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Prostaglandins in osteoid osteoma

F. Greco[1], F. Tamburrelli[1], and G. Ciabattoni[2]

Departments of [1] Orthopaedic Surgery and [2] Pharmacology, Catholic University, School of Medicine, I-00168 Rome, Italy

Summary. *Osteoid osteoma is a tumour of bone characterised by pain which is relieved by aspirin and nonsteroidal anti-inflammatory drugs. Very high levels of prostaglandins have been found in the lesion. In five patients with osteoid osteoma, prostaglandin E_2 (PGE_2) and prostacyclin (PGI_2) synthesis in the nidus yielded 1155.6± 496.5 (mean ± SD) and 245.2± 89.8 pg/mg respectively, values which are 33 and 26 times higher than in fragments of normal bone. The sclerotic bone around the nidus produced both prostaglandins at the same rate as normal bone. In three patients the excretion rate of the major urinary metabolite of systemic PGI_1 was reduced to 50% one month after removal of the tumour. The urinary excretion rate of 6-keto-$PGF_1\alpha$, reflecting intrarenal PGI_2 synthesis, was not changed after operation. These results offer new insight into the pain mechanism in osteoid osteoma.*

Résumé. *L'ostéome ostéoïde est une tumeur osseuse caractérisée par des douleurs qui sont calmées par l'aspirine et les anti-inflammatoires non stéroïdiens. Des taux très élevés de prostaglandines ont été trouvés dans cette lésion. Chez trois malades présentant un ostéome ostéoïde la prostaglandine E_2 (PGE_2) et la prostacycline (PGI_2) synthétisés dans le nidus atteignaient respectivement 1155.6± 496.5 et 245.2± 89.8 pg/mg, valeurs qui étaient 33 et 26 fois plus élevées que dans des fragments d'os normal. L'os scléreux entourant le nidus produisait les deux prostaglandines au même taux que l'os normal. Chez trois malades le taux d'excrétion des principaux métabolites urinaires de la PGI_2 systémique était réduit de moitié un mois après l'ablation de la tumeur. Le taux d'excrétion urinaire de la 6-keto-$PGF1\alpha$, traduisant la synthèse rénale de la PGI_2, n'a pas été modifié par l'opération. Ces résultats permettent une nouvelle approche du mécanisme de la douleur dans l'ostéome ostéoïde.*

Offprint requests to: F. Greco, Department of Orthopaedic Surgery, Catholic University of Rome, Policlinico Universitario A. Gemelli, lg. Gemelli 8, I-00168 Rome, Italy

Introduction

Osteoid osteoma is a benign osteoid-forming tumour which was first described by Jaffe in 1935. The typical pain is deep, aching and intense, and is often the principle symptom of the disease. It is usually worse at night and is relieved by aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs). Attention has been directed in recent years towards the clinical features, and the radiographic and scintigraphic appearances, but the underlying pain mechanisms are largely unknown.

Several hypotheses have been put forward to explain the pain. Golding suggested that nerve endings could be stimulated by the high pressure caused by the increased blood flow within the tumour [7]. The radial arrangement of the trabeculae in the nidus, as seen under polarised light, is evidence of increased pressure which is presumably vascular in origin. Sherman and McFarland identified nerve fibres in the fibrous zone around the nidus which were believed to be part of the autonomic nervous system [16]. Byers [2] and Schulman and Dorfman [15] observed free nerve fibres close to the blood vessels in the nidus by using histochemical techniques based on silver staining; no specialised nerve endings or myelinated fibres were seen. These authors concluded

that their findings could explain the characteristic pain. The presence of unmyelinated fibres in the nidus has also been reported [5, 9, 10, 11]. Unlike Steiner [17] who did not identify nerve structures by electron microscopy, we observed poorly myelinated nerve fibres in the nidus which were recognised as δ-afferent group A fibres [8].

The morphological findings thus far observed explain neither the mechanisms, nor the relief given by aspirin and other NSAIDs. Prostaglandins (PGs) and other products of cyclo-oxygenation of arachidonic acid mediate inflammation, vasodilatation and pain. Aspirin and NSAIDs inhibit cyclo-oxygenase activity, thereby reducing prostaglandins, thromboxane and free radical generation. The aim of the present study is to characterise the prostaglandins synthesised by osteoid osteoma tissue.

