Effects of flurbiprofen on serum level of interleukin-6, prostacyclin and corticosteroid A2 in patients with bone metastases of cancer

YANWEI YIN, YUSHENG YI, JUNMIN YU, XIUMING SUN, CHUANSHENG LIU and FENGHE XU

Department of Pain Treatment, The Affiliated Hospital of Qingdao University, Qingdao, Shandong 266003, P.R. China

Received July 25, 2017; Accepted November 14, 2017

DOI: 10.3892/ol.2017.7482

Abstract. The present study aimed to investigate the effects of flurbiprofen on serum level of interleukin-6 (IL-6), prostacyclin (PGI2) and corticosteroid A2 (TXA2) in patients with bone metastases of cancer. A total of 210 patients with bone metastasis of cancer were randomly divided into two groups: Flurbiprofen axetil analgesia group (group A) and dezocine analgesia group (group B), 105 cases in each group. The analgesic effect was evaluated using visual analogue scale (VAS) scoring system at 1, 12, 24 and 48 h after treatment. Serum levels of IL-6, PGI2 and TXA2 at 12 and 24 h after treatment were detected using double-antibody sandwich enzyme-linked immunosorbent assay. No significant differences in VAS scores were found between the two groups at 1, 12, 24 and 48 h after treatment, and no gastrointestinal adverse events and abnormal bleeding were observed. No significant differences in the serum levels of IL-6 were found between the two groups at 12 and 24 h after treatment. Significantly lower serum levels of TXA2 and PGI2 were found in group A compared to group B at 12 and 24 h after treatment ($P<0.05$). Serum level of PGI2 was positively correlated with serum level of TXA2 ($r=0.7212$, $P<0.05$) and VAS score ($r=0.7159$, $P<0.05$). Serum level of IL-6 was positively correlated with VAS score ($r=0.7997$, $P<0.05$). The results show that flurbiprofen axetil can effectively relieve pain in patients with bone metastases of cancer, can inhibit platelet activation, adhesion and aggregation, and reduce the formation of deep vein thrombosis, and can inhibit stress response and inflammatory response in the body.

Introduction

Bone metastasis is the most common type of tumor metastasis in patients with advanced malignant tumors, and approximately 1.5 million patients were diagnosed with bone metastases of cancer each year (1). Cytokines secreted by tumor cells can disturb the dynamic balance between bone formation and bone dissolution, and can increase the bone dissolution rate, which in turn leads the occurrence of bone pain, bone marrow infiltration and other bone-related pathological changes in patients (2,3), affecting the quality of life and prognosis of patients.

Flurbiprofen axetil cannot only induce preemptive analgesia (4), but also can reduce inflammatory response during extubation. As an analgesic carrier, lurbiprofen axetil has the features of a non-selective and non-steroidal drug (5) and achieves a targeted effect. Analgesia can be easily induced and the analgesic effect can last for a long period of time. Flurbiprofen axetil achieves its analgesic effect by inhibiting epoxidase and reducing the uptake of prostaglandins by prostaglandin synthesis cells (6,7). Side effects of flurbiprofen axetil, such as central inhibition and gastrointestinal bleeding are relatively rare (8). As a defensive behavior of the body, stress response achieves its biological roles by regulating immune function and coagulation. Levels of stress hormones and immune factors are commonly used to assess the degree of stress response (9). The dynamic balance between inflammatory and anti-inflammatory factors plays a major role in postoperative inflammation. Postoperative complications are closely correlated with changes in immune function caused by surgical trauma and other stimuli (10).

Therefore, this study aimed to investigate the effects of flurbiprofen axetil on the serum levels of interleukin-6 (IL-6), prostacyclin (PGI2) and corticosteroid A2 (TXA2) in patients with malignant tumors with the expectation of identifying a novel method to reduce postoperative inflammatory and stress responses (11).

Materials and methods

Clinical data. A total of 210 patients with lung cancer were selected in The Affiliated Hospital of Qingdao University (Shandong, China) from January 2016 to December 2016. Patients were randomly divided into flurbiprofen axetil and dezocine group, 105 cases in each group.

Inclusion criteria. Inclusion criteria for the study were: i) Patients diagnosed with bone metastasis of lung cancer;

Correspondence to: Dr Yusheng Yi, Department of Pain Treatment, The Affiliated Hospital of Qingdao University, 16 Jiangsu Road, Qingdao, Shandong 266003, P.R. China
E-mail: tiyv04@163.com

Key words: flurbiprofen, bone metastasis of cancer, interleukin-6, prostacyclin, corticosteroid A2

Table I. Comparison of basic information between the two groups.

