

Letters to the Editor

Relevance of bisphosphonate therapy in osteoporosis and cancer - no cause for alarm in dentistry (Dent Update 2016; 43: 235–242)

We write to challenge some of the assertions made in this recent paper.

Sadly, the attention grabbing title is rather naïve and/or misleading for general dentists and others. There **is** cause for concern and possible alarm in dentistry if patients, who have had *multiple IV injections* of bisphosphonates, usually for cancer, subsequently need to have dental extractions, or other operations **involving the bone** in their mouth.

While feeling great sympathy for patients who suffer from osteoporosis, the emphasis in the title of this paper and some of the content ought to be challenged, particularly in relation to intravenous bisphosphonates for patients with cancer.

Oral bisphosphonates are reputedly very beneficial in cases of osteoporosis. The risks of Medicine Related Osteonecrosis of the Jaw ('MRONJ') after surgery to the jaws with **oral** bisphosphonates are so low that they should not be an issue for over 99% of oral surgical interventions. If oral bisphosphonates are taken for very many years and/or if they are combined with other risks, such as a long history of steroids, then the risks of MRONJ following jaw bone surgery are increased, but they are still low.¹

The authors make many sensible points about the frequency of occurrence and seriousness of osteoporosis but, sadly, they fail to draw attention to balancing points about how serious osteonecrosis of the jaw can be in altering patients' quality of life when it does occur (Figure 1).

Unfortunately, the emphatic title of the paper breezily glosses over the reported occurrence of MRONJ, especially in such cancer cases. One of the references they cited referred to this happening in from **1.6% to 15%** of cases. That is huge range and probably reflects reporting issues, or the presence of other risk factors, such as the number of years on the drugs, or whether patients were taking other drugs, or whether the patients

have had **jaw bone surgery** in the mandible or in the maxilla. At the risk of stating the obvious, it is the **combination** of these more potent drug(s) and surgery to the jaw that produces the risk of MRONJ. Many patients who are on long-term bisphosphonate drugs along with steroids, or those being given IV bisphosphonates, may well *not* need extractions, or other surgical intervention to the jaw bone, thereby reducing the reported **percentages**. About 73% of cases occur in the mandible as opposed to the maxilla, which is rarer at 23%, with about 4% occurring in both.¹

It is the *combination* of multiple IV bisphosphonate infusions and extractions that produces the main causes for concern about MRONJ, but there are also significant risks with some other drugs used for their anti- bone resorptive effects, such as RANKL inhibitors, eg Prolia® (denosumab).

No mention is made in that paper of the prescribing doctors giving patients appropriate detailed warnings of those real risks of MRONJ when multiple infusions of these powerful bisphosphonates, or other anti-resorptive alternatives, are about to be employed, **particularly in patients with seriously compromised dentitions**. That would seem to be prudent following the Montgomery 2015 Supreme Court judgement in relation to issues of consent. That failure to mention serious potential possibilities is probably because those authors clearly felt strongly that there is no real problem. In our opinion, that almost casual mention of potential problems, particularly in cancer cases, has to be challenged because it is at variance with the reported and emerging, possibly delayed or under-reporting, of the problems of MRONJ problems in patients **who subsequently need surgical procedures involving jaw bone**.²

Interestingly, there was no suggestion in this article of patients who are being advised to have elective annual intravenous bisphosphonate, rather than staying on their oral bisphosphonates, having careful dental assessment first if they have a compromised dentition in order to reduce the risks to them of leaving potentially infected teeth, which subsequently might need riskier extractions in the future. That

seems to us to be an opportunity missed and the rather bland suggestion to 'go for dental check-ups' does not allow for detailed appropriate assessment of this group, and just an apparent routine check-up is unlikely to lead to the elimination of predictable future dental problems, particularly under the NHS UDA system. Furthermore, it does not allow for 'aggressive preventive' measures to be instituted for these vulnerable patients early on in order to prevent them having problems in the future.^{1,2}

Increasingly cancer, even with metastases, has become a chronic disease.² Many patients now survive for many years having had, and continuing to have, intravenous bisphosphonate therapy, which can be a brilliant drug in many such cases. As a consequence of this increase in patient survival, it is more likely that many such survivors will present to general dental practitioners at some stage. Unfortunately, traditional medical questionnaires used in many general dental practices do not specifically alert dental teams to the possibilities that their patient has had IV bisphosphonate therapy in the past, nor that they continue to have IV infusions on an annual basis. This is because patients often forget to enter the fact that they have had annual infusions, or a series of infusions, on these routine medical questionnaires and, in most cases, the question is not specifically put to them.

It should be stressed that



Figure 1. MRONJ: 5 months after extraction in a patient who had been off IV bisphosphonates for six months and both dentist and patient had been reassured by the haematologist that there was no risk in extracting the tooth.

routine restorative treatment, including aggressive preventive treatment, is not a problem in such cases. However, some busy dentists, based on the scanning of the patient's completed medical questionnaire, may not realize that there is a real potential problem with *oral surgical procedures involving bone* and by doing, for example, an apparently routine surgical extraction, unintentionally cause MRONJ in that patient.