Material and method

Five patients with osteoid osteoma were studied during their hospital admission. Pain was present in four of them, and they all commented on the relief given by aspirin or other NSAIDs. One patient had no pain and he was admitted for investigation of a sclerotic lesion on the medial side of the shaft of the tibia, which was a chance radiological finding.

The patients had radiographs and tomographs before operation. Particular attention was paid to the study of scintigraphic images 5 min after the injection of Tc^{99} MDP (blood pool images). The diagnosis was confirmed by biopsy in every case.

All the patients were men and aged between 14 and 21 years. The lesions were in the medial side of the shaft of the tibia in four cases (cortical type) and in the distal metaphysis in one (subperiosteal type).

Treatment was en bloc resection, including the sclerotic bone. The tumours, and also specimens of normal cortical and cancellous bone away from the lesion, were transferred to Krebs-Ringer bicarbonate (KRB). Immediately after removal, the tumours were dissected in an ice-chilled Petri dish to obtain 2–3 mm specimens from the nidus and the peripheral sclerotic bone. Each was separately incubated in 1 ml KRB for 10 min at 37° C in 5% CO_2 and 95% O_2. Thereafter the incubation medium was aspirated and freshly replaced; incubation was carried out at 37° C for 1 h. The solution was then aspirated, centrifuged and stored at −20° C until it was assayed. Fragments were weighed and fixed for histology. The synthesis of prostaglandin E_2 (PGE_2) and 6-keto-$PGF_1\alpha$, the stable hydrolysis product of prostacyclin (PGI_2), were measured by immuno-assay [3, 14].

In case 5 we also measured PGE_2 and 6-keto-$PGF_1\alpha$ production by nidus specimens incubated in medium containing α-dl-2-(3-phenoxyphenyl)proprionic acid sodium salt at a concentration of 10 μg/ml which is a potent cyclo-oxygenase inhibitor. This was used instead of aspirin because of its high solubility in water [13].

In 4 patients the urinary excretion rate of 6-keto-$PGF_1\alpha$ (reflecting intrarenal PGI_2 synthesis) and 2,3-dinor-6-keto-$PGF_1\alpha$ (the most abundant urinary metabolite of systemic PGI_2 synthesis) was measured on 3 consecutive days before operation and, in three cases, on a separate occasion 1 month after excision of the lesion. The techniques for the extraction, chromatographic separation and RIA measurement of 6-keto-$PGF_1\alpha$ and 2,3-dinor-6-keto-$PGF_1\alpha$ are described in detail elsewhere [4, 14].

Table 1. PGE_2 and 6-keto-$PGF_1\alpha$ synthesis in osteoid osteoma

	6-keto-$PGF_1\alpha$ pg/mg wet weight of bone /h			PGE_2		
Case	N	SBR	NB	N	SBR	NB
1	192.1	1.2	1.8	1,682.6	10.7	16.1
2	234.2	28.1	26.1	1,708.5	167.6	142.5
3	150.5	2.6	2.3	847.5	0.3	0.3
4	262.7	4.0	4.2	840.3	6.0	5.2
5	386.7	4.8	12.1	699.1	29.1	13.7
Mean ± SD	245.2 ±89.8	8.1 ±11.2	9.3 ±10.3	1,155.6 ±496.5	42.7 ±70.6	35.6 ±60.1

N = nidus; SBR = sclerotic bone reaction; NB = Normal bone

Results

Prostaglandin production is shown in Table 1. PGE_2 and PGI_2 synthesis in the fragments of nidus were 33 and 26 times greater than in the fragments of normal bone. The peripheral sclerotic bone seemed to produce both prostaglandins at the same rate as normal bone (Table 1). Specimens of nidus incubated in medium containing cyclo-oxygenase inhibitor synthesised 136.3 ± 63 (mean ± SD) of PGE_2 and 65.9 ± 33.9 of PGI_2 (mg net weight). These values were respectively 80.5% and 83.0% less than the values for PG produced by the nidus specimens of the same patient incubated in medium without PG-inhibitor (case 5).

