Comparison of the use of different analgesics in the course of anesthesia care based on pharmacoeconomics

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Abstract: Narcotic analgesics play an important role in the treatment of pain. If the drug is not standardized, it is easy to cause tolerance and addiction, so scientific management and rational application is very important. In this article, we analyzed the use of narcotic analgesics in a tertiary hospital in 2015-2017. The results showed that the top 3 drugs in DDDs (defined daily doses) were fentanyl transdermal patch (4.2 mg), fentanyl transdermal patch (8.4 mg) and morphine sulfate sustained-release tablets (30 mg). Because of its strong analgesic activity and dosage form, fentanyl has become one of the first choices for severe and moderate pain in clinical practice. Morphine sulfate sustained-release tablets (30 mg) DDDs ranked third in 2015-2017, and the B/A value was 1.75. At the same time, morphine sulfate sustained-release tablets' DDDs declined in 2017 because of the analgesic advantage of bucinnazine hydrochloride injection in emergency treatment. The dosage of pethidine hydrochloride injection is declining year by year, because its analgesic action time is very short and easy to be addicted to, and the long-term application of its metabolite, normethidine, will accumulate in the body, causing neurotoxic symptoms. The price of oxycodone hydrochloride prolonged-release tablets is relatively high, which limits its use to a certain extent. Therefore, recommend rational use of narcotic analgesics in hospitals.

Keywords: Analgesics, anesthetic care, adverse reactions, daily cost of drugs.

INTRODUCTION

Narcotic analgesics are like a double-edged sword. The rational use of narcotic drugs is of great help to clinical treatment (Volkow *et al.,* 2017). It can relieve the pain of the patient and increase its tolerance. It is often used in the anesthesia and analgesia of advanced cancer patients and trauma surgery (Wingfield *et al.,* 2001; Tsaousi *et al.,* 2016). However, if the body repeatedly contacts with the drug for a long time, it will easily paralyze the central nervous system and cause the body to rely on it. Drug abuse can cause serious harm to patients themselves and society because of repeated use of such dependent drugs for long-term non-medical purposes (Wasser *et al.,* 1997). The study shows that the abuse and addiction of narcotic analgesics are very different in different countries and regions, and may be related to social, economic, cultural and personal psychological characteristics and behavioral habits in different countries (Wu *et al.,* 2006 Chen *et al.,* 2015). If the drug is too large or mistakenly injected into the blood vessels of local narcotic drugs, the body can cause the body to produce toxic reaction, including the central nervous system poisoning reaction and the toxic reaction of the heart deficiency tube system (Yang *et al.,* 1999; Keating, 2015). The central nervous system poisoning caused by local anesthesia drugs is manifested as the first inhibition and after excitation (Zhang, 1998; Siriussawakul *et al.,* 2016). The local anesthesia drugs make the excitation and inhibition of the central nervous system out of balance, and the patients show abnormal exuberance. Convulsion is caused by peripheral diffusion of excitatory foci on the nervous system, which can be caused by excessive use of local narcotic drugs (Arora *et al.,* 2015). Narcotic analgesics are addictive, if it is not standardized, the addicts are addicted to the addiction, and the patients have serious mental and physical dependence, such as neurasthenia, paleness, sweating, abdominal pain, headache, vomiting and vertigo (Lee *et al.,* 2016). Clinical rational use does not usually make patients dependent (Kakka *et al.,* 2016). The dosage of narcotic drugs should be strictly controlled through calculation.

Narcotic analgesics are drugs that are prone to physical dependence and addiction after continuous use, so the vast majority of these drugs are classified as controlled drugs. Narcotic analgesics play an important role in the treatment of pain. If the drug is not standardized, it is easy to cause tolerance and addiction, so scientific management and rational application is very important. The application of narcotic analgesics in a three grade lever hospital in Ji'nan for the year 2015-2017 was analyzed. The purpose is to provide reference for the rational use of this kind of drugs and the standardized management of such drugs in the hospital.

MATERIALS AND METHODS

Research objects

The data was collected from the HIS system in a three

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grade lever hospital in Ji'nan, it mainly included the statistical data as the application of narcotic analgesics for hospitalized patients in the year 2015-2017, including the name, specification, dosage, sales amount and sorting information of the drug. All patients were approved by ethics committee of our hospital, ethical approval number as 13SPCHD12 and all patients signed on the informed consent.

