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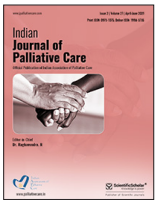

Original Article

Flupirtine in the Management of Taxane-induced Pain in Cancer Patients

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ABSTRACT

Objectives: Paclitaxel and docetaxel are two commonly used chemotherapeutic agents in the treatment of various types of cancers. However, debilitating taxane-induced arthralgia and myalgia are among the most common adverse reactions associated with taxanes, which has greatly influenced medical practitioners. Most of the mild and moderate analgesics were found to be less effective in the management of taxane induced pain. So we used flupirtine, a non-opioid analgesic, in the treatment of taxane-induced pain.

Materials and Methods: In this study, we analysed the baseline pain score and follow-up data of 60 patients receiving a taxane-based chemotherapy regimen. Baseline data of these study populations experiencing significant taxane-induced pain were compared with follow-up data after treating them with analgesic flupirtine (200 mg/day). The baseline and follow-up data representing pain were assessed with the help of the Visual Analogue Scale (VAS), and the quality of life was determined using the Brief Pain Inventory (BPI) scale questionnaire.

Results: The mean baseline and follow-up VAS score was compared using paired sample *t*-test, which showed a significant reduction in taxane-induced pain after treatment with flupirtine ($P < 0.001$). Similarly, the mean BPI score representing the quality of life before and after treatment with flupirtine was compared, and a notable improvement in quality of life was seen after treatment with flupirtine. The mean and follow-up data of aspartate aminotransferase and alanine aminotransferase levels of patients were also compared to assess the adverse drug reaction profile of the drug, and the analyzed data was found to be statistically insignificant (no significant liver toxicity) which indicates that drug can be used effectively for a period of <2 weeks.

Conclusion: We believe that flupirtine can be used as an effective analgesic in dire situations where patients require opioid analgesics for the management of taxane-induced pain, provided that the drug is given for <2 weeks to avoid drug-related hepatotoxicity.

Keywords: Cancer, Flupirtine, Pain, Taxane, Paclitaxel, Docetaxel

INTRODUCTION

Pain is an afflictive and distressful feeling that leads to unpleasant sensations and emotional experience associated with potential tissue damage or can be regarded as a symptom of an underlying condition. More than half of the patients will receive anticancer treatment, and two-thirds of the patients whose disease will become advanced or metastatic will suffer from cancer-related pain.[1] The meta-analysis data reveals that the prevalence rate of cancer pain in patients at all disease stages were 53–59% for patients under anticancer treatment.[2] Paclitaxel and docetaxel are two anticancer drugs that have been successfully used in chemotherapy for various cancers such as breast, ovarian, lung, bladder, prostate, melanoma, oesophageal, and other types of solid tumour cancers.[3,4] By inhibiting microtubules, taxane causes neurotoxicity that might necessitate the discontinuation of chemotherapy due to decrease in quality of life in patients. It was found that debilitating taxane-induced arthralgia and myalgia are the greater clinical challenge.[5] These symptoms typically begin 48–72 h after the taxane infusion and last for 3–5 days.[6] Currently, there is no standard treatment regimen for managing taxane-induced arthralgia and myalgia. Some of the drugs tried in the treatment include melatonin, amifostine, gabapentin, pregabalin, glutathione, glutamine, corticosteroid, and a wide variety of analgesics.[7]

Analgesics comprise a class of drugs that specifically relieve pain without interfering with the conduction of nerve impulses, considerably changing sensory perception or affecting consciousness. Most of the mild and moderate analgesics were found to be less effective in managing taxane-

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induced pain.[8] This necessitated using the drug flupirtine, a non-opioid analgesic, which acts as a selective neuronal potassium channel opener.[9] The drug does not show tolerance or physical dependence, which is an added advantage over other analgesics. The drug was effective for treating various types of acute and chronic pain such as postoperative pain, traumatic injury, headache, migraine, musculoskeletal pain, cancer pain, orthopedic, and gynaecological problems.[10,11] However, the drug cannot be used for more than 2 weeks due to hepatotoxicity. Still, it can be used for fewer than 10 days by frequently monitoring the aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels.[12] In this study, we evaluated the effectiveness of flupirtine in the management of taxane-induced arthralgia and myalgia.