Urinary 2,3-dinor-6-keto-$PGF_1\alpha$ (an index of total PGI_2 production) measured on 3 consecutive days before operation at the end of a 2 week drug-free period, averaged 484 ± 87 (SD) pg/mg creatinine in case 2, 415 ± 66 in case 3, 678 ± 212 in case 4 and 461 ± 128 in case 5. The mean excretion rate of this metabolite in 23 healthy volunteers aged from 23 to 50 years was 257 ± 117 (SD) pg/mg creatinine (range 91–419). Urinary 6-keto-$PGF_1\alpha$ before operation averaged 4.4 ± 1.0 (SD) ng/h in case 2, 6.1 ± 0.9 in case 3, 4.0 ± 0.5 in case 4 and 3.8 ± 0.4 in case 5. The mean urinary excretion rate of 6-keto-$PGF_1\alpha$ in healthy volunteers was 4.5 ± 0.9 (SD) ng/h (range 3.0 to 6.8). One month after operation, urine was collected for 24 h from cases 3, 4, and 5. The excretion rate of 2,3-dinor-6-keto-$PGF_1\alpha$ had decreased to 257, 246 and 247 ± 72 (SD) pg/mg of creatinine, while urinary 6-keto-$PGF_1\alpha$ was 7.3, 3.8 and 4.5 ± 1.1 (SD) ng/h in the same cases respectively.

Discussion

Our results offer new insight into the pain mechanism of osteoid osteoma.

Increased PG synthesis, particularly of PGE_2, was described by Makley and Dunn [12]. Our findings confirm and extend this original report and strongly support the important pathophysiological role of prostaglandins as mediators of pain in patients with this condition.

High PGE_2 and 6-keto-$PGF_1\alpha$ production was found only in fragments of the nidus which suggests that increased PG synthesis is a characteristic manifestation of the condition, particularly as PG synthesis at nearly the same level as in normal bone was found in the sclerotic bone surrounding the lesion. Moreover, Makley and Dunn described a case of osteosarcoma in which they found normal rates of synthesis of PGs.

Inhibition of PG production by using a NSAID drug in the incubation medium may indicate that PGs are locally synthesised by the tissue of the lesion and they do not represent accumulation by sequestration.

The dinor metabolite of 6-keto-$PGF_1\alpha$ is the most abundant derivative of systemically administered PGI_2 in humans [1, 6]. Thus urinary 2,3-dinor-6-keto-$PGF_1\alpha$ is assumed to reflect extrarenal PGI_2 synthesis, whilst urinary 6-keto-$PGF_1\alpha$, the stable hydrolysis product of PGI_2, reflects intrarenal PGI_2 synthesis [14]. In the 4 patients with painful osteoid osteoma measurement of 2,3-dinor metabolite showed a urinary excretion rate close to, or a little over, the upper limit of distribution of 2,3-dinor-6-keto-$PGF_1\alpha$ values in healthy subjects. In the three patients (cases 3, 4 and 5) where measurement was possible one month after excision, urinary 2,3-dinor-6-keto-$PGF_1\alpha$ excretion dropped to 62%, 36% and 54% respectively of the pre-operative levels, thus falling within the normal range. However, the excretion rate of 6-keto-$PGF_1\alpha$ in the same patients was in the normal range before operation and had not changed one month later, suggesting that an increasing extrarenal PGI_2 production may be a consequence of increased synthesis within the lesion. The evidence over the last 2 decades indicates that prostaglandins play a major role in inflammation; PGE_2 and PGI_2 are powerful vasodilators and determine the extent of the oedema. They also mediate pain and hyperalgesia by lowering the receptive threshold of the nociceptive endings and sensitising vessels and nerve endings to other inflammatory agents. Thus two mechanisms for the production of pain in osteoid osteoma may be suggested: (1) the enhanced blood flow induced by exaggerated prostaglandin synthesis may increase the pressure within the tumour and stimulate nerve endings close to blood vessels [7], or (2) prostaglandins may directly stimulate free nerve endings inside, or close to, the tumour by lowering the nociceptive threshold. Combined action of both mechanisms is also possible, resulting in potentiation of the painful stimuli.

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