Variables	Flurbiprofenaxetil group n=105	Dezocine group n=105	P-value
Age (years)	60±5.3	56±4.7	>0.05
Sex (male/female)	53/52	49/56	>0.05
Temperature	37.62±0.57	37.82±0.63	>0.05
Alanine aminotransferase	36.12±26.89	36.25±27.13	>0.05
Creatinine	24.39±6.79	22.33±6.31	>0.05
White blood cell count	9.59±3.71	9.88±3.99	>0.05
Platelet count	133±10.32	152±11.49	>0.05

Table II. Comparison of VAS scores between the two groups.

Time	Group A	Group B	t-value	P-value
1 h	5.3±0.4	6.1±0.5	4.13	>0.05
12 h	5.1±0.6	5.9±0.4	3.79	>0.05
24 h	4.8±0.4	5.4±0.5	4.21	>0.05
48 h	4.4±0.8	4.9±0.3	4.89	>0.05

VAS, visual analogue scale.

Table III. Comparison of serum levels of IL-6, TXA2 and PGI2 between the two groups.

	Groups			
Variables	A	B	t-value	P-value
IL-6				
12 h	73.92±7.21	78.81±9.24	0.16	>0.05
24 h	68.83±6.93	72.56±8.39	0.24	>0.05
TXA2				
12 h	52.82±7.31	88.52±8.72	5.27	<0.05
24 h	44.43±6.8	78.64±7.98	5.39	<0.05
PGI2				
12 h	47.15±6.68	79.24±5.87	6.03	<0.05
24 h	40.26±5.79	75.41±6.03	6.11	<0.05

PGI2, prostacyclin; IL-6, interleukin-6; TXA2, corticosteroid A2.

Table IV. Correlation between VAS score and serum levels of IL-6, TXA2 and PGI2 (r-value).

r-value	VAS score	IL-6	TXA2	PGI2
VAS score	-	r=0.7997	0.2145	0.7159
IL-6	0.7997	-	0.1978	0.2239
TXA2	0.2145	0.1978	-	0.7212
PGI2	0.7159	0.2239	0.7212	-

VAS, visual analogue scale; IL-6, interleukin-6; TXA2, corticosteroid A2; PGI2, prostacyclin.

ii) ASA (12) (American Association of Anesthesiologists) grade from I to II; iii) patients without liver, kidney and other organ dysfunction before surgery; iv) patients without abnormal bleeding or abnormal coagulation; v) patients who did not receive radiotherapy and chemotherapy before surgery; and vi) patients or their family members who signed informed consent.

Exclusion criteria. Exclusion criteria for the study were: i) Patients allergic to non-steroidal drug; ii) patients with a history of gastrointestinal ulcers or gastrointestinal bleeding; and iii) pregnant women or lactating women.

Intravenous infusion of flurbiprofen axetil or dezocine. Analgesia for patients in group A (flurbiprofen axetil group) was performed by intravenous infusion of flurbiprofen axetil (0.05 g), while intravenous infusion of dezocine (0.05 g) was performed for patients in group B (dezocine group).

Observation indicators. Visual analogue scale (VAS) scores at 1, 12 , 24 and 48 h after surgery were recorded. Double-antibody sandwich enzyme-linked immunosorbent assay was used to detect erum levels of IL-6, PGI2 and TXA2 at 12 and 24 h after treatment.

Statistical analysis. SPSS 19 software (SPSS, Inc., Chicago, IL, USA) was used. Imitating normal distribution was performed by Student's t-test. P<0.05 was considered to indicate a statistically significant difference.

Results

Basic information. No significant differences in age, sex and temperature were found between the two groups of patients (P>0.05). Liver, renal and coagulation dysfunction were not found in patients. All the patients were found to be with normal levels of white blood cells (Table I). The patients were diagnosed with bone metastasis of lung cancer (Table I).

Comparison of VAS scores and serum levels of IL-6, TXA2 and PGI2 between the two groups. The VAS score was determined as previously established (13). No significant differences in VAS score were found between the two groups at 1, 12, 24 and 48 h after surgery (P>0.05) (Table II).

There was no significant difference in the serum level of IL-6 between the two groups at 12 and 24 h after surgery

(P>0.05). Compared with the dezocine group, serum levels of PGI2 and TXA2 were significantly decreased in the flurbiprofen axetil group (P<0.05) (Table III).

There was a positive correlation between the serum level of IL-6 and VAS score (r=0.7997, P<0.05). The serum level of PGI2 was positively correlated with the serum level of TXA2 (r=0.7212, P<0.05) and VAS score (r=0.7159, P<0.05) (Table IV).

Discussion

Bone metastasis of cancer can disrupt the dynamic balance between bone formation and osteolysis, thus increasing the bone dissolution rate and affecting bone structure, which in turn induces bone pain, bone marrow infiltration and other bone-related pathological changes, leading to severe effects on the quality of life and prognosis of patients.

