Original Article

Elucidation of Plasma Concentrations of Morphine, and it's Correlation with Pain in Cancer Patients Receiving Palliative Care

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ABSTRACT

Introduction: Palliative care is a special care designed to improve the quality of life of people with a terminal illness. Since the announcement of the ''WHO method of cancer pain therapy 1986'', Morphine has been considered as the principal drug. Due to increase in the number of reports of neuro-excitatory opioid-related side effects, it is of concern to assess the plasma concentration of Morphine. The study aimed to determine the plasma concentrations of Morphine in cancer patients on oral Morphine and its correlation with degree of pain relief.

Methodology: A total of fifty patients of either sex receiving oral Morphine for carcinoma-related pain were enrolled in the study. The intensity of pain was assessed by Edmonton Symptom Assessment Scale (ESAS) score which is a numerical pain score where 10 means the worst possible pain and 0 means no pain. Patient's blood samples were taken two hours before and two hours after administration of oral Morphine to determine its trough and peak concentrations.

Results: A positive correlation was observed between peak concentration of Morphine and point reduction in numerical pain score and it was statistically significant ($p<0.01$, ρ:0.785). A negative correlation was observed between peak concentration of Morphine after 2 hours and mean numerical pain score after 2 hours and it was also statistically significant ($p<0.01$, ρ:0.568).

Conclusion: A significant positive correlation was observed between peak concentration of Morphine and reduction in pain score, while a significant negative correlation was observed between peak concentration of Morphine after 2 hours and mean pain score after 2 hours.

Keywords: Cancer related pain; ESAS; Morphine; Palliative Care.

INTRODUCTION

Palliative care is a special care designed to improve the quality of life of people with chronic and terminal illnesses. It focuses on patient's needs and managing pain which helps or soothes a person who is experiencing significant pain. Various opioid medicines such as Codeine, Morphine, and Pethidine are used as pain relievers. Since the announcement of the "WHO method of cancer pain therapy 1986", Morphine has been considered as the principal drug. After 1986, the utility of Morphine has suddenly increased globally. However, there has also been an increase in the number of reports of dreaded neuro-excitatory opioid-related side effects (e.g. allodynia, myoclonic jerks, seizures) observed in patients receiving large doses of systemically administered Morphine.[1-5] After administration, Morphine (M) undergoes extensive metabolism, which primarily occurs in the liver. Glucuronidation is the main metabolic pathway, by which morphine-3-glucuronide (M3G) predominates over morphine- 6-glucuronide (M6G) production. A very small amount of normorphine is also produced.[6,7]

These major metabolites play a significant role in dynamic responses to Morphine therapy. M6G exhibits affinity to opioid receptors similar to that of M[8] in contrast, M3G is devoid of analgesic effects.[9] Monitoring of Morphine concentration in biological fluids is thus important not only for the investigation of relationships among doses of drug applied, plasma levels, and analgesic effect but also for the study of adverse effects, if any.

Morphine has been successfully analyzed by various methods e.g. immunoassay methods, gas chromatography (GC) coupled with mass spectrometry (MS)[10,11], Isotachophoresis (ITP)[12], and capillary zone electrophoresis

Table 1: Distribution of study subjects according to age, sex, and type of pain

Variable		Frequency (N=50)	Percent (%)
Age groups	< 25 years	4	8.00
	26 - 50 years	25	50.00
	> 50 years	21	42.00
Sex	Male	36	72.00
	Female	14	28.00
Type of pain	Visceral pain	26	52.00
	Visceral + Bone pain	5	10.00
	Visceral + Neuropathic pain	19	38.00

(CZE)[13,14], but these methods do not exhibit adequate sensitivity for biological fluids. Therefore, we used HPLC assay with UV detection of Morphine in the serum of patients after administration of Morphine.

The study clarifies the relationship of plasma concentrations of Morphine and its correlation with pain and this would subsequently facilitate the development of optimal cancer pain therapy using standard dose of Morphine having minimal side effects and better symptom outcome in patients.

METHODS

After due approval from the Institutional Ethics Committee, the study was conducted on fifty patients of either sex who sought treatment in a tertiary care hospital of government medical college and received oral Morphine for carcinoma-related pain in palliative care centre and fifty healthy human samples were taken as controls. Patients not giving informed consent, patients with dementia, psychosis, or other major psychiatric disorders, and patients with acute and/or chronic liver and kidney involvement were excluded from the study.

The intensity of pain was assessed by Edmonton Symptom Assessment Scale (ESAS). Patient's blood sample was taken at baseline and two hours after oral Morphine administration to determine trough and peak concentrations of Morphine by HPLC system using an ultraviolet detector and various internal standards.[15]

Statistical Analysis: Data collected were entered in Microsoft Excel 2010 Worksheet in the form of master chart. SPSS version 20 was used to get inferences. Qualitative data were expressed in the form of percentage and proportions. Spearman's rank order correlation 'ρ' was calculated to know the correlation between peak concentration of Morphine and decrease in ESAS pain score.

