Abstract: Cyanoacrylate (CA) and its homologues have a variety of medical, dental and commercial applications as adhesives. The increasing use of CA in dentistry, particularly as an adhesive and sealing glue, has raised concerns regarding its potential toxicity in humans. Reported toxicity of CA is uncommon in the dental workplace, but may manifest as conditions such as urticaria, contact dermatitis and other dermatoses. Dental staff using CA adhesives should avoid direct contact with CA and use appropriate personal protective measures. Maintaining higher levels of humidity, optimizing room ventilation and using special air conditioning filters in the working environment may be useful in minimising the toxicity of volatile CA adhesives.

Key words: Cyanoacrylate, Toxic effects, Dental services, Occupational health, Occupational allergy, Occupational skin diseases

Introduction

Cyanoacrylates (CA) were first described in 1949 and their potential as adhesives was quickly recognised\(^1\). Various homologues of CA adhesive have been studied and used, including methyl- (MCA), ethyl- (ECA), isobutyl-, isohexyl-, and octyl-CA. Commercial CA adhesive or ‘superglue’ now has widespread use as an all-purpose adhesive in various industries and around the home. CA’s also have clinical applications in dentistry and medicine, especially as tissue adhesives and sealing materials. Despite their increasing use, the toxicity of these substances is not widely known. This paper reviews studies relating to applications and toxicity of CA and its homologues in dentistry, updating a previous literature review\(^2\).

Biochemistry of CA

The chemical properties of one of the homologues of CA, ECA, are given in Table 1. CA adhesive is a compound synthesised by condensation of a cyanoacetate with formaldehyde in the presence of a catalyst\(^3\). The application of an adhesive film of CA develops by rapid polymerization (5–60 s), triggered by hydroxyl groups on the surface to be glued\(^4\). Water can act as a catalyst to activate this anionic polymerisation\(^4\). Given that proteinaceous tissue contains many base residues, the potential for both good wetting of proteins makes CA’s extremely adhesive to biological tissue, perhaps even useful for grafting\(^5\). CA’s retain their adhesive qualities even in the presence of moisture and also have the added benefits of being bacteriostatic and haemostatic\(^5\).

Diluted CA surgical glues, however, did not appear to have significant antimicrobial activity against cultures of *Bacillus subtilis* var. niger, when trialed recently for a three-week period\(^6\).
**Dental Applications**

Applications of CA’s in dentistry have been reviewed elsewhere, and a summary of current applications of CA is given in Table 2. In endodontics, CA has been used to seal the remaining dentin of endodontically treated teeth as it was found to control micro-leakage of oral fluid at the tooth / filling interface. CA also has applications in periodontics, such as in desensitising teeth; and oral surgery, as a tissue adhesive similar to other surgical applications. In preventive dentistry, CA was also the first material modified for use as a pit and fissure sealant to help prevent dental decay, especially on the occlusal surface. However, because this material biodegrades and does not last long in the oral cavity, it was later replaced with other dental materials, such as glycidyl methacrylate dimethacrylate. Nevertheless, CA adhesives have been successfully trialed in treating early enamel lesions, being used to infiltrate porosities in early caries tissue.

Recently, CA, in particular isocyanoacrylates, has been studied for their potential use as dental adhesives. N-butyl-2-cyanoacrylate has been employed as a tissue adhesive, being used for wound closure in oral surgery in a comparative trial with sutures, leading to the normal healing of incisions and immediate hemostasis, as well as pain relief when used for dressing donor sites and mucosal ulcerations. Furthermore, Iso butyl CA has also been used to repair traumatic lacerations to the lip. In orthodontics, CA has been successfully trialed in bonding orthodontic brackets, while reducing the total bonding time. An innovative use of CA was reported from Brazil where a broken endodontic instrument was retrieved from the root canal of a molar tooth using CA. More recently, the development of isocyanatoacrylate copolymers have also been trialed as dental adhesives.

Certain anecdotal and published reports have described situations where patients have repaired their own dentures, mainly acrylic dentures, using commercial CA adhesive. Acrylic is still widely used as a denture base material for the construction of dental prostheses, particularly for people living in the developing world, due to its relative inexpensive. However, this form of prosthesis can be problematic for patients when it fractures and when patients attempt to repair the denture rather than having a new one made. This situation occurs when the repaired denture is not correctly aligned and CA can be difficult to remove, particularly if the prosthesis does not fit well. It is well known that poorly fitting and mal-aligned dentures can cause oral mucosal ulceration.

**Toxicity in Dental Patients**

Little has been written concerning the toxicity of CA adhesives. The main concern of CA’s in dental use has been...
the possible release of substances that may be harmful to the oral mucosa. CA produces a histiocytic proliferation and the formation of giant cells in tissues. The giant cell response is more pronounced when CA is more deeply placed, such as in a tooth socket, compared to more superficial use. The metabolism of CA is largely unknown, however some radio-label is detected in the urine of rats following dermal application and oral administration of MCA and also in the feces following oral administration of MCA. There is no toxicokinetic information available for ECA.

