Closing the Gap of Unmet Needs in Inflammatory Pain Management: Case Series of Predimenol for Pain

Rizaldy Pinzon

Duta Wacana Christian University School of Medicine/ Bethesda Hospital Yogyakarta

Abstract

Chronic inflammatory pain is major medical problem worldwide. Nonsteroidal anti-inflammatory drugs (NSAIDs) and selective cyclooxygenase (COX)-2 inhibitors are commonly used medications to treat chronic pain. However, these agents have been associated with serious gastrointestinal, renal and cardiovascular adverse effects. This limitation indicates a clear unmet need in terms of safety of current treatment options for the management of chronic inflammatory pain. Those adverse effects may caused by overlapping roles of COX-1 and COX-2 in physiological and pathophysiological processes. Predimenol is a herbal medicine that can be used to treat pain. Recent findings showed that these phytochemicals may directly act upon several inflammatory processes and offer compelling evidence that predimenol could reduce pain and inflammation. We report two cases and short review of the use of predimenol for pain management. Our review showed that predimenol formulations could be a valuable alternative treatment to relieve symptoms of pain with good safety profile. Further researches through large, high quality RCTs to investigate the clinical benefit of predimenol for pain management are needed.

Keywords: predimenol, inflammation, safety, NSAID, coxib

Introduction

Inflammatory pain is the leading cause of physical disability and impairment in elderly.[1] An effective management for certain inflammatory condition (e.g. osteoarthritis) remains inconclusive. Typically, this chronic pain condition is managed with palliative measures that focus on pain reduction.[2,3] There were significant group of patients in whom these treatments do not provide adequate pain relief.[4] Studies upon treatment options that can be proven to stop or reversing the degenerative process are limited.[5,6]

Modification of disease progression and symptom reduction are the ultimate goals for chronic pain treatment. The most common agents for the treatment of these conditions are nonsteroidal anti-inflammatory drugs (NSAIDs) and selective cyclooxygenase (COX)-2 inhibitors. This medications have been associated with some serious adverse events, especially in high-risk patients.[7] Previous reviews showed that NSAIDs are associated with GI side effects.[8] The use of selective COX-2 inhibitors showed reduction in GI effects, but similar to NSAIDs in terms of the risk for renal impairment. Concerns have also been raised over their cardiovascular safety.[9]

These multiorgan safety risks limit the use of NSAIDs and/or coxib, especially for long-term use. There is still unmet need for chronic pain treatment in terms of safety profile in pain reduction.[10] Predimenol is one of the extensively investigated natural products for the treatment of inflammatory conditions and pain. Previous studies showed that the use of predimenol is promising in pain treatment.[10,11]

It is therefore apparent that there are unmet needs in chronic pain management. The gap is found especially either in the safety of treatment options and the disease modifying ability of therapeutic agents. Adverse events of NSAIDs and selective COX-2 inhibitors may limit their use. This limitation can have negative impact on pain control and inflammatory reduction. This case series report two cases of predimenol use for pain, and review the evidence about the potential use of predimenol to address some of the unmet needs in chronic pain management.

Case series

Case 1

A 64-year-old female presented with right knee pain more than 4 months. The pain felt like aching and burning around the knee. Walking and stair climbing will elicit the pain. Crepitation is found in the physical examination. Other clinical findings are unremarkable. Patient has history of GI bleeding related with the use of NSAID. Previous medication (coxib) was reported to cause GI discomfort. Paracetamol 1500 mg in three divided doses can slightly reduce the pain. Knee X-ray showed grade 2/3 osteoarthritis (figure 1). We add predimenol (Herbapain) two times daily as an add-on to paracetamol therapy for 14 days. The average numeric pain scale decreased from 6 to 3 after two weeks of treatment. The subjective global assessment showed that this patient satisfied with the treatment. No GI discomfort during 2 weeks of predimenol therapy. The activities of daily living are also improved.

