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Case Report: Beware the Silver Nitrate Stick – A Risk Factor for Bisphosphonate-Related Osteonecrosis of the Jaw (BRONJ)

Abstract: Topical silver nitrate may be used in oral and maxillofacial clinical settings owing to its astringent, caustic and disinfectant properties. Uses of the toughened silver nitrate pencil stick include haemostasis at bleeding points and for the management of aphthous ulcers, hypergranulation tissue, warts and verrucas. We present an interesting case of apparent silver nitrate-induced, bisphosphonate-related osteonecrosis of the hard palate following mucosal lesion biopsy in a multiple myeloma patient receiving zoledronic acid intravenous infusions. Our review of the literature indicates that this is the first report of such a scenario. CPD/Clinical Relevance: Clinicians must consider all potential sources of chemical and mechanical trauma to the bone and overlying mucosa when managing patients at risk of developing bisphosphonate-related osteonecrosis of the jaw. Dental Update 2015; 42: 735-743

Topical silver nitrate, in its toughened pencil stick form (Figure 1), has a wide variety of medical uses in the head and neck region (Table 1). Its caustic nature dictates its cautious use. Overzealous use may result in painful chemical burns of the oral mucous membranes/skin. For the patient on bisphosphonate therapy, this may result in osteonecrosis of the underlying bone.

Michelle C de Souza, BDS, MJDF RCS(Eng), Specialty Doctor in Oral and Maxillofacial Surgery and Gabriela Stepavoi, Stat Exam, FDS RCS(Eng), Associate Specialist in Oral and Maxillofacial Surgery, Oral and Maxillofacial Surgery Department, Princess Alexandra Wing, Kingston Hospital, Surrey, KT2 7QB, UK. Bisphosphonate-related osteonecrosis of the jaw (or BRONJ/BONJ) is defined as a minimum eight-week history of exposed non-vital (necrotic) maxillary/mandibular bone in the absence of a history of radiotherapy to the jaw but in the presence of current or past bisphosphonate therapy (BST).¹ It can develop spontaneously or following oral mucosal and/or bony trauma and can be a highly unpleasant and protracted problem for the affected patient. It is now a widely recognized and increasingly documented, though still considered rare, adverse consequence of BST.

Risk of developing BRONJ is higher for those on regular, long-term, high dose and potency intravenous BST² (0.8–12%, compared to 0.0003–0.06% for oral BST).¹ The clinical benefits of intravenous BST for patients with metastatic and osteolytic bone diseases, including multiple myeloma (MM) and hypercalcaemia of malignancy include reduction of bone pain and risk of pathological fracture. Given that no effective clinical treatment currently exists for managing BRONJ, emphasis lies on prevention and minimizing risk of BRONJ development.

The majority of BRONJ described in the literature is as a sequela of dental extraction.^{3,4} Existing literature reviews use the umbrella term 'dento-alveolar surgery' to categorize this local risk factor.^{1,3,5} The authors feel that this term fails to draw attention to other non-mechanical forms of trauma adequately (eg chemical and thermal forms of trauma), that are often part of dento-alveolar surgery.

MEDLINE and PubMed searches of English literature from 1960 to January

Composition	Typically 75% Silver nitrate* BP (AgNO ₃) fused with 25% potassium nitrate BP (KNO ₃) (*also available in 65% and 95% preparations)
Properties	Astringent/styptic (constrictor eg of blood vessels ie haemostatic) Caustic (burns/corrodes/destroys living tissue) Disinfectant (destruction of living organisms)
Uses	Management of hypergranulation tissue , warts and verrucas Control of bleeding points , epistaxis Pain relief for aphthous ulcers Wound dressings
Adverse Reactions	Dermatologic/mucocutaneous: burning, ulceration and skin irritation Argyria/tattooing (blackened staining of the skin and mucous membranes) – produced by silver deposition Endocrine and metabolic: Hyponatremia Haematologic: Methemoglobinemia
Mechanism of Action	Silver chloride is formed by free silver ions combining with chloride in tissue; bacterial proteins are precipitated An eschar (slough of dead tissue) is formed by the coagulation of cellular protein Effect : growth inhibition of gram positive and gram negative bacteria
Contra- indications	Ophthalmic uses
Advantages	Ease of use (more convenient than surgery or cryotherapy) Economical Disposable
Disadvantages	Corrosive Irritant Toxic Staining

Table 1. Topical silver nitrate (AgNO₃) applicator stick facts.

2012 were conducted using the following Medical Subject Headings (MeSH) terms: osteonecrosis, avascular necrosis, bisphosphonates, zoledronic acid, multiple myeloma, silver nitrate, haemostatic agents, chemical trauma. No previously documented cases of silver nitrate use as a risk factor for BRONJ were found. This article introduces a previously undocumented interesting chemical risk factor for BRONJ.

