Periodontal debridement in medically compromised patients receiving bisphosphonate treatment
This evidence summary aims to locate and summarise evidence on periodontal debridement in medically compromised patients taking bisphosphonates. It does not include detailed descriptions of the studies cited nor does it include information that was not presented in the literature.

The Curious about website encourages dental professionals to raise issues where a review of the available evidence would provide a useful resource for other dental professionals. Where there is a lack of evidence, the topic is considered for research and an award is made available.

These activities are sponsored by the Shirley Glasstone Hughes Fund, a restricted fund within the BDA Trust Fund. The focus of the fund is research into primary care dentistry and aims to generate a body of relevant research for practising dentists.
Key findings

- Due to the absence of research data no conclusion could be reached on whether the available evidence supports or refutes periodontal debridement in medically compromised patients taking bisphosphonates.
- Guidelines and recommendations, based on expert opinion, for managing the oral health of patients who have been/are being prescribed bisphosphonates have been published.
- The publications recognise that preventative procedures, including those for the treatment of periodontal diseases, are important in reducing the risk of developing osteonecrosis of the jaw.

Review question

This evidence summary was prepared in response to the following question: Does the available evidence support or refute periodontal debridement in medically compromised patients taking bisphosphonates?

Key terms

Periodontal debridement: Removal or disruption of dental deposits and plaque-retentive dental calculus from tooth surfaces and within the periodontal pocket space without deliberate removal of cementum as done in root planing and often in dental scaling.[1]

Bisphosphonate: A class of drugs used to inhibit bone resorption.

The case for action

Medically compromised patients
The impact of a patient’s medical condition on their dental treatment is dependent on the medical condition and the dental procedure. A patient with well controlled diabetes and no complications will require little special consideration in this regard, for example, but if a patient has diabetes with complications there may be a heightened potential for infection or poor wound healing that may in turn affect treatment decisions.[2]

Bisphosphonates
Bisphosphonates, which preserve and increase bone mass, are a class of drug used in the treatment of bone diseases associated with excessive resorption. In adults they are prescribed in the treatment of primary and secondary osteoporosis to reduce the risk of fractures[3-6] and for diseases such as Paget’s disease of bone[6] and fibrous dysplasia.[7] In the treatment of cancer (e.g. breast, prostate, multiple myeloma) they can prevent skeletal complications, relieve bone pain and prevent treatment-induced bone loss[8-11]. The drugs are not widely prescribed to children though they can be employed in the treatment of bone diseases including osteoporosis[12] and osteogenesis imperfecta.[13]

Of the one billion prescription items dispensed in the community during 2013 (England only) approximately 8.3 million items were bisphosphonates with an approximate cost of £20.7 million.[14]

Bisphosphonates can be administered either orally or intravenously. Some information covering bisphosphonates currently prescribable in the UK is given in Table 1.[15-17]

Pharmacology
Bisphosphonates are structural analogues of inorganic pyrophosphate; an enzyme that functions as a bone mineralisation regulator.[18,19] Intestinal absorption is variable and low (1–10 per cent), with 20 – 80 per cent of absorbed bisphosphonate rapidly taken up by bone and the remainder rapidly excreted in the urine, the half-life of bisphosphonates in the blood circulation is short (0.5–2 hours).[20] Following IV administration over 50 per cent of the initial dose is available for incorporation into bone and due to the drug’s incorporation without degradation the estimated half-life can be high with that of alendronate (Fosmax®; Novartis Pharmaceuticals) being up to 12 years.[20,21]

Once taken up bisphosphonates interfere with various chemical pathways ultimately resulting in a decrease in bone turnover, an increase in bone density and an improvement in mineralisation.[22,23]

The mode of action, and potency, of bisphosphonates is dictated by the structure of the drug, more specifically - the presence or absence of nitrogen. Bisphosphonates containing nitrogen (second or third generation bisphosphonates) are the more potent of the two groups and inhibit farnesyl pyrophosphate synthase.[24] This in turn inhibits the function of guanosine-5’-triphosphate (GTP)-binding proteins, in the mevalonate pathway, which are required for osteoclast formation, function and survival. Non-nitrogen containing bisphosphonates induce apoptosis and premature cell death by forming a toxic adenosine triphosphate (ATP) analogue.[18,21]

1 GTP - binding proteins are regulatory proteins, for example Rab, Rho, Rac and Ras, which act as molecular switches by controlling a range of biological processes for example receptor signaling and intracellular signal transduction pathways.
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Bisphosphonate-associated osteonecrosis of the jaw (BAONJ)

BAONJ is a relatively new phenomenon; the first formal notification of the complication was published in 2003. The disorder has been defined as exposed, necrotic bone in the maxilla or mandible that has persisted for more than eight weeks in patients taking bisphosphonates and where there has been no history of radiation therapy to the jaw.