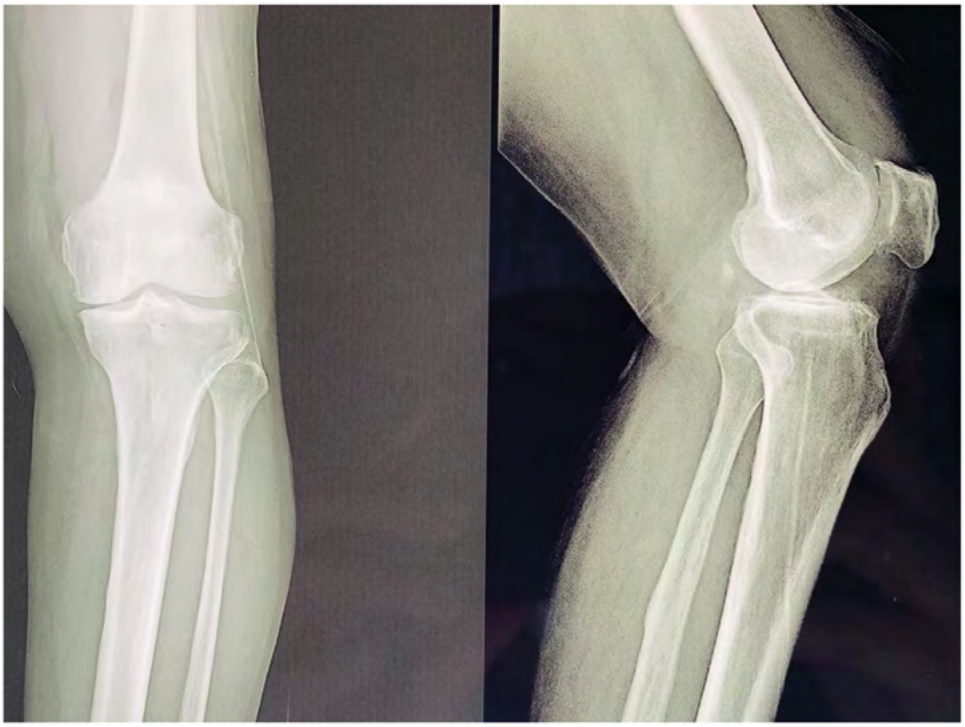

Figure 1. X-ray imaging of the first case. Pain improved significantly after 2 weeks treatment with paracetamol and predimenol.

Case 2

A 57-year-old female presented with acute (2 weeks) right shoulder pain. No history of significant trauma. There was a range of movement limitations. The pain affected her sleep quality and ability to do daily activities. She had history of ischemic heart disease and on aspirin therapy. The average pain intensity in the movement is 6. She was treated with paracetamol with only small benefit. The ultrasound showed tendinosis in the supraspinatus muscle. We add predimenol (Herbapain) two times daily for 2 weeks, and refer the patients for physical therapy. The pain decreased significantly, and the range of movement was improved. No adverse events were reported after 2 weeks therapy.

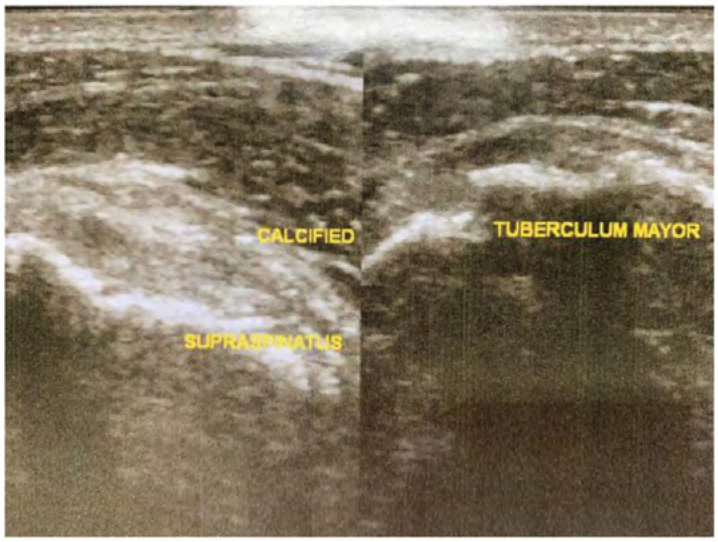

Figure 2. Ultrasound of the second case showed calcified tendinosis of supraspinatus muscle. The pain improved after 2 weeks treatment with paracetamol and predimenol.