RESULTS

In the present study, a total of 100 samples were obtained (50 patients were enrolled and each of them had one sample collected at baseline and another two hours after administration of 10 mg of oral Morphine). 10 mg Morphine oral dose was given to each patient irrespective of their age and gender.

Out of 50 cases, majority of patients (72%) were male and 28% were females. Twenty-five (50%) patients were in the age group of 26-50 years, followed by 21 (42%) in more than 50 years of age, and only 4 (8%) were below the age of 25 years. Visceral pain was encountered in 52% participants while 38% participants had visceral and neuropathic pain combined and 10% had visceral pain along with bone pain (Table 1).

After 2 hours of administration of 10 mg oral Morphine, almost all patients showed a significant reduction in pain score. 8-9 point reduction was observed in 10% cases while 5-7 point reduction was seen in 72% cases and 2-4 point reduction was seen in 18% cases.

Table 2: Distribution of study subjects according to decrease in ESAS pain score

Decrease in ESAS pain score	Frequency	Percent
2 - 4 Points	9	18.00
5 - 7 Points	36	72.00
8 - 9 Points	5	10.00
Total	50	100.00

Table 3: Correlation of peak concentration of Morphine with decrease in ESAS pain score

Variable	Number	Spearman's rank order correlation (ρ)	p-Value
Peak concentration of Morphine with decrease in ESAS pain score	50	0.785	0.001

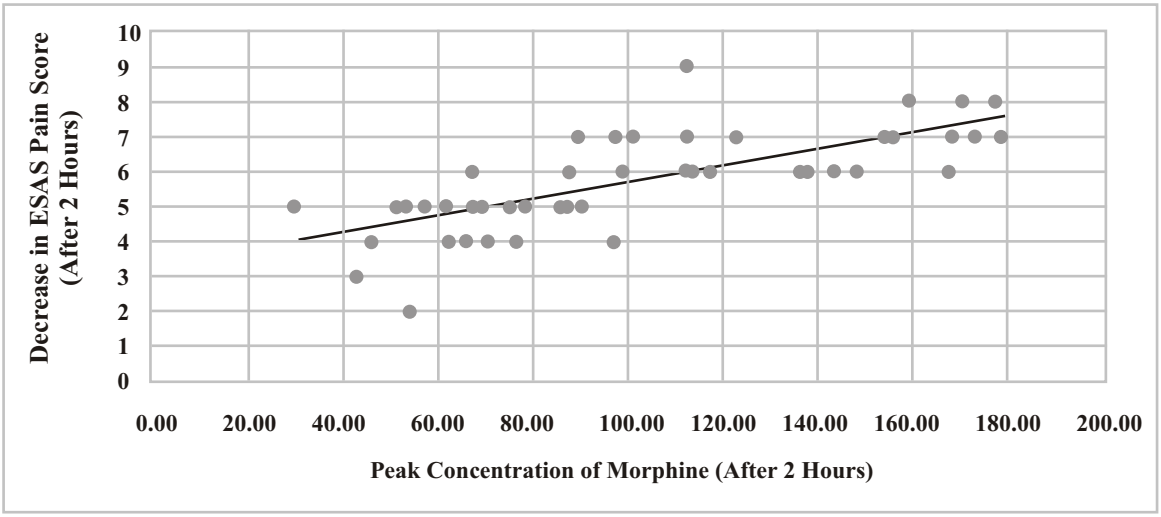

Figure 1: Correlation of peak concentration of Morphine with decrease in ESAS pain score.

Table 4: Correlation of peak concentration of Morphine (after 2 hours) with ESAS pain score (after 2 hours)

Variable	Number	Spearman's rank order correlation (ρ)	p-Value
Peak concentration of Morphine after 2 hours and ESAS pain score after 2 hours	50	-0.568	0.001

There was no significant correlation observed between peak concentration of Morphine (after 2 hours) with age ($p>0.05$, r:0.065). The mean peak concentration of Morphine (after 2 hours) in male patients was 104.08 ± 43.22 ng/L and in female patients was 102.57 ± 43.76 ng/L which was statistically insignificant ($p>0.05$). Similarly, no significant correlation was observed between reduction in pain score with age ($p>0.05$). The mean reduction in pain score (after 2 hours) in male patients was 5.89 ± 1.39 points and in female patients was 5.57 ± 1.7 points which was also statistically insignificant ($p>0.05$) (Tables 2, 3, and 4) (Figures 1 and 2).

