Is Formocresol Still Safe for Use in Pediatric Dentistry? (Part I)

This is the first paper in a series that will review the role of formocresol and alternative pulp therapy medicaments for primary teeth in paediatric dentistry.

Many of the publications on the management of the exposed pulp in primary teeth have been anecdotal, and so are based on opinion rather than scientific data. Currently, dentists still tend to use a traditional-based approach to their treatment that has evolved from their accumulated knowledge, experience and innate adherence to long-held standard practices.

However, we are in the era of evidence-based dentistry; a process that should restructure the ways in which clinical situations are managed, with an emphasis on the integration of good judgement in conjunction with the best available evidence and the patient’s views and values in the making of clinical decisions. Thus, clinical decision making should rely on evidence rather than authority, and it should encourage practitioners to audit their own clinical performance.

The use of formocresol for the management of the exposed vital pulp in primary teeth is a dilemma that has been vigorously debated over the past two decades. Nevertheless, formocresol is regarded as the gold standard and remains the most commonly used material for pulpotomies. Probably the first report of a formaldehyde containing pulp medicament being used was in 1874 when Nitzel applied a tricresol-formalin tanning agent. Buckley’s formulation consists of 19% formaldehyde, 35% cresol, 15% glycerine and water, was introduced in 1904 for the treatment of non-vital permanent teeth following his presentation on the action of several chemicals on human tissues. At about this...
Formocresol produces an area of necrosis in the adjacent pulp tissue with the fixative effect on the tissues diminishing towards the apex. The apical third of the pulp is said to be unaffected, and remains vital for an extended period of time. The technique of applying formocresol in the pulpotomy on a primary tooth has undergone several changes: from its application in several sessions at full concentration in order to fully fix the pulp, to a single 5-minute application and subsequently at a concentration of 20% of the original formula.

Some reservations have always been expressed about the use of formocresol in primary molar pulp treatment. The use of formocresol has been challenged because of its deleterious effects, potential carcinogenic in action, immune sensitization, mutagenicity and cytotoxicity. The concern has been with the formaldehyde component of the formocresol, because formaldehyde has been shown to be distributed systemically after a pulpotomy. Moreover, the International Agency for Research on Cancer (IARC) Working Group, stated that there was now 'sufficient evidence that formaldehyde causes nasoharyngeal cancer in humans'. Recently, in the European Union, commercial dental products containing formaldehyde have been withdrawn from the market, a restriction which, however, does not exist in North America. Thus, Paediatric Dentistry is now confronting the dilemma of whether to continue using formocresol, which has a well established high success rate but entails a "presumed" risk of toxicity.

**Formaldehyde in the Environment**

Formaldehyde is present in the environment in the air, drinking water and even food, as a result of natural processes and from man-made sources. Formaldehyde is produced industrially in large quantities and used in many processes and materials applications including many household products. Two other important man-made sources are automotive exhaust from engines not fitted with catalytic converters, and residues, emissions, or waste products produced during the manufacture of formaldehyde or by materials derived from, or treated with formaldehyde. Thus, people are exposed to formaldehyde every day. The daily intake of formaldehyde from food, according to the World Health Organization, has been estimated, from available data, to be in the range of 1.5-14 mg/day (mean 7.8mg/day), 0.2mg/day from drinking water and approximately 1mg/day from breathing the air. This leads to an average adult intake of 9.0mg of formaldehyde per day.

Children are considered to be exposed to a lesser amount because of their lower food intake, but no pediatric exposure data are available at present. Milnes estimated the systemic dose of formaldehyde, associated with one pulpotomy procedure, using 1:5 dilution of formocresol, placed on a total of four squeezed dry cotton pellets, to be 0.02 to 0.1 mg. The actual dose delivered to the pulp tissue is probably much smaller than this as most of the formocresol will remain in the cotton pellet. Compared to the recognized daily intake by humans, it is unlikely that these small quantities of formaldehyde associated with a formocresol pulpotomy will have any significant impact on a child's daily exposure to formocresol.

**Kinetics and Metabolism of Formaldehyde**

As a normal cellular constituent, it is mostly present in a non-reactive, reversibly bound form. Formaldehyde is produced endogenously from certain amino acids and choline, as well as by oxidative demethylation of steroids and xenobiotics. The concentration of endogenous formaldehyde in the blood of rats, monkeys, and humans is approximately 0.1mM, and this concentration is not measurably altered by exposure to airborne formaldehyde. The concentrations in the liver and nasal mucosa of the rat are 2 to 4 times higher than that found in the blood. Owing to its solubility in water, formaldehyde is rapidly absorbed in the respiratory and gastrointestinal tracts where it is subsequently metabolized. Over 90% of inhaled formaldehyde gas is absorbed in the upper respiratory tract of rats and monkeys. Although formaldehyde and its metabolites can penetrate human skin and induce allergic contact dermatitis in humans, dermal absorption appears to be relatively minor.