Discussion

Our cases showed that predimenol given as add-on therapy on paracetamol can give significant improvement in pain and activities. The use of predimenol was not associated with the increase of adverse events after two weeks therapy, even in high-risk patients.

The GI risks of NSAID are well established. Endoscopic evidence of mucosal injury in the upper GI tract is common with chronic use of NSAIDs, affecting as many as 70% of chronic NSAIDs users compared with 10% of people not taking NSAIDs.[12] In recent metaanalysis, all NSAID regimens, including nonselective and COX-2 selective agents increased the risk of upper GI complications.[13] This can be explained by the impairment of the protective role of prostaglandins in stimulating the synthesis and secretion of GI mucous.[14]

Regarding CV safety, there is considerable evidence that different COX-2 selective inhibitors and nonselective NSAIDs have different CV safety profiles.[15] Diclofenac as a nonselective NSAID posseses significantly greater CV risk compared to ibuprofen, naproxen, paracetamol, and non-analgesic medications. The moderate doses of celecoxib had similar CV safety to ibuprofen and naproxen.[16]

In addition to the GI and CV effects of NSAIDs, epidemiological and pathologic data also show association between NSAID use and the risk for both acute and chronic kidney disease (CKD).[17] Renal side effects which include sodium and water retention with edema, hyponatremia, hyperkalemia, and acute kidney injury may precipitate renal failure resulting in acute dialysis. Mechanism of NSAID-induced kidney damage is related to inhibition of prostaglandin synthesis and are known to be dose- also duration-dependent.[18]

Recent progress in inflammatory pain research has improved our understanding of the pathophysiology of the disease. *In vivo* and *in vitro* studies have suggested that the use of predimenol could halt or slow the catabolic actions of key inflammatory mediators, and could continue to block inflammatory pathways.[19] *Phaleria macrocarpa* fruit extracts has shown this effect due to the presence of phenolic and flavonoid compounds or other phytochemicals such as terpenoid compound.[20] Anti-inflammatory properties of predimenol is mediated through flavonoids. Flavonoids have been widely used for their antioxidant, analgesic, and anti-inflammatory effects along with preclinical and clinical safety profile.[20,21]

DLBS1442 is a proprietary and standardized bioactive extract of *Phaleria macrocarpa*. Previous preclinical study showed that DLBS1442 demonstrated capacity to down-regulate ER-b, COX-2 and phospholipase-A2 (cPLA2) gene expression.[22,23] Previous clinical study by Tjandrawinata, et al. showed that DLBS1442 was well-tolerated by subjects with premenstrual syndrome and was effective in relieving dysmenorrhea, abdominal pain and other symptoms related to premenstrual syndrome. [22] Similar results were obtained from study by

Wiweko, et al. that DLBS1442 in 10 endometriosis patients showed the effectiveness in pain reduction. This study showed that VAS score reduction was noted in the first post-treatment menstrual cycle (approximately 5.3 weeks after treatment initiation), and VAS scores reduction continued until the final two menstrual cycles.[24]

Conclusion

The results of our review showed that there are many concerns in the use of NSAIDs/coxib, especially for long-term pain management. Our case studies suggest that predimenol formulations could be a valuable addition to pharmacological treatment regimen for pain reduction and function improvement, with good safety profile. Future research should consist of larger, higher quality RCTs that specifically examine the role of predimenol formulation as treatment for chronic pain patients who rely upon NSAID treatment.

Disclosure

The authors report no conflicts of interest in this work.

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