2.5 million patients received Trovan®, up to 300,000 prescriptions per month. In July 1998, the FDA advised revision of the package insert to reflect hepatic toxicity. A public health advisor reported 140 patients with serious hepatic events. Fourteen patients developed acute hepatic failure: 5 received liver transplants (1 died), 5 patients died without transplantation, and 4 others recovered. Hepatotoxicity occurs after an unpredictable trovafloxacin exposure time, ranging from 2 to 60 days. There appears to be increased risk with greater than 14 days of use, and some cases occurred after re-exposure. Six out of the first 40 reported patients had peripheral eosinophilia, suggesting a hypersensitivity reaction (Rubinstein 2001). The use of trovafloxacin has been significantly restricted due to substantial mortality and morbidity associated with liver toxicity (Bertino and Fish 2000).

The most common adverse events in clinical use of fluoroquinolones are nausea, diarrhea, headache, and dizziness. All fluoroquinolones have the potential to cause photosensitivity (Chignell 1998). Photosensitization can result when light interacts with chemical agents in the skin and eyes. This process can produce undesirable clinical consequences, such as phototoxicity (i.e. exaggerated sunburn), photoallergy or photocarcinogenicity. People receiving fluoroquinolones are warned on the product inserts not to expose themselves to direct sunlight. The first symptom is a developing rash on the exposed areas. In order to suppress the toxic effect of fluorine in chinolones, new compounds without the usual

6-fluorine substituent have been recently described as potent antibacterial agents. A series of non-fluorinated analogues of the antibacterial quinolone levofloxacin were synthesized and tested (Gray et al. 2003).

Moxifloxacin shares the quinolone-class warnings and precautions regarding use in pediatric populations, pregnant women, nursing women, and patients with central nervous system disorders. The class warnings regarding convulsions, increased intra-cranial pressure, psychosis, central nervous system stimulation, hypersensitivity reactions, pseudomembranous colitis, and tendon ruptures are also similar.

Since the introduction of fluoroquinolones on the market in 1987 more than 200 cases of rhabdomyolysis, tendinitis, tendon rupture etc. have been reported in the literature (Ramanujam 2001). In October 1994 the Japan Pharmaceutical Affairs Bureau (JPAB) was the first to amend the product information for fluoroquinolones to state that muscle destruction – a condition known as rhabdomyolysis may occur (JPAB 1994). For example ciprofloxacin, which has been in use since 1987 for a variety of other indications and was the most-widely used fluoroquinolone in humans and animals worldwide, was withdrawn because of strong adverse effects. Fatal liver failure associated with ciprofloxacin was reported by Fuchs et al. (1994). The most common side-effects of ciprofloxacin are gastrointestinal in nature such as nausea, diarrhea, vomiting, and abdominal pain. In 2000 the FDA approved its use in treatment for inhalational anthrax. As soon as the first cases of anthrax resulting from suspicious mail became known, ciprofloxacin was bought on a mass scale. Ciprofloxacin administration results in elevated serum fluoride levels. In a series of tests evaluating the safety of ciprofloxacin in children, serum fluoride levels increased after 12 hours in 79% of the children; on day 7 the 24-hour urinary fluoride excretion was higher in 88.9% of children observed (Pradhan et al. 1995). Ciprofloxacin has been implicated in several cases of acute renal failure (Zimpfer et al. 2004).

Fluorine-containing anti-inflammatory compounds

Anti-inflammatory drugs are medications which, as well as having pain-relieving (analgesic) effects, have the effect of reducing inflammation when used over a period of time. Also in this group of drugs there are quite a number of fluorinated derivatives. The drugs vary in strength and side effects. There are many other potential side effects, but these vary according to the drug chosen and the individual taking it. Fluorine-containing anti-inflammatory drugs can be metabolized by defluorination, which

favors formation of the stable and toxic fluoride ion (Boiteau et al. 1979). An example of the toxic action of the fluorinated anti-inflammatory drug, niflumic acid, has been described in France. An 86 year-old man who for many years took 500 mg of niflumic acid a day, suffered heavy osteofluorosis and had severe renal insufficiency (Welsch et al. 1990). Similar health problems were suffered by a 61 year-old man who consumed 2.5 l a day of Vichy St-Yorre (a mineral water containing 8 mg of fluorine ions per liter) for 11 years. These two observations serve as a reminder of the indispensable precautions to be observed when prescribing fluorine salts in the treatment of osteoporosis and prescribing fluorine-containing drugs generally.