MATERIALS AND METHODS

A prospective observational follow-up study was conducted in the Department of Medical Oncology. The study was conducted as a pilot study with a sample size of 60 patients since no data was available in the literature regarding the effectiveness of flupirtine in managing taxane-induced pain in cancer patients. The demographic details and baseline characteristics of the patients were obtained from patient medical and electronic medical records. The patient's pain severity was assessed using the Visual Analogue Scale (VAS). The patient's quality of life was assessed with the help of a quality control questionnaire from the Brief Pain Inventory (BPI) scale.

All cancer patients (age >18 years) receiving taxane-based chemotherapy who were mentally and physically competent to provide informed consent and answer the questions were selected for the study after obtaining their informed consent. Patients on strong analgesics were excluded from the study since they are likely to provide false-positive results. Patients with pre-existing liver disease were also excluded due to the known hepatotoxic effect of the drug flupirtine. Following chemotherapy, the onset of taxane-induced myalgia and arthralgia is usually seen within 48–72 h. During this interval, baseline data were obtained from the patients. The patient was requested to choose a score from 0 to 10 on the VAS scale that best described their pain severity after chemotherapy. Similarly, BPI scale parameters such as general activity, walking ability, mood, sleep, relationship with people and ability to work were assessed in the above manner to study the quality of life amidst the taxane-induced pain. Baseline AST and ALT levels of the patients were also obtained during this time interval before administering analgesic (flupirtine 200 mg/day) to assess the adverse drug reaction profile after taking the drug. Flupirtine was given 100 mg 2 times a day for a maximum 5–7 days. Follow-up data of patients were collected by providing them with a similar set of another questionnaire (VAS and BPI scale) after 48–72 h following analgesic administration (flupirtine). The follow-up data were compared with that of baseline to determine the effectiveness of flupirtine in managing myalgia and arthralgia induced by the taxanes. After obtaining approval from the Research and Ethics Committee of Amrita Institute of Medical Sciences and Research Centre (IEC-AIMS-2019-PHARM-242), the study was conducted. Paired sample *t*-test was applied using SPSS (version 25.0) to compare the mean pain score, mean quality of life score, mean AST and mean ALT before and after giving the drug flupirtine.

RESULTS

Demographics and patient characteristics

Out of the 60 patients (male: female = 8:52) enrolled, none withdrew from the study. The demographics of the patient revealed the median age of the study participants as 52.5 years. Breast cancer (61.7%) was the diagnosis in the majority of the patients; other diagnoses included carcinoma stomach, endometrium, ovary and lung. Paclitaxel alone and paclitaxel in combination with carboplatin was the major chemo regimen given to the patients. Out of the 60 patients, 28 received paclitaxel alone, and 32 patients received paclitaxel-carboplatin combination regimens. Details regarding the chemo regimen and diagnosis have been depicted in [Table 1].

Efficacy assessment

The intensity of the taxane-induced pain was assessed by comparing the VAS score at the baseline and at the end of treatment with flupirtine. The baseline data indicated that out of 60, 56 patients (93.3%) experienced significant myalgia and arthralgia (score above or equal to 5) after chemotherapy. At the end of the study, both the baseline VAS score and after treatment with flupirtine were analyzed. As shown in [Table 2], the mean VAS score after treatment was significantly less than that of baseline data ($P < 0.001$), indicating a remarkable reduction in taxane-induced arthralgia and myalgia after treatment with flupirtine.

Quality of life

The BPI score of patients before and after taking flupirtine was assessed to determine the impact of taxane-induced pain on patient's quality of life. The BPI score comprised general activity, mood, sleep, walking ability, relationship with other people and ability to work. Summarising the data from the above parameters, the baseline data indicates that out of 60 patients, in the majority of them, the quality of life was affected significantly (score above or equal to 5) due to taxane-induced pain after chemotherapy [Table 3]. The follow-up data of these patients indicate that a marked improvement in quality of life was seen after taking flupirtine in most of them. The mean BPI score after treatment was significantly different from that of the mean BPI score before treatment with flupirtine ($P < 0.001$), which suggests that quality of life improved after treatment in most patients.

Adverse reactions

In most patients, the AST and ALT levels after taking flupirtine were within the normal range. In few patients, a slight elevation in liver function was seen; however, it was statistically insignificant.

