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Biocompatibility of glass-ionomer bone cements

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SUMMARY

Glass-ionomer cements (GIC) have been extensively used in dentistry for over 30 years. Due to their excellent biocompatibility in dental applications GIC have been formulated for medical applications. The past decade has seen some impressive advances in the development of medical GICs, however these advances have been matched by serious critical problems. This review examines the properties of GICs, which can influence their behaviour in a biological environment. The progress made and the problems encountered in the development of these bone cements will also be addressed. The review will conclude with the research currently being employed to optimise the biocompatibility of these important biomaterials. There is little doubt that GICs compare favourably with alternative bone cements for specific applications, based on in vitro and in vivo studies. There is however, a degree of risk inherent in the use of any medical device or biomaterial. GICs must therefore be used carefully and in accordance with the instructions that are based on a significant body of research data.

1. Introduction

Glass-ionomer (or polyalkenoate) cements (GIC) were originally developed for use as restorative dental materials. In this role, beneficial properties included adhesion to untreated tooth mineral, and the release of fluoride ions that were thought to confer resistance against dental caries. Due to their excellent biocompatibility in the mouth, with no significant adverse reactions reported in over 20 years of use, attention was focused on the development of an in situ setting glass-ionomer bone cement. Much of the early work that supported the development of medical grade glass-ionomers was reviewed by Brook and Hatton in 1998, although relatively little was then understood regarding a series of serious adverse reactions reported in clinical journals.[1] The aim of this review is to examine the properties of glass-ionomers that influence their behaviour in the biological environment, and then to address both the progress made and problems encountered in their development as improved bone cements. One further objective is to explain why glass-ionomers are biocompatible in some clinical applications but less so in others. While the concept of application-specific biocompatibility is not new, the GI bone cement story represents an elegant and at times tragic illustration of this phenomenon.[1–3]

In the early 1990s, researchers noted several features of GICs that supported their development as bone cements.[4–8] Glass-ionomer setting occurs due to the transfer of ions from the glass to the acidic matrix. In contrast to acrylic cements, this setting reaction did not generate heat and would not cause thermal damage to tissues at the implant site, or temperature sensitive drugs incorporated into the glass-ionomer. Furthermore, unlike acrylic cements glass-ionomers do not shrink on setting. The ability to shape an implant material to conform to local bone topography, and set to a

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required shape, overcame many current problems associated with ceramic bone substitutes. Mechanical properties of the set cement were adequate for low to intermediate load bearing applications in the body. Freshly mixed glass-ionomers were able to chemically bond to both bone tissue and metals. Thus, they did not rely exclusively on a mechanical interaction to achieve fixation of cement or prosthetic implants. Most interestingly, specific glass-ionomer compositions were not "bioinert" but exhibited osteoconductive activity after implantation into bone. It was suggested that this behaviour was due to ion exchange with the biological environment. The biocompatibility and application of these materials as bone cements was comprehensively reviewed in 1998 and 2003.[1,9] This review will therefore concentrate on data published since these reviews or on previous studies that can be reassessed in the light of new knowledge.

2. In vitro evaluation of biocompatibility

Numerous in vitro models have been used to test bone cements. In using these methods to evaluate glass-ionomers, and in interpreting the results, it must be emphasised that this class of materials should be classified as bioactive rather than bioinert. It is now generally recognised that bioactive materials often perform less well in tissue culture tests than the more inert materials they are designed to replace in clinical use. These ideas are based largely on the early work of Gross et al.[10,11] and later Wallace et al.[12]

Ideally, in vitro evaluation should be carried out using a model that represents the clinical situation as far as possible. Models based on the ability of osteoblasts to migrate onto the surface of potential bone cements have consequently found widespread use. Through selection of cell source and culture conditions, and by addition of β-glycerophosphate and ascorbic acid to the medium, in vitro formation of a bone-like tissue may be induced. In vitro cell culture techniques have been used to demonstrate the biocompatibility of a range of glass-ionomers including dental materials, bone substitutes and cements. Tissues or cells used include neonate rat calvaria, osteoblasts, fibroblasts, bone marrow and osteoclasts. Where toxicity has been reported, this appeared to be due to the presence of a toxic leachate or rough surface. Previous studies of dental glass-ionomers have recorded a similar toxic response. Fluoride ion release has been suggested as a cause of cytotoxicity. The improved in vitro biocompatibility of glass-ionomers based on non-fluoride MP4 glass supports this hypothesis, although this interpretation is further complicated by the absence of phosphate from this material.[1,13] Metal ions have also been suggested as a possible cytotoxic factor. Aluminium has been localised in cells cultured on the surface of set glass-ionomers where it had no visible detrimental effect. Aluminium and fluoride are both reported to influence bone cells in vitro. These effects may be stimulatory or inhibitory, depending upon ion concentration and culture conditions. Finally, low pH of the cements while setting and maturing has been suggested as a cause of cyto- and neurotoxicity.[1] No reports of in vitro cytotoxicity identified aluminium ions as the sole toxic agent, and the mechanisms responsible for adverse reactions to glass-ionomers are undoubtedly complex. In vitro investigation of unset glass-ionomers has been hampered because of the extreme sensitivity of cultured cells to wet cements. Where wet cements have been placed directly onto neonate rat calvaria, the cultures have died. It must be concluded that data from in vitro studies of glass-ionomer biocompatibility should be interpreted with care, and this approach is of limited value in understanding the clinical performance of these biomaterials.

3. In vivo evaluation of biocompatibility and bone tissue response

More meaningful results have been obtained from in vivo testing of glass-ionomer bone cements. Set glass-ionomers have undergone in vivo evaluation with encouraging results. Extensive new bone formation was observed on the surface of certain formulations after only 6 weeks implantation in rat femora.[1] This tissue was apparently stable over the course of 1 year. In addition to demonstrating the osteoconductive nature of certain formulations, these experiments also highlighted the danger of relying on tissue culture experiments when evaluating bioactive materials. A glass-ionomer based on non-fluoride and non-phosphate MP4 glass was apparently biocompatible in vitro, yet failed to osseointegrate with bone after surgical placement.[14] Direct contact between bone and material was only observed with glass-ionomers containing fluoride. The transmission electron microscope (TEM) confirmed that bone tissue was in direct apposition to the glass-ionomers and a stable interface had been formed.

In contrast, there have been surprisingly few reports of in vivo evaluation of freshly mixed glass-ionomer bone cements. Early work in South Africa included studies based on diffusion chambers containing a glass-ionomer and bone marrow, which were then implanted into baboon femora for periods of up to 3 years.[5–7] The cement had no inhibitory effect on bone tissue and was reported to promote osteoblastic activity inside the chamber. However, these experiments did not represent true in vivo evaluation because the host was separated from the material by the microporous wall of the diffusion chamber. Where freshly mixed glass-ionomers have not been separated from host tissues the results have not always been as encouraging. Initially, after direct surgical placement on the rat femur, a glass-ionomer appeared to bond to the underlying bone. However, by 6 weeks there was evidence of a pronounced periosteal reaction with sub-periosteal resorption. By 12 weeks this reaction had not subsided, although new bone formation was also observed. In addition, in the short term there is an inflammatory response observed in soft tissues adjacent to the glass-ionomer. It is likely that the short-term adverse tissue reaction reported in these studies was caused by one or both of the following factors:

(i) Reduction of tissue pH due to poly(acrylic) acid. This is the most probable cause of local tissue necrosis in the early stages following placement. While probably not a serious biocompatibility issue, local pH will influence ion release from the cement.