

RESEARCH ARTICLE

Pharmacoeconomics Evaluation of Morphine, MS Contin and Oxycodone in the Treatment of Cancer Pain

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Abstract

Objective: To analyze cost-effectiveness of morphine, MS contin and oxycodone in the treatment of cancer pain, providing guidance for rational drug use in the clinic. **Methods:** Confirmed by histology, a total of 171 patients with various cancers who required analgesic treatment were selected and divided into 3 groups, 57 cases for each group, given morphine, MS contin and oxycodone, respectively. If there appeared a poor short-term effect or aggravated sudden pain during the treatment, a short-acting morphine injection was given and adverse reactions were processed by symptomatic treatment. The pain relief rate and adverse reactions of groups were observed and pharmacoeconomics evaluation was undertaken. **Results:** The pain relief rates with morphine, MS contin and oxycodone were 89.5% (51/57), 91.2% (52/57) and 93.0% (53/57), respectively, with no difference among groups ($\chi^2=4.4489$, $P=0.6162$). The occurrence rates of adverse reactions were 59.7% (34/57), 54.4% (31/57) and 43.9% (25/57), again with no significant variation ($P>0.05$). The ratios of cost-effectiveness (C/E) for the 3 groups were 14.6 ± 7.21 , 15.0 ± 7.44 and 16.1 ± 8.10 . When the price of 3 kinds of analgesics was reduced by 10%, the ratios of cost-effectiveness were 12.2 ± 6.53 , (13.4 ± 6.08) and 14.5 ± 6.74 but there was no differences when compared with before the price adjustment ($t=1.86$, $P=0.0651$; $t=1.30$, $P=0.1948$; $t=1.17$, $P=0.2453$). **Conclusion:** Morphine, MS contin and oxycodone give similar pain relief and adverse reaction rates but of all, morphine is the preferred drug for the treatment of cancer pain from the perspective of pharmacoeconomics.

Keywords: Cancer pain - morphine - MS contin - oxycodone - pharmacoeconomics - cost-effectiveness analysis

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Introduction

Pain is the most common clinical symptom in cancer patients and along with the rising of cancer incidence, the occurrence of cancer pain increases gradually. It has been reported that 60%~90% of patients with advanced cancer accompanies varying degrees of pain, 70% cancer patients are with pain as the main symptom and 50% cancer patients companies moderate and acute pain. Moreover, cancer pain is the major factor of influencing the life quality of cancer patients so alleviating pain is of great significance for the treatment of cancer (Meserve et al., 2014).

With the standardization and gradual popularization of cancer pain treatment and extensive use of opioid, the effective control rate of cancer pain is constantly increasing, especially mild and moderate cancer pain which is controlled to large extent. At present, drug therapy is the key method for the chronic cancer pain control and proper treatment can relieve 95% pain symptom of the patients (Shinde et al., 2014). As far as the selection and use of drugs is concerned, the cost is an important aspect of influencing clinical treatment decision-making and rational drug use. This study analyzed pharmacoeconomics

of morphine, MS contin and oxycodone applied in the treatment of cancer pain so as to seek for an therapeutic protocol with the similar effect, relatively mild adverse reactions and low cost.

Materials and Methods

General data

Confirmed by histology, a total of 171 cancer patients who required analgesic treatment from Henan Cancer Hospital Affiliated with Zhengzhou University from Jan., 2013 to June, 2014 were selected, in which there were 94 males and 77 females, aged from 39~74, with the median age of 62 years.