Cytotoxicity

Many studies have investigated the cytotoxicity of CA and its derivatives. CA has been found to be cytotoxic to cells in vitro both in direct contact and in extract dilution assays on cell culture. However, a 1:10 dilution of surgical CA glue was non-toxic to L929 cells after polymerization. The polymerisation or setting reaction of CA is exothermic and the heat released may cause cell damage in cell culture and possibly when used as a tissue adhesive or whenever CA comes into direct contact with cells. Even when filter paper is used as the vehicle for the adhesive to avoid direct cell contact with the adhesive, this form of polymerised commercial CA has been found to be cytotoxic to human oral fibroblast cell culture. This recent study also found that, while the cytotoxicity of commercial CA is reduced considerably following incubation with the media for 24 h, it still releases cytotoxic substances for at least 2 wk. Similar results were found with various commercially available CA adhesives.

Earlier work has proposed that CA adhesives may generate lipid hydroperoxides that activate prostaglandin and thromboxane biosynthesis and also oxidise and lyse cell membranes. This may at least partially explain thrombotic events associated with necrosis when CA adhesives are used in vivo. The use of inhibitors of prostaglandin H synthetase, such as acetylsalicylic acid (aspirin) and indomethacin, reduce the cytotoxicity of CA up to eight-fold in vitro. Conversely, CA surgical glues were not found to effect hemostatis or induce haemolysis in vitro.

Toxicity in Occupational Exposure

CA is widely used in various industries because of its adhesive properties and ease of handling, however, their volatility and chemical reactivity may produce a hazardous environment for workers, including dental staff. Dermatologic reactions, such as urticarial reactions and irritant dermatitis, and non-dermatologic reactions have been reported in one study of prosthodonists as being mainly attributed to monomers of acrylic resin, such as CA’s. Similarly, some dentists in a recent questionnaire survey conducted in southern Thailand, also associated their experience of contact dermatitis with exposure to CA adhesives.

Experience of skin patch testing for acrylate allergies, including to ECA, has been recently reported in a series of 275 patients, however no allergic reactions were reported to ECA. Patch testing has yield positive results, however, in one case study and in one patient of a three patient series. Patch testing with dried CA adhesive on adhesive plaster was useful in diagnosis of contact sensitization of CA adhesive used in the application of artificial nails causing severe onychodystrophy. In the other case, the diagnosis of allergic contact dermatitis due to CA was established in a 40 yr old man who had hyperkeratotic lesions of his fingers. The precise mechanism of the allergy requires further investigation, however allergic reactions to CA are probably of the Th2-type.

Rarely, CA has also induced asthma. A recent study of two assembly operators exposed to CA glue found that CA provoked variable airflow limitation and bronchial hyperresponsiveness. Interestingly, there was an increased likelihood of reversible eye and upper airway irritation was found in workers exposed to CA in a much larger occupational cohort of 450 at an adhesive production facility in Puerto Rico. Pulmonary obstructive symptoms were not seen in these workers.

A higher incidence of CA-related toxicity has been associated with lower humidity in some studies, with outbreaks of asthma and irritant dermatitis in dental staff where the environmental humidity was low. Higher levels of humidity are thought to induce polymerization of free monomers of CA, thereby reducing their volatility.

Reducing Occupational Exposure

Dental staff, using CA adhesives, should be informed of the hazards of the material and control exposure using relevant hygienic controls. In particular, dental staff should take care to avoid direct contact with CA, use CA in a well-ventilated area, and wear appropriate personal protective equipment. Recirculating room air filters with gas sorbents of acid carbon have also been studied for use in the workplace for methyl-2-CA vapour collection, and have been found to have potential application.
Genotoxicity and Carcinogenic Potential

Methyl 2-CA adhesives have been found to have direct mutagenic effects in standard in vitro Salmonella/microsome mutagenicity assay. Volatile compounds produced by vapours from methyl 2 CA have also been found to be mutagenic to a strain of Salmonella typhimurium (strain TA100) and concerns have been raised that methyl 2-CA may pose a carcinogenic hazard. There are no data available from long-term toxicity/carcinogenicity studies on MCA or ECA. While the possibility of CA-induced neoplasia raises some concerns, further longitudinal studies are needed.

Conclusion

CA’s have been used in dentistry for some time, however various adverse effects are known to occur. Hence, CA should be used appropriately. Although CA adhesives have been shown to be cytotoxic in vitro, it is possible that only commercial CA adhesives release cytotoxic substances for a prolonged period. Although there is not enough evidence to prove that CA is carcinogenic to humans, it can be toxic to the neurological system and respiratory system, as well as causing contact dermatitis and urticaria. These effects are harmful enough for dental staff and other workers to ensure that they take steps to avoid direct contact with CA and reduce environmental exposure. Patients should also avoid using commercial CA to repair broken acrylic dentures. Increasing the alkyl chain length of CA may also help to reduce toxicity by slowing the degradation rate of the molecule and reducing the toxic substances released. The metabolism and harmful effects of this material and its metabolites require further investigation, particularly as CA and related compounds are being more widely used in dentistry.

References

211 TOXICITY OF CYANOACRYLATE ADHESIVES IN DENTISTRY