Case report

A 61-year-old carpenter was referred to the oral and maxillofacial department by his GDP in March 2011 regarding an asymptomatic 'white patch' on the hard palate. Otherwise unaware of the lesion or any potential causal/precipitating factors, the patient's attention was drawn to the area following an appointment with his hygienist.

Of relevance in his medical history, the patient suffered with multiple myeloma (MM), Stage III IgG Lambda with anaemia, diagnosed 2 years previously. He had skeletal disease at presentation and had been treated with cyclophosphamide, thalidomide and dexamethasone (CTD) chemotherapy and 4 mg intravenous infusions of zoledronic acid, both on a monthly basis. He became intolerant to the CTD chemotherapy after six cycles and was changed to a Velcade-containing chemotherapy regimen (Cyclophosphamide, Velcade, Dexamethasone, CVD), of which he received 5 cycles. Five months later, he underwent an autologous stem cell



Figure 1. Typical silver nitrate stick used in UK Oral Surgery departments.



Figure 2. Example of a disposable punch biopsy tool.

transplant uneventfully. Since then, no further chemotherapy was given, but he continued with his once monthly zoledronic acid infusions. His bony pains resolved and his peripheral neuropathy was improving slowly.

The patient smoked up to a maximum of 10 cigarettes per day and consumed less than 14 units of alcohol on average per week. He was otherwise a regular dental attender with additional fourmonthly hygienist visits. He reported no active dental complaints or recent history of invasive dental treatment (within the previous 2 years).

Clinical examination demonstrated no cervical lymphadenopathy or facial asymmetry. No 'lesions' were identified apart from a generalized mild pallor affecting the hard palate. He reported no mucositis and demonstrated good oral hygiene with no obvious hard or soft tissue abnormalities. The patient was reassured, no intervention was advised and a review was organized for two months time.

At two month review, a small (approximately 3 mm in diameter), faint, speckled, irregular, non-tender, light brown patch was identified over the right hard palate mucosa approximately 5 mm adjacent to UR6. Provisional diagnosis was that it was a melanocytic macule and an incisional biopsy under local anaesthetic was advised to confirm diagnosis and

exclude malignancy.

Approximately 1 ml of 2% lidocaine hydrochloride with adrenaline (1:80 000) was infiltrated through palatal mucosa around the lesion and a 4 mm punch biopsy ring (Figure 2) was used to incise and remove the mucosal lesion. A 4 mm circular defect of exposed bone was left and haemostasis was achieved with a single 75% w/w silver nitrate stick (Figure 1) uneventfully. Standard minor oral surgery verbal and written postoperative instructions were provided with no additional prescription and a review was organized for 6 weeks.

At 6 week review, the patient remained asymptomatic but complained of a visible 'black spot and ridge of gum', felt with his tongue in the area biopsied, present since biopsy and unchanged in nature. On examination, non-healing of the well-defined circular mucosal punch biopsy defect (approximately 4 mm in diameter) was noted, the margins of which were slightly raised though not tender or inflamed. No bleeding on probing or exudate was seen. The exposed area of bone demonstrated a central blackened area, hard to probe. A clinical diagnosis of BRONJ was suspected and the patient advised. Histopathological analysis of the biopsied mucosa showed squamous mucosa with marked hyperkeratosis and minimal chronic inflammation. He was prescribed a 2-week course of Doxycycline 100 mg twice daily and advised to use chlorhexidine 0.12% mouthwash twice daily. Review was arranged at 2 weeks.

At subsequent 2 week review, little had changed clinically and the patient remained asymptomatic. As 2 months of 'non-healing' had elapsed, the bone remaining exposed and 'necrotic' in appearance, a diagnosis of BRONJ (Stage 1¹) was made. Photographs were taken for records with the patient's consent (Figure 3) and his GP and haemato-oncologist informed. Review interval was extended to once monthly, given that he remained asymptomatic and his condition, though apparently non-resolving, was not deteriorating. He was advised to continue twice daily chlorhexidine digluconate 0.12% mouthwashes, ie conservative management.

Three months later, 16 weeks post-biopsy, the patient continued to

remain asymptomatic. On examination, complete mucosal closure over the bony defect had occurred with a small saucerized depression remaining (Figure 4). The area was non-tender to touch with no evidence of suppuration. Review interval was extended to three monthly and the patient advised to perform local cleaning of the area with chlorhexidine digluconate 0.12% mouthwash soaked cotton bud twice daily. His haemato-oncologist advised an increase in interval between zoledronic acid infusions to four-monthly given his multiple myeloma was in haematological remission (stable paraprotein levels at 2g/L since October 2011).

At review, 36 weeks post-biopsy (February 2012), continued resolution of the area was noted with a reduction in the appearance of the saucerized depression centrally (Figure 5). The overlying mucosa remained healthy and non-tender to the touch. The patient described being aware of the 'ridge of gum' disappearing a month earlier.