There is a joint Restorative/Oral Surgery Bisphosphonates Clinic at King's College Hospital, London. This clinic is staffed by a joint team with specialist restorative and oral surgery knowledge and skills in managing this patient group. This clinic screens patients who are at more serious risk of osteonecrosis of the jaw from IV bisphosphonate infusions, which are often combined with other drugs, or when alternative drugs to bisphosphonates are likely to be involved, such as RANKL inhibitors Prolia® (denosumab).

The aims of this clinic include giving individual patients neutral balanced information about their potential oral disease problems and to help them to get such problems treated early, thereby avoiding later complications, as well as working out more effective customized preventive strategies for these unfortunate patients. The essential point is that 'risk is individual' and is dependant on many relevant factors. A dogmatic, rather sweeping statement that there is 'no cause for alarm' is worrying because such a headline is likely to be read as being 'gospel', rather than merely being one opinion. That is particularly the case when it appears in a peer reviewed journal but comes from authors whose interests are clearly more in research about osteoporosis, together with some oral surgeons at King's College Hospital who are not involved in that particular clinic.

Some points and emphasis in that article do **not** represent the rather more cautious and considered views of that King's College Hospital 'Bisphosphonate Clinic'. For many years there has been a dedicated osteonecrosis of the jaw clinic (ONJ) at Guy's Hospital. Neither of these clinics was put in place because there is not a problem of osteonecrosis of the jaw.

Rather simplistically oral surgery is the only thing that is mentioned in that article but there are other things, like decisions on periodontal surgery, or endodontic apical surgery, or prosthodontic planning which can be influenced by

the presence, or absence, of a history of intravenous bisphosphonates or other potent anti-resorptive drugs. Individual assessment of patients' specific risks prior to them starting intravenous bisphosphonates should be encouraged rather than being casually dismissed by people with an understandable vested interest in osteoporosis, but who have, perhaps, rather less experience in the complicated dental risk planning aspects of these unfortunate cancer patients.

Interestingly, the article does not elaborate on the dilemma of patients taking very low risk oral alendronic acid, who are considering medical advice to move on to the somewhat higher risks of intravenous zoledronic acid. Curiously, their Table 1 refers to the reduction of over 50% of the spine fractures and about 50% of a hip fracture being achieved with oral alendronic acid with virtually no risk of MRONJ. Superficially, that would appear to be an attractive proposition relative to patients going on to intravenous zoledronic acid, with a reduction in hip fracture of only 41%. The authors do not comment on this apparent anomaly, ie why would patients want to take a greater risk of osteonecrosis of the jaw with an intravenous injection when they could get somewhat better results with less risk from taking oral alendronic acid? One suspects that patient compliance, or perhaps more cynically, the quiet influences of some drug companies' profits are just two of the possible explanations.

General dentists, to whom the article was addressed, might well ask the question 'Whose responsibility is it for MRONJ occurring in patients on intravenous bisphosphonates or in those patients who have had multiple years of oral bisphosphonate as well as steroids, who get osteonecrosis of the jaw after oral surgical procedures? Is it the treating dentist? Is it the prescribing doctor who did not give the patient appropriate warnings or a warning card, or a written note, to show to any future dentists? Is it the haemato-oncologist who, understandably, is probably more concerned with keeping the patient alive than about possible future MRONJ? Is it the rheumatologist, possibly influenced by a drug company anxious to promote its more profitable drugs? Is it the prescribing geriatrician possibly worried about the general frailty and memory of his/her patient? Who do MRONJ patients sue if they were to

feel that they were given only some of the facts by a mono-focused specialist clinician, or one possibly influenced by pressures on their particular service, or by convenience issues, or subconsciously by some drug company presentation, when they now have a medicine-related osteonecrosis of the jaw problem that *might have been avoided?*'

Interestingly, the article, perhaps inadvertently, could be now used as a defence by some dental practitioner by citing just this peer reviewed headline title of '**Bisphosphonate Therapy in Osteoporosis and Cancer - No Cause for Alarm in Dentistry**'. However, some of the views in the paper are in conflict with the advice cited in one of its own references,¹ as well as being at odds with other warnings about the increased likelihood of MRONJ problems developing with different emerging new cancer drugs. Sadly, it largely ignored advising the more careful and caring dentists about what they might be able to do to prevent future problems in these particularly unfortunate patients.²

A more balanced view of the real and imagined risks in this rapidly changing field could have been more helpful to the dental profession at large and such an article is now in preparation for *Dental Update*.

References

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2. Patel V, Kelleher M, Sproat C, Kwok J, McGurk M. New cancer therapies and jaw necrosis. *Br Dent J* 2015; **219**: 203–207.

**Martin Kelleher
Mark McGurk
London**

Authors' response

We are writing in response to the letter from Martin Kelleher and Mark McGurk, received 20 June 2016 in response to our article.

On reflection, the title to the paper should not have included the