Flurbiprofen axetil is a non-selective and non-steroidal drug as an analgesic (14) that can achieve a targeting effect (15). Flurbiprofen axetil can be accumulated at the sites of injury and inflammation to inhibit the activity of cyclooxygenase (COX), which in turn achieves analgesic effect (16). In addition, flurbiprofen axetil can be absorbed by Mϕ and Neu and other periglomerular (PG) cells to inhibit the synthesis and release of PG, thereby reducing tissue edema and inflammatory response caused by surgical trauma (17,18). Flurbiprofen axetil can inhibit stress response and reduce the pain caused by extubation after surgery (17,18).

PG can cause inflammatory response, promote vasodilation, increase permeability of the vascular wall and induce swelling and other clinical features (19). TXA2 is mainly secreted by platelet (PLT). TXA2 plays an essential role in PLT aggregation and vasoconstriction, and is a specific marker of PLT activation in the body. Flurbiprofen axetil can inhibit the activity of COX and promote the synthesis and release of IL-6 (20). This in turn, reduces stress response and enhances the analgesic effect of flurbiprofen axetil. Both pro- and anti-inflammatory factors are involved in the inflammatory response. Pro-inflammatory factors can induce inflammatory response, while anti-inflammatory factors can affect immune function.

Continuous intravenous infusion of non-selective cyclooxygenase inhibitors may inhibit platelet function, leading to postoperative bleeding in patients (21). Therefore, monitoring of coagulation function should be performed.

In the present study, no significant differences in VAS scores were found between the two groups at 1, 12, 24 and 48 h after surgery, indicating that flurbiprofen and dezocine have similar efficiencies in analgesia.

No significant differences in serum levels of IL-6 were found between the two groups at 12 and 24 h after surgery, indicating that flurbiprofen axetil has no specific effect on stress response. However, flurbiprofen axetil can still reduce stress response to a certain extent, which is inconsistent with the findings reported by Zhang *et al* (22). Zhang *et al* found no significant changes in PG after flurbiprofen axetil treatment, which may be explained by the different sample size and detection method (22). Serum levels of TXA2 and PGI2 were significantly lower in the flurbiprofen than in the dezocine group, indicating that flurbiprofen axetil can significantly affect the inflammatory response and blood coagulation. This finding is consistent with the results reported by Jiang *et al*, who found that flurbiprofen axetil can reduce the level of TXA2 (23). IL-6 level was positively correlated with VAS scores. PGI2 level in serum was positively correlated with serum level of TXA2 and VAS score. Clinicians can roughly estimate levels of IL-6 and PGI2 in patients according to VAS scores. In patients with bone metastases of lung cancer, there is a link between stress and inflammatory responses (24).

In conclusion, Flurbiprofen axetil can effectively relieve the pain of patients with bone metastases of lung cancer, can prevent thrombosis and promote blood flow, and can inhibit stress and inflammatory responses in the body.