Final review, three months later, demonstrated continued healing with further resolution of the saucerized mucosal depression. The patient remained asymptomatic, was reassured and discharged.

Discussion

The authors believe this case to be the first highlighting the risk of developing BRONJ following use of silver nitrate in the oral cavity for patients with a history of BST. Cases of osteonecrosis

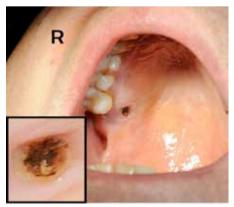


Figure 3. Clinical evidence of BRONJ (third review 11 weeks post-biopsy).

secondary to indirect and direct trauma from other chemicals, in the absence of a history of BST, have already been documented.^{6,7,8}

Categorizing BRONJ risk

The patient described in this case was at particularly high risk of developing BRONJ given that he had been receiving monthly intravenous infusions of zoledronic acid (a potent nitrogencontaining bisphosphonate) for nearly 24 months at the time of presentation.^{1,9} A study by Filleul et al, over a six-year period, found that nearly 90% of 2400 BRONJ patients reviewed had received zoledronic acid infusions as part of treatment for their malignancy.¹⁰ Other compounding risk factors, specific to our patient, included his age (over 60 years old), underlying malignancy (MM), immunosuppression (from the chemotherapy) and concomitant long-term steroid therapy (daily dexamethasone).^{1,11,12} As a smoker, the

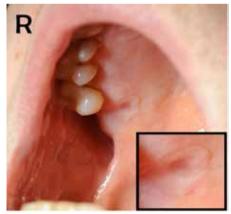


Figure 4. Evidence of healing at 16-week review post-biopsy.



Figure 5. Near complete healing at 36 weeks postbiopsy review.

nicotine in smoke is a vasoconstrictor¹¹ and anti-angiogenic (as is zoledronic acid¹³ and the thalidomide in CTD therapy). It can also destroy soft tissues and impair bony healing.¹⁴

Minimizing BRONJ risk

Given this knowledge above, the authors pose two important questions relating to the management of this patient. First, did the benefit of conducting a biopsy (of a non-sinister lesion) outweigh the risk of developing BRONJ? Secondly, what if anything could have been done to prevent the development of BRONJ based on the available evidence base?

The authors stand by their decision to confirm diagnosis through biopsy as this remains the only true way of ascertaining histopathology. As regards preventive measures, no pre-/ peri- or post-operative antibiotic therapy or mouthwash was provided at the time of biopsy. The patient was not undergoing chemotherapy at this time. No robust evidence currently exists to support the use of antibiotic prophylaxis for invasive dental procedures to prevent BRONJ.² Opinion on this, however, is divided and variation in recommendations to use pre- and/or postoperative chlorhexidine digluconate 0.12% mouthwash and/or antibiotics exist.5,15,16 Furthermore, the choice of antibiotic may depend on results of culture, patient tolerance and duration of the problem. Tetracycline therapy (eg doxycycline) is well tolerated in the long term if required and demonstrates good bony uptake, hence its use in this case. Doxycycline (100 mg OD) or Penicillin V (500 mg QDS) would be appropriate antibiotic regimens, given that most pathogens isolated in BRONJ are actinomyces, eikenella and moraxella species.2

Analysis of clinical intervention

Knowing that dento-alveolar surgery is a well documented risk factor for BRONJ,¹ the authors consider the method of biopsy technique. Did the BRONJ develop as a result of mechanical trauma from the punch biopsy itself or through chemical insult from the silver nitrate used to cauterize bleeding points?

The punch biopsy technique is frequently used in oral medicine/

surgery and dermatology settings. It is easy, inexpensive, safe and quick to use. It comprises a cylindrical blade (like a pastry cutter), whose diameter comes in sizes between 2 and 10 millimetres attached to a plastic handle (Figure 2). A core of tissue is cut by applying the punch at a right angle to the mucosa, entering into the tissues by continuous rotation under medium pressure. The tissue specimen is removed and the base released using a scalpel or curved scissors. It is considered an atraumatic technique producing fewer artefacts under histopathological examination than standard incisional biopsy technique. The residual defect is small and can be left unsutured.17,18

Local release of boneincorporated bisphosphonate, secondary to intra-oral trauma, has been proposed to inhibit epithelial cell proliferation, thereby delaying soft tissue healing and increasing exposure time of the underlying bone to micro-organisms of the oral cavity.^{2,19.} Perhaps therefore, a shallower biopsy to avoid bony exposure may have been preferential, although this in turn may have compromised the sample and made it less representative. Primary closure of the soft tissues of the hard palate with sutures is ideal to help protect underlying bone and forming a blood clot.^{11,20} In reality this can be difficult to achieve owing to their lack of elasticity.

