The analgesic effect of pamidronate is not caused by the elevation of beta endorphin level in Paget's disease – A controlled pilot study

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Abstract

BACKGROUND: Although an analgesic effect is an essential component of the mode of action of bisphosphonates, its physiological mechanisms are still unclear. Beta-endorphin release plays an important role in the analgesic effect of both calcitonin and raloxifene. As patients with Paget's disease receive large doses of bisphosphonates within relatively short time periods, we examined whether repeated pamidronate infusion therapy would cause measurable change in beta-endorphin levels

MATERIALS & METHODS: Visual analog scale (VAS) scores of pain intensity, beta-endorphin levels, and alkaline phosphatase activity of 11 patients with Paget's disease (7 with the mono- and 4 with the polyostotic form) were determined at baseline, as well as after 3 and 6 infusions (on Days 6 and 12 of treatment, respectively). Eleven untreated patients with Paget's disease (7 with the mono- and 4 with the polyostotic form) served as controls.

RESULTS: It was established that in the course of pamidronate infusion therapy BE levels remained constant, whereas the values in serum alkaline phosphatase and pain intensity scores were significantly reduced.

CONCLUSIONS: Although high-dose pamidronate therapy does mitigate pain substantially (as demonstrated by the reduction of VAS scores), its analgesic action is probably unrelated to the enhancement of beta-endorphin release.

ORIGINAL ARTICLE

Introduction

Beta-endorphin (BE) is one of the most well known among endogenous opiate derivatives. A variety of exogenous stimuli can induce the elevation of BE levels in the organism and thereby contribute to the endogenous mechanisms of pain relief. [1, 2] The mode of the analgesic action of bisphosphonates has not yet been elucidated completely but past studies suggest that the analgesic property of calcitonin – an anti-osteoporotic agent – potentially involves the elevation of BE level. [3,4] Moreover, raloxifene, a drug used for the treatment of the postmenopausal syndrome, also enhances BE release [5]. Zoledronate was shown to have a pain killing activity in metastatic bone disease as demonstrated by a significant change in the VAS score which correlated with the decrease of alkaline phosphatase and C telopeptid levels [6]. This study was intended to explore the potential effects of pamidronate on BE levels. Pamidronate was selected from the bisphosphonate family, because patients with Paget's disease receive this agent in relatively high doses over a short period.

Materials & methods

The study population comprised eleven patients with Paget's disease (7 with the mono- and 4 with the polyostotic form, see Table 1). Patients who were considered active/severe and required pamidronate by the expert opinion of a consultant rheumatologist were included in the study group. Eleven patients with Paget's disease (7 with the mono- and 4 with the polyostotic form) receiving no bishosphonate therapy served as controls. Subjects received 30 mg pamidronate intravenous infusion every other day, in 6 successive treatment sessions (i.e. 180 mg in total). Serum alkaline phosphatase (AP) activity, BE level, and VAS scores of pain intensity were recorded at baseline, as well as after the third and the sixth infusion (on Days 6 and 12, respectively). Colorimetric assay was used to determine AP values. Beta-endorphin level was measured as follows: A highly specific rabbit antiserum, showing negligible cross-reactivity with BE-related peptides (e.g. alpha- or gamma-type endorphins) and affording direct determination without previous extraction was used. Tracer was produced by radio-iodination of human beta-endorphin (1–31) using the chloramine-T method. Measured values are given in units fmol/ml. The sensitivity of the assay was about 0.5 fmol/ml.[7] Normal range for the beta endorphin level which in the literature depends greatly on the method and the population studied.

Pain intensity was scored using a 10-grade VAS [8] Changes in AP activity, pain intensity and beta endorphin levels were calculated with a paired T test. Differences between AP activity, pain intensity and beta endorphin levels between treated and untreated patients were analyzed using unpaired T test. Non-parametric data were compared with Mann-Whitney U test. Differences were considered significant at $p<0.05$. Statistical calculations were carried out using Prism Version 3.0 software for Windows (GraphPad, San Diego,CA).