Of all patients, there were 48 cases with lung cancer, 13 with pancreatic cancer, 30 with liver cancer, 15 with gastric cancer, 21 with nasopharynx cancer, 25 with colorectal cancer and 19 with bone metastases; 49 with moderate pain and 122 with severe pain. All patients had moderate or severe stable pain, the KPS score >50 , Expected survival >3 months, no obvious respiratory depression or airway obstruction, normal liver function and blood routine examination, no drug allergy history, no use of other analgesics at 5 h before treatment. All patients

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Table 1. Comparison of Relief Rates of 3 Kinds of Opioid Analgesics for Cancer Pain

Groups	Pain relief (n)					Pain relief rate(%)	χ^2	P
	0 degree	I degree	II degree	III degree	IV degree			
Morphine	0	6	21	19	11	89.47	4.4489	0.6162
MS contin	0	5	19	20	13	91.23		
Oxycodone	0	4	13	22	18	92.98		

were randomly divided into morphine group, MS contin group and oxycodone group, 57 cases for each group. The 3 groups were comparable for there was no difference in mean age, gender, disease categories, KPS score, pain types and degrees among 3 groups ($P>0.05$).

Methods

Treatment protocol: Morphine group was given oral morphine, 30 mg/12 h as initial dose, provided by Taiji Group· Southwest Pharmaceutical Co. Ltd.. MS contin group was given oral MS contin, 30 mg/12 h as initial dose and oxycodone group was given oral oxycodone, 10 mg/12 h as initial dose, and both are provided by Mundipharma (China) Pharmaceutical Co., Ltd.. The above-mentioned drugs must be swallowed wholly, not partially or trituration. If the patients cannot take the drugs, the same dose of rectal administration was considered. The dose was evaluated once every 48 h and regulated according to the degrees of pain relief. The dose was added and each dose was increased by 50%~100% due to poor control of disease but the administration frequency was not changed until the cancer pain was relieved satisfactorily. During the treatment, if the unsound short-term effect or sudden aggravated pain, a short-acting morphine injection was given.

Pharmacoeconomics evaluation: ① The cost: Besides drug price, pharmacoeconomics cost includes experimental examination and delivery cost. ②The ratio of cost-effectiveness (C/E) analysis: C/E was calculated and the incremental ratio of cost-effectiveness ($\Delta C/\Delta E$) was calculated with reference to the minimum-effect group. $\Delta C/\Delta E = (\text{the cost of the other group} - \text{the cost of minimum-effect group}) / (\text{the pain relief rate of the other group} - \text{the pain relief rate of the minimum group})$. ③Sensitivity analysis: Supposed that the drug price of 3 groups was reduced by 10% for calculating the indexes of pharmacoeconomics evaluation, the stability of evaluated results was verified.

Observational indexes

Drug analgesic effect of 3 groups was observed for calculating the relief rate. The adverse reactions such as nausea, vomiting, dizziness and somnolence were observed. Medical fee, drug expense, examination fee were recorded for calculating the cost and analyzing the cost-effectiveness.

Evaluation criterion

Pain classification standard according to WHO: Level 0 refers to painless. Level 1 refers to mild pain and patients are with tolerance to pain and no need to use drugs. Level 2 refers to moderate pain which influences sleep due to the occasional acute pain and the analgesics are needed.

Level 3 refers to severe pain which has a strong impact on sleep and the analgesics are needed.

Pain relief standard: 0 refers to non-remission pain. The I degree refers to mild pain relief, pain which is reduced by 1/4. The II degree refers to the moderate pain relief, reduced by 1/2. The III degree refers to the obvious pain relief, reduced by 3/4. The IV degree refers to complete pain relief and pain disappears. The pain relief rate refers to the rate of moderate or above pain, that is, The pain relief rate = patients of The II degree and the above/the total selected patients.

Statistical data analysis

SAS 9.3 statistical package was employed for all data analysis. Measurement data was expressed by $\bar{x} \pm s$ and pairwise comparison of measurement data of normal distribution was analyzed by t test while pairwise comparison of measurement data of non-normal distribution was analyzed by rank sum test. Enumeration data was expressed by percentage and the ratios of groups were analyzed by χ^2 test. $P<0.05$ was considered to be statistical difference.