If primary closure and the haemostasis it creates are not possible, other methods of achieving haemostasis in the hard palate region must also be considered carefully in the BRONJ susceptible patient. MM patients may be at higher risk of intra-oral bleeding if they are thrombocytopenic as a consequence of plasma cell proliferation in the bone marrow. Therefore, the need for good haemostasis at the time of surgery is even more important.

In our case report, a junior grade clinician (senior house officer) performed the procedure and overzealous/incorrect use of the silver nitrate stick may have occurred. Silver nitrate applicator sticks should be applied carefully and directly in light and small rotational movements to dampened lesions. This allows dissolution of the chemical and adequate concentration to be reached. Topical silver nitrate of 95% concentration has shown double the

penetration depth of its 75% concentration equivalent when used on tonsillar mucosal tissue in a nasal cautery study.²¹ Perhaps, therefore, use of the lowest concentration (65%) available in applicator stick form may have been prudent. However, this does not detract from the fact that, irrespective of concentration, silver nitrate is caustic and can increase the depth of injury in tissues to which it is applied.²² Even its minimal use could produce sufficient chemical trauma to trigger BRONJ. Marked spreading local necrosis of the tongue has been reported following single topical application of an aphthous ulcer with a toughened (25% potassium nitrate) 75% silver nitrate stick.²³ Thus the authors propose the use of silver nitrate in the oral cavity to be absolutely contra-indicated for patients with a history of BST, irrespective of the experience level of the clinician handling the substance and concentration of silver nitrate used.

Alternatives for achieving haemostasis

These include electrocautery and the application of a temporary sterile dressing pack, with or without holding sutures or cover plate. For a small biopsy of the palate, the authors consider whether simple gauze pressure with a haemostatic agent, such as tranexamic acid, may be adequate if bleeding is minimal.

Electrocautery

Surgical diathermy or electrosurgery/cautery is often used in oral and maxillofacial surgery for the cutting ('dry incision') and coagulation (haemostasis) of soft tissues. An electric current excites tissue molecules to produce heat, causing cellular explosion followed by tissue division and cellular desiccation with blood protein coagulation, respectively. A study by Sudhindra et al found clinicians at all levels and across multiple specialties to have significant lack of knowledge regarding the use of surgical diathermy equipment.²⁴ Of the two modes of diathermy, bipolar diathermy is safer and produces less tissue damage than monopolar diathermy. Use of monopolar diathermy in periodontal surgery has dropped significantly owing to reports of soft and hard tissue necrosis.²⁵ The authors have found no literature to support or refute the safe use of bipolar diathermy for

soft tissue bleeding points in the BRONJ susceptible patient.

Dressing/pack placement

The secure placement of a non eugenol-containing periodontal dressing paste (eg CoePak[™]) or sterile pre-soaked gauze pack (eg betadine-soaked gauze, bismuth iodoform paraffin paste BIPPimpregnated gauze) with sutures or a pre-fabricated custom-made cover plate for the larger palatal biopsy has its uses.²⁶ Unfortunately, again, no literature exists to support its use in preventing BRONJ.

The authors feel that, although a number of patient and operator factors were at play in the development of BRONJ for this patient, the causticity of the silver nitrate coupled with the potential/actual bony exposure created in performing mucosal biopsy of the hard palate were significant triggers.

Management of quiescent BRONJ

The therapeutic aims of managing BRONJ are to eliminate pain, control infection and minimize further disease progression. Fortunately, our patient remained asymptomatic throughout with no clinical signs of infection or disease progression (eg pain, swelling, suppuration, etc) and so conservative management was followed. The effect of the patient's haemato-oncologist's decision to increase the interval between zoledronic acid infusions from 2-4 monthly from the point of BRONJ diagnosis on the rate of BRONJ resolution cannot be correlated. The effects of dose reduction, interval extension and/or a drug holiday altogether on an established BRONJ are unclear as data is lacking.²⁷ It has been postulated that a drug holiday may help stabilize and reduce the appearance of established BRONJ;1 this is providing the patient's systemic condition allows for discontinuation of BST.

Conclusion

- The use of topical silver nitrate in the oral cavity should be contra-indicated in BRONJ-susceptible patients and in the hands of inexperienced clinicians.
- There is a need to consider the implications of all forms of potential soft and hard tissue trauma (mechanical, chemical, thermal, etc) when managing

patients on BST.

- The category of risk for development of BRONJ must be assessed for individual patients as this will influence approach to treatment.
- All members of the clinical team (including junior grades) must ensure up to date awareness of the issues and developments surrounding the causes, prevention and management of BRONJ and identification of susceptible patients.
- Liaison between specialties (eg oncologists and dentists) is essential to prevent BRONJ.

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CPD ANSWERS July/August 2015

1. C	6. B
2 . C	7. B
3. D	8. C
4. C	9. A
5. A	10. B





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