Analysis method

Using the defined daily dose (DDD) analysis recommended by the World Health Organization (Keating, 2015), the DDD values of various drugs refer to the average daily adult dose prescribed in the new pharmacology and the pharmaceutical instructions. Defined daily dose system (DDDs) = drug usage quantity * specification / DDD value of the drug can be used to measure the frequency of drug use. The greater the DDDs value, the higher the frequency of use (Wu *et al.,* 2006 Chen *et al.,* 2015).

Daily dose cost (DDC) = the sales amount of the drug / the DDDs of the drug, reflecting the average daily cost of the drug used by the patient, the greater the DDC value, the heavier the patient's economic burden and the poorer the economy. The ranking ratio (B/A) = drug sales amount ordering (B) /DDDs ranking (A), which reflects the synchronicity of the amount of drugs and DDDs, reflects the social and economic benefits of drugs, and the rationality of drug use.The value of B / A is close to or equal to 1 (0.50 ~ 1.50), indicating that the drug has a good synchronization, high frequency of application and a large market share, and the B/A value > 1. It shows that the drug is low in price and high in frequency, but the market share is relatively small; the value of B/A <1, indicating the high cost of the patient. It is suggested that the drug has the trend of better economic performance than social benefits. Using Excel 2010 software, the amount, DDDs, DDC and B/A value of narcotic analgesics used by patients were statistically analyzed.

Anesthetic care

The nursing process from anesthesia to revival is completed under the vertical management of the anesthesiology medical treatment. The anesthesiologist can arrange the nursing staff to participate in the work according to the needs of the anaesthetized task and complete the duties and responsibilities of the anesthesiologist. Under the direct guidance of doctors, the anesthetic techniques of nursing staff can be improved rapidly.

Precautions for drugs

In the use of narcotic analgesics, we should pay attention to: (1) The combined subcutaneous injection of atropine and morphine can inhibit the multiple secretion of respiratory tract and reduce the amount of ether. (2) The use of narcotic analgesics for at least 6 hours before the use of narcotic drugs can prevent vomiting during use. (3) Many narcotic drugs should be flammable and explosive. Therefore, under the conditions of use, Mars and EDM should not be prohibited and all substances with combustion supporting properties should be avoided. (4) Patients with chronic liver dysfunction, diabetes and obstructive diseases should not use narcotic analgesics.

Attention should be paid to patients who need oral anesthetics: (1) Prohibition of anaesthetized drugs; (2) children and patients with heart disease, chronic liver and renal insufficiency and respiratory diseases need to be cautious when taking oral narcotics; (3) because of the fat contained in the oral anesthetics, the patients with fat metabolism disorders should be careful with reference to the instructions; (4) the patients in pregnancy and lactation are not suitable for use; (5) after oral narcotic drugs, no technical operation can be carried out, such as driving or using precision instruments.

STATISTICAL ANALYSIS

Statistical analysis was carried out using SPSS14.0 software, the measurement data using mean value, compared with two groups of data of mean t test, count data using $\chi 2$ test, $P<0.05$, the difference was statistically significant.

RESULTS

Sales amount and sorting statistics of narcotic analgesics

The narcotic analgesics used in the year 2017 mainly consist of 13 specifications. Morphine, pethidine and oxycodone are multi drug products according to clinical requirements. In 2017, the top 3 drug sales of narcotic analgesics in the inpatient department were fentanyl transdermal patch (8.4mg), oxycodone hydrochloride prolonged-release tablets (10 mg), fentanyl transdermal patch (4.2 mg) and 2015-2017 years of hospitalized patients with narcotic analgesics sales and sorting, as shown in table 1.

DDDs and sequencing of narcotic analgesics

In 2017, the top 3 drugs in the inpatient department in 2017 were fentanyl transdermal patch (4.2 mg), fentanyl transdermal patch (8.4 mg), and morphine sulfate sustained-release tablets (30 mg) and the DDDs values were 7384, 6248 and 2640 respectively. At the same time, we can see that the DDDs and sorting order of narcotic analgesics is basically remained unchanged. DDDs and sequencing of narcotic analgesics for hospitalized patients (table 2).