DISCUSSION

The notional basis for giving flupirtine in our study was based on two scenarios; first, the patient experienced taxane-induced arthralgia and myalgia after chemotherapy; second, the patient had normal AST and ALT level before administering the drug. Considering these annotations, at baseline, 56 patients experienced significant myalgia and arthralgia after chemotherapy. However, following flupirtine treatment, only ten patients experienced significant pain.

Table 1: Demographics and patient characteristics.

Gender *n* (%)	
Male	8 (13.3%)
Female	52 (86.7%)
Median age	52.5 years
Diagnosis	
Carcinoma breast	37 (61.7%)
Carcinoma endometrium	7 (11.7%)
Carcinoma stomach	6 (10%)
Carcinoma ovary	7 (11.7%)
Carcinoma lung	3 (5%)
Chemotherapy regimen	
Paclitaxel	28 (46.7%)
Paclitaxel/Carboplatin	32 (53.3%)

Table 2: Paired sample statistics (VAS Score).

Score	Mean±Standard deviation		*P* value
	Baseline	After treatment	
VAS	6.85±1.35	3.08±1.59	P<0.001

VAS: Visual analogue scale

Table 3: Paired sample statistics (BPI score for quality of life).

BPI Score (Parameters)	Mean±Standard deviation		*P* value
	Baseline	After treatment	
General activity	6.85±1.40	3.15±1.52	*P*<0.001
Mood	6.38±1.48	2.95±1.58	*P*<0.001
Walking ability	6.80±1.56	3.12±1.66	*P*<0.001
Normal work	6.76±1.52	3.02±1.70	*P*<0.001
Relationship with other people	6.28±1.62	2.67±1.48	*P*<0.001
Sleep	6.88±1.40	2.88±1.67	*P*<0.001

BPI: Brief pain inventory

Based on an in-depth analysis, we drew the following speculations, which are neither definitive nor accurate. Flupirtine can be used as an effective analgesic in the management of taxane induced pain. However, the chances of drug-induced hepatotoxicity cannot be completely ruled out as most of the candidates are cancer patients and the chances of hepatotoxicity are high.

Surprisingly a small proportion of patients in whom the drug was ineffective received paclitaxel and carboplatin combination regimens. However, in the rest of the majority of the patients receiving the above regimen, the drug (flupirtine) was effective. The mechanism of taxane-induced myalgia and arthralgia is believed to be due to inhibition of tubulin depolymerization, which leads to aggregation of intracellular microtubules.[13,14] Fully functional microtubules are required for both anterograde and retrograde axonal transport, which is vital for the survival of neuronal cells. Aggregation of these microtubules secondary to taxanes affects retrograde and anterograde axonal transport preventing the transport of growth factors and other substances disrupting nerve physiology.[15] Nonetheless, the reason for the elevation of pain in combination (paclitaxel and carboplatin) regimen is unknown. Although the exact mechanism by which flupirtine tackles the taxane induced myalgia and arthralgia is not known, flupirtine being a selective neuronal potassium channel opener along with its NMDA receptor antagonism properties prevents neuronal excitability and thereby decreases calcium ions influx into cells, the mechanism is crucial for transmission of pain signals to motor neurons.

Fortuitously, 61.7% of the patients enrolled in the study were suffering from carcinoma breast, and in most of them, the drug was found to be effective. In most patients, the day-to-day activities were affected due to taxane induced pain. Admissible improvement in quality of life was seen in these patients after treatment with flupirtine. Though it can be argued that the change in the quality of life cannot be estimated accurately since it can be influenced by the disease, in our study, the assessment of the quality of life was only for a brief period that is from the development of taxane-induced pain and its management with flupirtine. We believe that flupirtine can be used as an effective analgesic in dire situations where patients require opioid analgesics to manage taxane-induced pain, provided that the drug is given for a short period to avoid drug-related hepatotoxicity.

CONCLUSION

The results of the present study indicates that flupirtine had the potential to relieve pain in majority of the study population, who struggled with uncontrolled taxane-induced arthralgia and myalgia. Flupirtine can be used as an alternate analgesic because there is no serious adverse effect such as sedation, confusion, pleuritis, urinary retention, tolerance and dependence as seen with opioids. However, the chances

of drug-induced hepatotoxicity cannot be completely ruled out. We believe that further studies should be carried out to explore the therapeutic efficacy of flupirtine in the management of taxane-induced pain in cancer patients.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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