A positive correlation was observed between peak concentration of Morphine and point reduction in pain score and it was found to be statistically significant ($p<0.01$, ρ:0.785). A negative correlation was observed between peak concentration of Morphine after 2 hours and mean pain score after 2 hours and it was also statistically significant ($p<0.01$, ρ-0.568).

No baseline Morphine levels were detected in the plasma of control patients**.**

DISCUSSION

The present study was designed with the aim to identify the relationship between plasma concentrations of Morphine and degree of pain relief to develop optimal cancer pain therapy using standard dose of Morphine with minimal side effects. We gave 10 mg Morphine to each patient irrespective of their age and gender and found satisfactory correlation between peak concentration of Morphine and point reduction in baseline and post two hours pain score.

In the present study, peak plasma Morphine concentrations were associated with more reduction in score and overall better response to Morphine therapy and higher level of

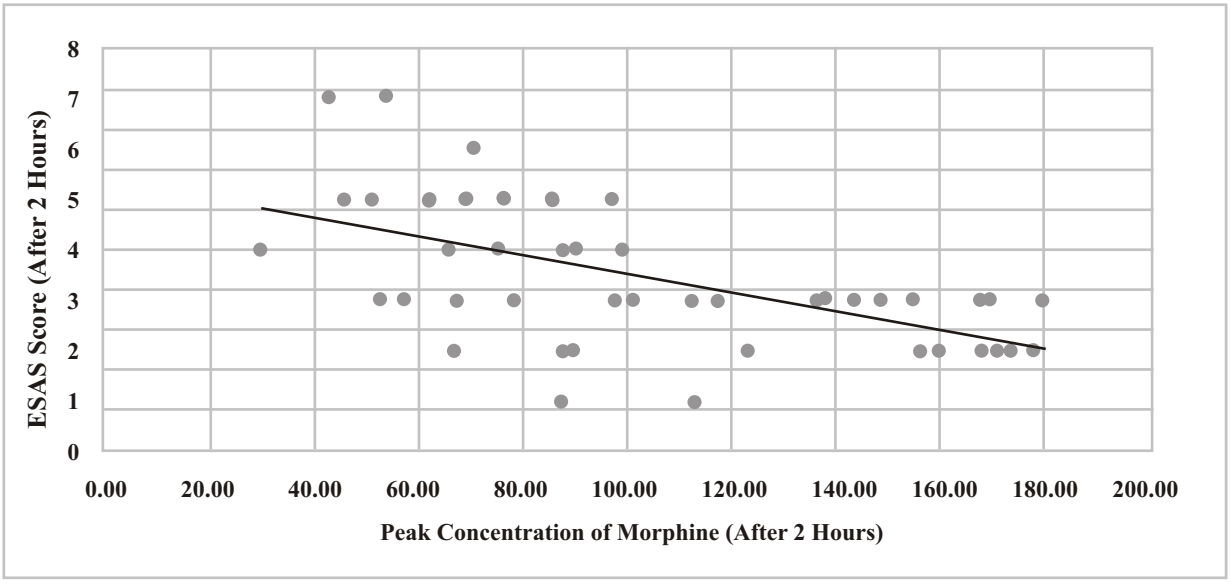

Figure 2: Correlation of peak concentration of Morphine (after 2 hours) with ESAS pain score (after 2 hours).

analgesia. In itself this result is not surprising; we know that Morphine mediates analgesia via activation of opioid receptors in the central nervous system and suggests that higher levels of these compounds will result in higher levels of analgesia. However, these suppositions have been difficult to demonstrate in previous trials. The only study to demonstrate similar results was by Faura et al.[16] Other studies[17-19] have failed to demonstrate an association between plasma concentrations and clinical effect likely due to variation in sample size and patient populations, confounding effects from patient-related factors (renal and hepatic function), differences in defining clinical phenotypes (thresholds used for defining the presence of side effects), and factors associated with plasma sampling (timing of blood sample in relation to Morphine).[18]

CONCLUSION

A significant positive correlation was observed between peak concentration of Morphine and reduction in pain score while a significant negative correlation was observed between peak concentration of Morphine after 2 hours and mean pain score after 2 hours.

Limitation of the study: Major limitation of the present study was that pure Morphine could not be procured as a standard due to regulatory restrictions. Therefore injectable Morphine was used as a standard as it qualified as the next best pure formulation.

Morphine metabolites levels--M3G and M6G were done for academic interest, but were not included in the study because their pure forms which were required to be used for standardization in the HPCL machine could not be procured in spite of all efforts due to the prevailing Narcotics and Substance Abuse Act. The readings obtained were on the basis of M3G and M6G levels indicated in other articles/papers published and thus have not been included in this study.

Conflicts of Interest: There are no conflicts of interest.

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