Results

Comparison of dose and analgesic effect of 3 groups

The average dose in morphine group was 44.7 mg/12 h and pain relief rate was 89.47% (51/57). The average dose in MS contin group was 42.8 mg/12 h and the pain relief rate was 91.23% (52/57). And the average dose in oxycodone group was 16.2 mg/12 h and the pain relief rate was 92.98% (53/57). However, there was no statistical difference in pain relief rate among 3 groups ($P>0.05$) as shown in Table 1.

Evaluation of adverse reactions

There was no patients with severe adverse reactions in 3 groups who withdrawn from the treatment during the observational period. The adverse reactions of 3 groups, mainly manifested with nausea, vomiting, dizziness and constipation, were relieved after given symptomatic treatment which didn't affect the whole treatment protocol. Addiction had not been found. The total incidences of adverse reactions were 59.65% (34/57), 54.39% (31/57) and 43.86% (25/57), respectively and there was no statistical difference between the incidence rate of each adverse reaction and the total incidence rate of adverse reactions ($P>0.05$), as shown in Table 2.

Cost-effectiveness analysis

Three groups received oral administration and there was no statistical difference in registration fee, diagnosis

Table 2. Comparison of the Incidence of Adverse Reactions of 3 groups

	Morphine group	MS contin group	Oxycodone group	χ^2	P
Nausea [n (%)]	15 (26.32)	14 (24.56)	11 (19.30)	0.8485	0.6543
Vomiting [n (%)]	10 (17.54)	6 (10.53)	5 (8.77)	2.2800	0.3198
Constipation [n (%)]	3 (5.26)	5 (8.77)	6 (10.53)	1.0892	0.5801
Dizziness [n (%)]	3 (5.26)	4 (7.02)	2 (3.51)	0.7037	0.7034
Insolence [n (%)]	1 (1.75)	1 (1.75)	1 (1.75)	0.0000	1.0000
Dysuria [n (%)]	2 (3.51)	1 (1.75)	0 (0)	2.0357	0.3614
Total incidence rate [n (%)]	34 (59.65)	31 (54.39)	25 (43.86)	2.9556	0.2281

Table 3. Cost-Effectiveness Analysis of 3 Kinds of Opioid Analgesics for Cancer Pain

	Cost (RMB)	Effectiveness (%)	C/E	$\Delta C/\Delta E$
Morphine group	1276.35±547.19	89.47	14.59±7.21	—
MS contin group	1359.21±526.33	91.23	15.03±7.44	48.01±5.22
Oxycodone group	1503.46±574.68	92.98	16.09±8.10	63.97±6.05

Table 4. Sensitivity Analysis of 3 Kinds of Opioid Analgesics for Cancer Pain

	Cost (RMB)	Effectiveness (%)	C/E	$\Delta C/\Delta E$
Morphine group	1148.72±505.21	89.47	12.19±6.53	—
MS contin	1223.29±499.86	91.23	13.37±6.08	43.37±5.49
Oxycodone	1353.11±513.14	92.98	14.46±6.74	58.92±5.84

and treatment fee and examination fee, so cost only referred to the total fee of analgesics in each group. C/E of 3 groups were (14.59±7.21), (15.03±7.44) and (16.09±8.10) and C/E in morphine group was minimum, that is, the unit net cost of the effect of morphine was minimum. Compared with oxycodone, the cost of MS contin group was lower than morphine group when increased effect of 1 unit. As shown in Table 3.

Sensitivity analysis

When the price of 3 kinds of analgesics was reduced by 10%, the ratios of cost-effectiveness were (12.19±6.53), (13.37±6.08) and (14.46±6.74) but there was no differences when compared with before the price adjustment ($t=1.86$, $P=0.0651$; $t=1.30$, $P=0.1948$; $t=1.17$, $P=0.2453$), as shown in Table 4.