Fluorine-containing psycho-pharmaceuticals

The introduction of fluorine into psycho-pharmaceuticals escalates penetration of the drug across membranes to the site of action – obviously the central nervous system. Centrally acting drugs must pass through the blood-brain barrier in sufficient concentration to elicit their pharmacological effect. For example some neuroleptics that act by blocking dopamine receptors in the CNS, such as butyrophenones, diarylbutylamines or tricyclics contain either fluorophenyl or trifluoromethyl group, which contribute to the pharmacological activity of these drugs by enhancing CNS penetration. The most widely used butyrophenone is haloperidol. In the search for more potent neuroleptics, it was found that a compound which contains fluorophenyl groups was longer acting than haloperidol (Park and Kitteringham 1994). Also fluorine-containing phenothiazines – fluphenazine, trifluoropromazine, and trifluperazine, are more active than the mother compound chlorpromazine (Resnati 1990).

The most often used fluorine-containing psycho-pharmaceuticals are antidepressants and antipsychotics. Particularly, fluoxetine (Prozac) and citalopram are very favored. Prozac is widely used for the treatment of depression, obsessive-compulsive disorder, and bulimia nervosa. Fluoxetine and citalopram can cause nausea, headache, anxiety, insomnia, drowsiness, and loss of appetite (Edwards and Anderson 1999).

Fluoxetine has been implicated in serious skin rashes and vasculitis (Sannicandro et al. 2002). Increased blood pressure can occur and should be monitored. Seizures have been reported. Life-threatening interactions can occur in combination with MAO inhibitors. MAO inhibitors and fluoxetine should not be taken together and a waiting period of 14 days between taking these two

classes of medications is strongly advised (Sternbach 1988).

Other fluorine-containing drugs

It has been shown that fluorinated analogues of naturally occurring biologically active compounds including amino acids, often exhibit unique physiological activity. Fluorination of natural hormones can lead to molecules with new pharmacokinetic and/or pharmacodynamic properties. For example the introduction of fluorine into corticosteroids has a dramatic effect on their metabolism (Bush and Mahesh 1964). Because the metabolism of steroid hormones is very important for their physiological activities, the exchange of a hydrogen atom under fluorine atom can be very meaningful. Also other endogenous compounds markedly exchange their biological properties, if one or more fluorine atoms are installed into their molecule. For example, the potent platelet aggregating agent thromboxane A_2 has a half-life *in vivo* of only 32 seconds. Incorporation of two fluorine atoms into the oxetane ring of thromboxane A_2 reduces the rate of carbonium ion formation and acid hydrolysis, so that 7,7-difluoro-thromboxane A_2 has a rate of hydrolysis 10^8 -fold slower than the natural substance (Fried et al. 1984). Likewise prostacyclin, which is an inhibitor of platelet aggregation, has a very short biological half-life. Fluorination improves the stability of the molecule toward acid hydrolysis and the stability in organisms. Thus 10,10-difluoro-13-dehydroprostacyclin exhibits a half-life 150 times, and has equal potency to, the natural compound (Fried et al. 1980).

Cerivastatin, a fluorinated drug from the statin class, which had caused deaths and serious adverse health effects was withdrawn from the market in 2001 (Furberg and Pitt 2001). It had been linked to at least 31 deaths. Cerivastatin also induced muscle destruction (rhabdomyolysis) and displayed compounded toxicity when used with other drugs.

CONCLUSION

The trend toward fluorinating pharmaceuticals contributes to well-documented human fluoride overload from the living environment (Bryson 2004). Of particular concern must be those who are most vulnerable to fluoride's toxic effects, which include infants and children, high water consumers, the elderly, those who are hypersensitive to fluoride, those with poor health and kidney dysfunction. Fluoride in the presence of trace amounts of

aluminum (which is present everywhere) can act as the messenger of false information, activating G proteins and evoking numerous pathological changes. Moreover, fluoride in the form of aluminofluoride complex might potentiate the subclinical pathophysiological alterations. Serious health problems can arise after application of fluorinated hormones. No one can responsibly predict what happens in a human body after administration of fluorinated compounds. Large groups of people, including neonates, infants, children, and ill patients serve thus as the subjects of pharmacological and clinical research.

Albert Gilman said in his Nobel prize lecture: "The ultimate dream is to design drugs that will prevent aberrant G protein action." Fluoride plus aluminum produce aberration of G proteins. How many human subjects will applied biomedicine need, to accept this knowledge? The awareness of the health risks of an increasing load of fluoride and aluminum ions would contribute significantly to the decline of risks of many severe disorders in the 21st century.

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✉ **Address:**

Anna Strunecká, Department of Physiology and Developmental Physiology, Faculty of Sciences, Charles University, Viničná 7, 128 00 Praha 2, Czech Republic; strun@natur.cuni.cz