References

1. Yang L and Du S: Efficasy and safety of zoledronic acid and pamidronate disodium in the treatment of malignant skeletal metastasis: A meta-analysis. Medicine (Baltimore) 94: e1822, 2015.
2. Silva SC, Wilson C and Woll PJ: Bone-targeted agents in the treatment of lung cancer. Ther Adv Med Oncol 7: 219-228, 2015.
3. Winter MC and Coleman RE: Bisphosphonates in the adjuvant treatment of breast cancer. Clin Oncol 25: 135-145, 2013.
4. McCormick Z, Chang-Chien G, Marshall B, Huang M and Harden RN: Phantom limb pain: A systematic neuroanatomical-based review of pharmacologic treatment. Pain Med 15: 292-305, 2014.
5. Kushwaha N, Sahu S and Tyagi RK: Flurbiprofen axetil loaded coaxial electrospun poly(vinyl pyrrolidone)-nanopoly(lactic-co-glycolic acid) core-shell composite nanofibers: Preparation, characterization, and anti-adhesion activity. J Appl Polym Sci 132: 899-907, 2015.
6. Lin X, Zhang R, Xing J, Gao X, Chang P and Li W: Flurbiprofen axetil reduces postoperative sufentanil consumption and enhances postoperative analgesic effects in patients with colorectal cancer surgery. Int J Clin Exp Med 7: 4887-4896, 2014.
7. Wen Y, Wang M, Yang J, Wang Y, Sun H, Zhao J, Liu W, Zhou Z, Deng H, Castillo-Pedraza C, *et al*: A comparison of fentanyl and flurbiprofen axetil on serum VEGF-C, TNF-α, and IL-Iβ concentrations in women undergoing surgery for breast cancer. Pain Pract 15: 530-537, 2015.
8. Baid M, Kar M, De U and Mukhopadhyay M: Conventional laparoscopic appendicectomy and laparoscope-assisted appendicectomy: A comparative study. Indian J Surg 77: 330-334, 2015.
9. Schiavone S and Trabace L: Redox dysregulation biomarkers: Clinical outcomes and pharmacological implications for psychosis. Front Psychiatry 8: 203, 2017.
10. Antoun M, Edwards KM, Sweeting J and Ding D: The acute physiological stress response to driving: A systematic review. PLoS One 12: e0185517, 2017.
11. Tabellini G, Borsani E, Benassi M, Patrizi O, Ricotta D, Caimi L, Lanzi R, Micheli F, Iorno V, Bettaglio R, *et al*: Effects of opioid therapy on human natural killer cells. Int Immunopharmacol 18: 169-174, 2014.
12. Pillai AK, Kovoor JM, Reis SP, Kho K, Sutphin PD and Lucas E: Expulsion of a uterine fibroid into the small bowel through uteroenteric fistula presenting with bowel obstruction after uterine fibroid embolization: Case report with histopathologic correlation. J Vasc Interv Radiol 27: 762-764, 2016.
13. Shen JC, Sun HL, Zhang MQ, Liu XY, Wang Z and Yang JJ: Flurbiprofen improves dysfunction of T-lymphocyte subsets and natural killer cells in cancer patients receiving post-operative morphine analgesia. Int J Clin Pharmacol Ther 52: 669-675, 2014.
14. Zhang L, Zhu J, Xu L, Zhang X, Wang H, Luo Z, Zhao Y, Yu Y, Zhang Y, Shi H, *et al*: Efficacy and safety of flurbiprofen axetil in the prevention of pain on propofol injection: A systematic review and meta-analysis. Med Sci Monit 20: 995-1002, 2014.
15. Geng W, Hong W, Wang J, Dai Q, Mo Y, Shi K, Sun J, Qin J, Li M and Tang H: Flurbiprofen axetil enhances analgesic effects of sufentanil and attenuates postoperative emergence agitation and systemic proinflammation in patients undergoing tangential excision surgery. Mediators Inflamm 2015: 601083, 2015.

16. Wu TT, Wang ZG, Ou WL, Wang J, Yao GQ, Yang B, Rao ZG, Gao JF and Zhang BC: Intravenous flurbiprofen axetil enhances analgesic effect of opioids in patients with refractory cancer pain by increasing plasma β-endorphin. Asian Pac J Cancer Prev 15: 10855-10860, 2014.
17. Clancy NT, Arya S, Stoyanov D, Singh M, Hanna GB and Elson DS: Intraoperative measurement of bowel oxygen saturation using a multispectral imaging laparoscope. Biomed Opt Express 6: 4179-4190, 2015.
18. Shen JC, Sun HL, Zhang MQ, Liu XY, Wang Z and Yang JJ: Flurbiprofen improves dysfunction of T-lymphocyte subsets and natural killer cells in cancer patients receiving post-operative morphine analgesia. Int J Clin Pharmacol Ther 52: 669-675, 2014.
19. Zhou M, Li B and Kong M: Effects of flurbiprofen axetil on postoperative analgesia and cytokines in peripheral blood of thoracotomy patients. Cell Biochem Biophys 72: 429-432, 2015.
20. Celik IH, Demirel G, Uras N, Oguz ES, Erdeve O and Dilmen U: The role of serum interleukin-6 and C-reactive protein levels for differentiating aetiology of neonatal sepsis. Arch Argent Pediatr 113: 534-537, 2015 (In Spanish).
21. Patricio JP, Barbosa JP, Ramos RM, Antunes NF and de Melo PC: Relative cardiovascular and gastrointestinal safety of non-selective non-steroidal anti-inflammatory drugs versus cyclo-oxygenase-2 inhibitors: Implications for clinical practice. Clin Drug Investig 33: 167-183, 2013.
22. Zhang L, Shu R, Zhao Q, Li Y, Wang C, Wang H, Yu Y and Wang G: Preoperative but not postoperative flurbiprofen axetil alleviates remifentanil-induced hyperalgesia after laparoscopic gynecological surgery: A prospective, randomized, double-blinded, trial. Clin J Pain 33: 435-442, 2017.
23. Jiang WW, Wang QH, Peng P, Liao YJ, Duan HX, Xu M, Li Y and Zhang PB: Effects of flurbiprofen axetil on postoperative serum IL-2 and IL-6 levels in patients with colorectal cancer. Genet Mol Res 14: 16469-16475, 2015.
24. Zhang L and Gong Z: Clinical characteristics and prognostic factors in bone metastases from lung cancer. Med Sci Monit 23: 4087-4094, 2017.