Discussion

International Association for the Study of Pain (IASP) defines pain as a kind of the unpleasant feeling and emotional feelings, accompanied by the actual or potential tissue damage. Severe pain can influence the recovery of diseases and damage. Chronic pain can affect sleep, appetite and normal life, lead to irritability, depression and resent, even erosion of sense of survival. Cancer pain is the important factor of influencing life quality of cancer patients (Gong et al., 2013; Liang et al., 2013; Mahigir et al., 2013; Budkaew et al., 2013; Lee et al., 2014). If acute pain doesn't get relieved, it will develop chronic pain and finally becoming a disease.

Opioid analgesics is at present the strongest analgesic drugs, without ceiling effect and liver and kidney function

damage when large dose is used, so it is ideal drug for the treatment of cancer pain (Mercadante et al., 2014; Simon et al., 2014). Opioids have pharmacological action on the opioid receptor of multiple central nervous systems because it inhibit the release of substance P through binding with opioid receptor on shallow sensory neurons of spinal dorsal horn, thus achieving the effect of pain relief. Currently there are 3 kinds of opioid receptors, including μ receptor, λ receptor and κ receptor. The transmembrane structure and intracellular loop structure of those receptors, which are highly conserved, can be activated by not only endogenous opioid peptide but also by exogenous opioid agonist. Besides, opioids has descending inhibition effect on cerebral center of the pain to stop the pain transmitting into the brain (Mika et al., 2014). Morphine, the most representative drug for the treatment of cancer pain, makes voltage-gated potassium channels of caudate nucleus neurons excited mainly through acting on μ receptor, which can inhibit voltage-gated calcium channel, make cytomembrane hyperpolarization and reduce the excitability of neurons which then cuts down the release of neurotransmitter of neuron axon endings, consequently blocking the transmission of nerve impulses and playing the role of nalgesic effect (Yang et al., 2014). The first pass effect of oral morphine is obvious, with low bioavailability (Shen et al., 2014). At present, there were 3 kinds of commonly-used opioids, belonging to long-acting formulations, such as morphine hydrochloride sustained-release tablets (morphine), sustained-release morphine (MS contin) and oxycodone hydrochloride controlled-release tablets (oxycodone). Riley et al (King et al., 2011; Riley et al., 2014) employed oxycodone and morphine to treat cancer pain, both the effects are obvious, so there was no significant difference in pain relief rate between oxycodone and morphine.

Pharmacoeconomics, is an edge discipline on the basis of health and economy integrating economics and pharmacology, with intention to make comprehensive judgment of the cost of drug efficacy based on drug effectiveness and safety evaluation and further provide reference and objective basis for the selection of therapeutic regimen. It mainly includes 4 kinds of methods, namely cost minimization analysis (CMA), cost - effect analysis (CEA), cost - utility analysis (CUA) and cost - benefit analysis (CBA). CEA is a commonly-used method applicable to the comparison of same clinical regimens and drugs, simple and intuitive, easy to be accepted. In this study, pharmacoeconomics was used for economic evaluation of morphine, MS contin and oxycodone, and the result showed that they all had good analgesic effect, so there was no significant difference in pain relief rate and adverse reactions and drug economics analysis revealed that morphine was minimum in C/E and didn't affect the treatment regimen when its cost was reduced by 10%. This was consistent with the part result of Ise et al' study (Ise et al., 2009; Wiffen et al., 2014). And other studies showed that there was no abundant evidence to prove which is better (Fredheim et al., 2010; Zhou et al., 2012).

In conclusion, from the perspective of economics, morphine is the preferred choice for the treatment of

cancer pain, but the selection of treatment protocol is determined depending on the adverse reactions of drugs and patient compliance. The study preliminarily analyzed the economic evaluation of 3 kinds of analgesics and rescheduling cost of the patients was not included, thus the measurement of the cost was rough. Therefore, the further evaluation should be done from the perspectives of therapeutic evaluation, the overall economic costs and adverse reactions.

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