BAONJ is a more likely side effect with intravenous bisphosphonates as the drugs are given at higher doses and considered to be significantly more potent than those delivered orally. However recent drug developments mean that high potency bisphosphonates can now be administered intravenously, for osteoporosis, at significantly lower doses than those required for the management of malignancies. Emerging evidence suggests that tailored high potency yet low dose and low frequency IV regimens for osteoporosis have similar reduced risks to lower potency oral preparations.

The mechanism(s) by which bisphosphonates lead to BAONJ is not entirely understood. One suggested contributing factor is the suppression of remodelling processes, essential for bone healing, that is induced by bisphosphonate-mediated inhibition of osteoclasts.

Risk factors associated with the disorder can be categorised as follows:

- Drug-related - for example, bisphosphonate potency, method of administration, duration of therapy
- Local - for example, dentoalveolar surgery, concomitant oral disease
- Demographic or systemic for example, age, tobacco use
- Genetic - for example SNPs in CYP2C8 (involved in drug metabolism and synthesis of cholesterol, steroids and other lipids.)
- Preventative - for example, receiving necessary dental treatment before commencing bisphosphonate therapy

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Table 1: Bisphosphonates currently prescribable in the UK

<table>
<thead>
<tr>
<th>Drug name (generic/ proprietary) and manufacturer</th>
<th>Generation</th>
<th>Nitrogen containing</th>
<th>Indication</th>
<th>Administration</th>
<th>Potency*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etidronate (Didronel; Warner Chilcott)‡</td>
<td>First</td>
<td>No</td>
<td>Osteoporosis, Paget’s disease</td>
<td>Oral</td>
<td>1</td>
</tr>
<tr>
<td>Clodronate (Bonefos; Bayer Loron; Intrapharm Laboratories) (Clasteon; Beacon Pharmaceuticals)</td>
<td>First</td>
<td>No</td>
<td>Hypercalcaemia of malignancy, Osteoporosis, Paget’s disease, skeletal metastases,</td>
<td>Oral or intravenous</td>
<td>10</td>
</tr>
<tr>
<td>Pamidronate (Aredia; Novartis Pharmaceuticals)</td>
<td>Second</td>
<td>Yes</td>
<td>Hypercalcaemia of malignancy, Osteoporosis, Paget’s disease, skeletal metastases,</td>
<td>Intravenous</td>
<td>100</td>
</tr>
<tr>
<td>Alendronate (Fosamax; Merck Sharp &amp; Dohme)</td>
<td>Second</td>
<td>Yes</td>
<td>Osteoporosis, Paget’s disease</td>
<td>Oral</td>
<td>500 - 1,000</td>
</tr>
<tr>
<td>Ibandronate (Bondronat; Roche), (Bonviva; Roche)</td>
<td>Second</td>
<td>Yes</td>
<td>Hypercalcaemia of malignancy, Osteoporosis, Paget’s disease, skeletal metastases,</td>
<td>Oral or intravenous</td>
<td>1,000</td>
</tr>
<tr>
<td>Risedronate (Actonel; Warner Chilcott)</td>
<td>Third</td>
<td>Yes</td>
<td>Osteoporosis, Paget’s disease</td>
<td>Oral</td>
<td>2,000 - 1,000</td>
</tr>
<tr>
<td>Zoledronate (Zometa; Novartis Pharmaceuticals) (Aclasta; Novartis Pharmaceuticals)</td>
<td>Third</td>
<td>Yes</td>
<td>Hypercalcaemia of malignancy, Osteoporosis, Paget’s disease, skeletal metastases,</td>
<td>Intravenous</td>
<td>10,000+</td>
</tr>
</tbody>
</table>

* In comparison with Etidronate/Didronel the bisphosphonate cited as being the least potent.
‡ Discontinued but expected to remain in circulation until 31st July 2014.
In 2012, the mean incidence of BAONJ of patients receiving intravenous bisphosphonates was given as seven per cent with the observed incidence varying from 0 – 27.5 per cent. The length of the examined studies varied from five to 75 months. The overall incidence of BAONJ in patients receiving oral bisphosphonates is cited as being 0.12 per cent with incidence rates varying from 0 – 4.3 per cent. The length of the studies varied from 24 months to more than 60 months.

BAONJ is likely to become more common as the number of patients and duration of time on oral or intravenous bisphosphonate therapy is increasing. While studies have examined the effects of bisphosphonate use, few have examined long term use (greater than 5 years). The US Food and Drug Administration has reviewed the effectiveness of bisphosphonates for osteoporosis and little, if any, benefit was noted after three to five years. Furthermore it is now being recognised that osteonecrosis of the jaw can occur with antiresorptive medications other than bisphosphonates such as denosumab (Prolia®; Amgen and Xgeva®; Amgen).

The evidence

Due to the absence of research data this summary could reach no conclusion on whether the available evidence supports or refutes periodontal debridement in medically compromised patients taking bisphosphonates. Though no research evidence for this question appears to be available, guidelines and recommendations, based on expert opinion, for managing the oral health of patients who have been/are being prescribed bisphosphonates have been published.