Results

Pamidronate treatment reduced AP activity consistent with past experience [9]. There was no significant change in the AP value after the 6. days. The magnitude of this reduction reached the level of statistical significance as early as Day 12. Pain intensity scores also decreased significantly by the end of treatment. BE levels did not change during or after treatment with pamidronate (Table 2). No changes were ascertained in the control group. Considering that control subjects were off therapy owing to the lack of explicit disease activity, their AP activity was lower, than in the treatment group.). Similar BE values were found in the mono- and polyostotic form of the disease.

Discussion

Paget's disease of bone is characterized by accelerated bone turnover, abnormally enhanced activity of osteoclasts, and consequently, of osteoblasts [10].Bone pain is a leading symptom of this disease and can result from both pagetic lesions and secondary arthrosis involving adjacent joints. Currently, bisphosphonates are the treatments of choice for Paget's disease.

There is some data available on the mode of action of bisphosphonates. These agents are known to inhibit the activity of osteoclasts, as well as to mitigate hypercalcemia. In animals, the antinociceptive effect of pamidronate has no evident influence on gastrointestinal motility, that is, it does not act as a modulator of peripheral opioid receptors. Pamidronate exerts its antinociceptive activity both centrally and peripherially, however, its mechanism of action has not yet been clarified. Induction of osteoclast and macrophage apoptosis has been suggested as one of the mechanisms of action of bisphosphonates. Recently,induction of macrophage apoptosis was found to be associated with the inhibitory effect of pamidronate on TNF-alpha release [11]. Bisphosphonates are characterized by diverse mechanisms of actions. For example, nitrogen-containing agents exert their action by inhibiting the mevalonate pathway of osteoclasts, whereas other bisphosphonate derivatives act differently. [12] In animal experiments, the analgesic property of alendronate was observed at almost toxic dose levels. [13] El Shaffei described the analgesic action of pamidronate in his report of three cases. [14] Pamidronate administered by intravenous infusion was shown to reduce pain intensity scores measured using a VAS. [15] As seen in our study, AP activity decreased in agreement with past literature. Beta-endorphins are present both centrally and in peripheral tissues, e.g. in foci of inflammation. Presumably, the activation of BE may exert an extremely potent immunosuppressive effect. Moreover, the elevation of

Table 1 : Patient characteristics.

	Treatment group	Controls
Mean age ± S.E.M	67.6 ± 3.2	69.5 ± 3.3
Male/female ratio	6/5	6/5
Mono/polyostotic disease	7/4	7/4

Table 2 : Effect of pamidronate treatment on patients with Paget's disease.

	Beta-endorphin level			AP activity			VAS Score		
	Day 0	Day 12	p	Day 0	Day 12	p	Day 0	Day 12	p
Treatment group	9.66 ± 1.24	9.97 ± 0.94	0.81 NS	667.82 ± 162.71	487.42 ± 93.62	0.04 S	3.91 ± 0.62	2.54 ± 0.51	0.0006 S
Controls	10.64 ± 1.12	11.73 ± 2.82	0.19 NS	249.55 ± 31.46	246.36 ± 29.71	0.66 NS	4.54 ± 0.91	4.09 ± 0.81	0.53 NS

Values are means ± S.E.M.
S= significant; NS= not significant

BE levels has been observed in a variety of mechanisms related to pain relief, [16, 17] and might therefore be interpreted as a sign of analgesic action. Nevertheless, placebo effect of pamidronate in Paget's disease of bone cannot be ruled out, either [18].

Conclusion

This study failed to demonstrate any elevation of BE levels, despite the evident analgesic effect reflected by the reduction of VAS scores. This suggests that beta-endorphin and the activation of endogenous opiates may have an ancillary role in the mechanism behind the antinociceptive property of pamidronate.

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