Exposure of humans, monkeys or rats to formaldehyde by inhalation does not alter the concentration of endogenous formaldehyde in the blood because of its rapid metabolism. Following intravenous infusion, the biological half-life of formaldehyde in monkey blood is approximately 1.5 minutes, with a concurrent rise in formic acid levels indicating metabolism of the formaldehyde. As may be expected exogenous formaldehyde has with a biological half-life of 1.0 to 1.5 minutes in human plasma.

Formaldehyde, and the oxidation product formate, are key intermediates compounds in the "one-carbon pool", which in turn is utilized for the biosynthesis of purines, thymidine, and certain amino acids, which are incorporated into DNA, RNA, and proteins during macromolecular synthesis. Formaldehyde also reacts covalently with amino and sulfhydryl groups in target tissues and with DNA, forming unstable hydroxymethyl protein...
adducts, known as DNA-protein cross-links (DPX). It has been shown that DPX may act as a replication block,22-25 which could lead to a variety of deleterious effects including chromosomal aberrations, deletions, or even cell death.

Levels of formaldehyde induced DPX are used as a dosimeter in risk assessment,26 and quantitative pharmacokinetic models have been developed to describe the relationship between DPX and the exposure concentration in different species.27,28 It has also been suggested, that at low concentrations approximately 93% of formaldehyde deposited in rat nasal respiratory mucosa is eliminated via metabolism, 7% is eliminated by non-saturable pathways other than DPX formation, and only 7x1^-6% is covalently bound as DPX.28 Because DPX appears to play a critical role in the clastogenic effects of formaldehyde, attempts have been made to determine whether this occurs in tissues other than those of the upper respiratory tract.

Studies have demonstrated the systemic distribution of labeled C from formaldehyde and paraformaldehyde after pulpotomies in mammals.29,30 However, other in-vitro and in-vivo studies in mammals have shown that formaldehyde, in low concentrations does not exhibit mutagenic activity.31,33

Formaldehyde was found to demonstrate a mutagenic potential in studies that evaluated DNA-protein crosslinks and that induced unscheduled DNA synthesis.34,35 The DNA-protein crosslinks act as a replication block in mammal cells, and such lesions can be repaired completely or may result in a mutation if repair is incomplete.36 An organism’s protective mechanism becomes compromised when exposed to formaldehyde concentrations of greater than 5mg/ml. Consequently, the formation of DNA-protein crosslinks with cellular DNA is less likely to occur at lower concentrations.37 Similarly, Heck and Casanova reported that the use of low formaldehyde concentrations in mammals to evaluate DNA-protein crosslinks showed negative results.38

Mutagenicity, Genotoxicity and Cytotoxicity

Studies of the dental pulp of rats, dogs and monkeys have shown that formaldehyde labeled with radioactive carbon (^14C) was found in the muscle, liver, kidney, heart, spleen and lungs. The quantities detected were extremely small; approximately 1% of the total dose that was administered.29,39-41 The studies by Myers and co-workers42 and Pashley and co-workers42 found that ^14C labeled formaldehyde is absorbed systemically from pulpotomy sites. However, Casanova-Schmitz and co-workers43 demonstrated that the labeling of the tissues was due to metabolic incorporation of the radiolabelled metabolite of formaldehyde and not covalent binding.

The possibility that inhaled formaldehyde might induce toxicity at a distant site has been proposed, but no convincing evidence has been obtained from experiments. Heck and Casanova43 reviewed the present evidences and concluded that there is: (i) a lack of detectable protein adducts, or DPX in the bone marrow of normal rats exposed to ^3H and ^14C formaldehyde at concentrations as high as 15 ppm; (ii) a lack of detectable protein adducts or DPX in the bone marrow of glutathione-depleted (metabolically inhibited) rats exposed to ^3H and ^14C formaldehyde at concentrations as high as 10ppm; (iii) a lack of detectable DPX in the bone marrow of Rhesus monkeys exposed to ^14C formaldehyde at concentrations as high as 6 ppm; (iv) failure of formaldehyde to induce leukemia in any of seven long-term inhalation bioassays in rats, mice, and hamsters;44-46 and (iv) failure of formaldehyde to induce chromosomal aberrations in the bone marrow of rats exposed to high airborne concentrations (15 ppm) or intraperitoneal injection of high doses of formaldehyde at a dose of 25 mg/kg.47

Genotoxicity assays are of special concern since genotoxicity has gained widespread acceptance as an important and useful indicator of carcinogenicity. Hagiwara and co-workers48 showed that 14 chemical agents including formocresol elicited chromosome aberrations in Syrian hamster embryo (SHE) cells. However, the formocresol they used was a mixture of formalin and tricresol by weight in the ratio 1:1 diluted with culture medium. Conflicting evidence from other studies has demonstrated that formocresol has a negative genotoxicity on human skin fibroblasts and mouse lymphoma,49 Chinese hamster ovary (CHO) cells50,51 and human peripheral lymphocytes.52

Zarzar and co-workers53 investigated the mutagenicity of formocresol, in Buckley’s original formulation, using lymphocyte cultures obtained from the peripheral blood of 20 children aged from 5 to 10 years old. Although there were no statistically significant differences between the control and the treated groups, Buckley’s formocresol was found to be mutagenic for one patient. The authors concluded that formocresol is not mutagenic, at least statistically; however,