Guidelines and recommendations

Although some guidelines and recommendations provide guidance for the management of periodontal disease, periodontal debridement is not covered specifically. The publications recognise that preventative procedures, including those for the treatment of periodontal diseases, are important in reducing the risk of developing BAONJ but the original indication needs to be considered before a treatment decision is made. Maintaining good oral hygiene will help reduce the need for invasive dental procedures. Leaving periodontal disease untreated can lead to future complications that could require more extensive or invasive treatment and consequently increase the risk of BAONJ development.

Guideline and recommendation extracts covering periodontal, and some general, treatment for those taking or have taken bisphosphonates are presented in Tables 2 – 4. Generally, patients are grouped according to the method of drug administration (Table 2) though some guidance separates patients according to indication (Table 3) or osteonecrosis risk (Table 4).

Methods

Search strategy

A search of Ovid MEDLINE was carried out. Controlled vocabulary terms used included:

- Diphosphonates
- Periodontal debridement
- Bisphosphonate-associated osteonecrosis of the jaw
- Dental care for chronically ill
- Dental care for disabled

Corresponding free text terms were also employed. No limits were placed on publication language or date. Filters for systematic reviews, meta-analysis, economic evaluations, observational studies and RCT were employed. Searches are current as of April 2014.

The following databases were also searched using similar strategies:

- Cochrane library (DARE, NHS EED, HTA Database, Cochrane reviews)
- PubMed MEDLINE
- Science Direct

Grey literature was searched and a snowballing strategy was employed once publications relating to the questions were located. Studies were included if they met the following criteria:

- Participants of any age who had, or were receiving, bisphosphonate treatment.
- Any test group that had undergone periodontal debridement from any type of dental professional.
- A control population who received no periodontal debridement.
- Occurrence of BAONJ as an outcome measure
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Publications were excluded if they were editorials, letters or abstracts.

Three hundred and three journal publications (non-deduplicated) were returned through searches and following sifting by the author none were judged to be relevant. Twelve official guidelines and/or recommendations were located through grey literature searches. Following examination of the full text, ten were found to contain information relating to periodontal care. Though not strictly related to the question, they are included to provide steer. The two excluded publications in this category were excluded as they had either been superseded or did not contain information related to the topic.

Results

No clinical trials, systematic reviews, meta-analysis or economic evaluations were located that have compared periodontal debridement in those taking bisphosphonates and those not. A number of related guidelines published by dental associations, advisory committees or expert panels were identified. Two such publications are from the United Kingdom with the others originating from the USA and Australia.

References

### Table 2

<table>
<thead>
<tr>
<th>Guideline author and country of origin</th>
<th>Route of administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV</td>
<td>Oral</td>
</tr>
<tr>
<td>American Association of Endodontists[^34,37] USA</td>
<td>Preventive procedures are very important to reduce the risk of developing BONJ. Preventive care might include caries control, conservative periodontal and restorative treatments, and, if necessary, appropriate endodontic treatment.</td>
</tr>
<tr>
<td>American Society of Bone and Mineral Research[^43] USA</td>
<td>None given</td>
</tr>
<tr>
<td>American Dental Association Council on Scientific Affairs[^36] USA</td>
<td>None given</td>
</tr>
<tr>
<td>American Association of Oral and Maxillofacial surgeons[^33] USA</td>
<td>Maintaining good oral hygiene and dental care is of paramount importance in preventing dental disease that may require dentoalveolar surgery.</td>
</tr>
</tbody>
</table>
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**Table 3**

<table>
<thead>
<tr>
<th>Guideline author and country of origin</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Malignancies</strong></td>
<td><strong>Osteoporosis</strong></td>
</tr>
<tr>
<td>American Dental Association Council on Scientific Affairs(^{(35)}) USA</td>
<td>None given</td>
</tr>
<tr>
<td>Department of Health, Social Services and Public Safety(^{(38)}) Northern Ireland</td>
<td>None given</td>
</tr>
</tbody>
</table>

Guideline extracts covering periodontal, and some general, treatment for those taking or have taken bisphosphonates for osteoporosis or malignancies

**Table 4**

<table>
<thead>
<tr>
<th>Guideline author and country of origin</th>
<th>BAONJ Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>High</strong></td>
<td><strong>Low</strong></td>
</tr>
<tr>
<td>NSW Health(^{(39)}) Australia</td>
<td>None given</td>
</tr>
<tr>
<td>Scottish Dental Clinical Effectiveness Programme(^{(26)}) Scotland</td>
<td>Treat routinely for scale and polish, simple restorations, recall and radiological review.</td>
</tr>
</tbody>
</table>

Guideline extracts covering periodontal, and some general, treatment for those taking or have taken bisphosphonates who are at either a high or low risk of BAONJ