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Evaluation of Antiresorptive Agent-Related Osteonecrosis Therapy by measuring concentrations of Penicillin G in Jawbone

Background and Importance Antiresorptive agent-related osteonecrosis of the jawbone (ARONJ) is a severe complication after therapy with bisphosphonates or denosumab. The current ARONJ guideline by the German Dental and German Oral and Maxillofacial Associations states the administration of systemic antibiotics intended as an adjunct to surgery to be obligatory in all operative ARONJ treatment. Penicillin-based antibiotics (alone or in combination with beta-lactamase inhibitors or metronidazole) were the agents administered most frequently [1]. Knowledge of the achievable antibiotic concentrations is important specially as the efficacy of antibiotic treatment depends significantly on the penetration to the infection site.

Aim and Objectives The aim of this study was to measure qualitative and quantitative data on penicillin G concen-trations in bone affected by ARONJ following intravenous administration and get comparable results to other concentrations measured with the same extraction method.

Results: As expected, the values of the bone concentrations were lower than the comparable results reported for healthy jawbone. However, the minimum inhibitory concentrations (MIC/MIC90) values for penicillin G were exceeded in 16 of 19 samples with regard to bacteria commonly found in bone affected by ARONJ. The median penicillin concentration in jawbone was 2.7 µg/g (2.3% of the median serum concentration), see Table1 [1].

Table 1. Summary of bone and serum concentration of penicillin G, weight of bone samples, infusion parameters of penicillin G, and body mass index (BMI) of the patient sample.

Sample Number	Extracted Penicillin G per g Bone (µg/g)	Bone Concentration Calculated (µg/mL) [1]	Bone Weight (mg)	Serum Concentration Preoperative (µg/mL)	Serum Concentration Intraoperative (µg/mL)	BMI	Duration of Infusion	Intervals: Start of Infusion to Resection of Bone
1	<LOD	<LOD	536	<LOD	104	23.1	14	45
2	1.0	1.5	16	<LOD	43	23.5	9	32
3	2.1	3.15	41	<LOD	208	21.4	10	31
					118	23.6	16	88
5	2.0	3.0	155	<LOD	144	29.7	14	54
6	0.2	0.3	39	<LOD	37	32.5	11	58
7	5.7	8.55	20	<LOD	113	27.7	16	40
8	<LOD	<LOD	411	<LOD	116	20.8	15	80
9	1.3	1.95	550	<LOD	79	33.1	6	62
10	7.3	10.95	176	<LOD	171	20.2	9	36
11	2.8	4.2	107	<LOD	119	16.9	6	29
12	5.3	7.95	76	<LOD	193	24.2	8	37
13	2.5	3.75	116	<LOD	116	24.8	14	43
14	4.3	6.45	26	<LOD	232	23.2	6	58
15	3.1	4.65	26	<LOD	203	19.1	8	30
16	<LOD	<LOD	118	<LOD	46	23.0	22	40
17	3.9	5.85	76	<LOD	131	21.8	18	61
18	8.8	13.2	215	<LOD	1	23	10	33
19	1.9	2.85	69	<LOD	103	27.5	12	48
median	**2.7**	**3.98**	**76**		**116**	**23.2**	**11**	**43**

LOD: limit of detection, [1] Calculated by multiplying the bone concentration (in µg/g) by 1.5 [2]

Materials and methods: After permission of the Ethics Committee and informed consent, bone samples and pre- and intraoperative blood samples were obtained at 18 to 72 min after completion of infusion of 10 million IU (6000 mg) of penicillin G from a total of 19 patients meeting all inclusion criteria. The bone samples were extracted with phosphate buffer solution in a proportion of 1:10 as in the comparative studies. We used LC-MS (q-TOF) to analyze the extracts and calculated the bone concentrations. The serum concentrations were measured with the same LC-MS method after deproteinization with acetonitrile [1].

Conclusions As in bone tissue, this penetration capacity is lower than in other, well perfused tissues and can be further impaired in the case of poorly vascularized or necrotic bone [3,4]. The discussion about the most realistic bone concentrations will continue but the conventional method established in the hospital pharmacy leads to comparable results and was relevant to evaluate the well-established therapy. As oral administration of antibiotics is common in clinical practice, a similar study might be carried out focusing on antibiotics administered orally.

References:

[1] Poxleitner et al. Antibiotics 10, 17 (2021) *https://dx.doi.org/10.3390/antibiotics10010017*
[2] Landersdorfer et al. Clin. Pharmacokinet. 48, 89–124 (2009)
[3] Egle et al. Poster award EAHP Congress Sevilla 9 (2004)
[4] Heibel et al. Mund Kiefer GesichtsChir 9, (2005)

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