DDC and sequencing of narcotic analgesics

According to the formula, the DDC value = the drug single price * the drug DDD / drug specifications are all

Table 1: Sales sum and ordering of narcotic analgesics in inpatients

Drug name	Specifications	2015		2016		2017	
		Sales amount	Sort	Sales amount	Sort	Sales amount	Sort
Pethidine Hydrochloride Injection	0.1 g	5147	10	2150	11	2468	9
Pethidine Hydrochloride Injection	50 mg	15580	7	8412	8	4570	8
Morphine Hydrochloride Injection	10 mg	27914	6	11056	7	12591	6
Morphine Sulfate Sustained-release Tablets	30 mg	8013	9	40361	5	26471	5
Fentanyl Transdermal Patch	8.4 mg	183426	1	186130	1	157570	1
Fentanyl Transdermal Patch	4.2 mg	96701	3	164016	2	89547	3
Morphine Hydrochloride Tablet	5 mg	37896	5	20167	6	0	0
Oxycodone ER	20 mg	74657	4	85641	4	65712	4
Oxycodone ER	10 mg	152410	2	119072	3	113240	2
Bucinnazine Hydrochloride Tablets	30 mg	10580	8	4210	10	2067	10
Bucinnazine Hydrochloride Injection	0.1 g	1328	12	6248	9	6840	7
Tramadol Hydrochloride Sustained Release Tablets	100 mg	2655	11	1045	12	1452	11

Table 2: DDDs and sequencing of narcotic analgesics

Drug name	Specifications	2015		2016		2017	
		DDDs	Sort	DDDs	Sort	DDDs	Sort
Pethidine Hydrochloride Injection	0.1 g	182	9	203	9	205	9
Pethidine Hydrochloride Injection	50 mg	562	6	598	6	497	6
Morphine Hydrochloride Injection	10 mg	1118	5	1205	4	1012	5
Morphine Sulfate Sustained-release Tablets	30 mg	2640	3	2891	3	2634	3
Fentanyl transdermal Patch	8.4 mg	7571	2	7643	2	6248	2
Fentanyl transdermal Patch	4.2 mg	9564	1	9608	1	7384	1
Morphine Hydrochloride Tablet	5 mg	162	10	127	10	0	0
Oxycodone ER	20 mg	357	7	426	7	402	7
Oxycodone ER	10 mg	135	11	105	11	121	10
Bucinnazine Hydrochloride Tablets	30 mg	69	12	71	12	48	11
Bucinnazine Hydrochloride Injection	0.1 g	1570	4	1103	5	1247	4
Tramadol Hydrochloride Sustained Release Tablets	100 mg	297	8	305	8	274	8

quantitative values, so the DDC of the analgesic narcotic drugs in use is equal in all the inpatient departments. In 2017, the top 4 drugs of narcotic analgesics DDC in the hospital of our hospital were oxycodone hydrochloride prolonged-release tablets 10mg, oxycodone hydrochloride prolonged-release tablets 20 mg, fentanyl transdermal patch 8.4 mg, morphine sulfate sustained-release tablets 30 mg respectively, and 305.7 RMB (RMB is Chinese currency, 1RMB≈0.145USD), 278.3 RMB, 48.2 RMB and 35.6 RMB respectively, and the DDC of other drugs were all less than 30 RMB. The DDC and sequencing of narcotic analgesics for inpatients were shown in table 3.

Statistics of B / A value of narcotic analgesics

In 2017, the B/A value of narcotic analgesics for patients in the inpatient department was 1.5 for morphine sulfate sustained-release tablets 30 mg, Fentanyl transdermal patch 4.2 mg, and Bucinnazine Hydrochloride Injection 1.80, and the B/A value of other drugs was 0.40 - 1.50, and the analgesics of decreasing B/A value were pethidine hydrochloride injection 0.1g and piperidine hydrochloride injection. The injection was 50 mg, morphine hydrochloride injection 1, fentanyl transdermal patch 4.2 mg, bucinnazine hydrochloride tablets 30 mg. The B/A value of other drugs were higher than that of the previous year. Inpatient narcotic analgesics B/A in 2015-2017 (as show in table 4).

DISCUSSION

In recent years, with the increase of the demand for anesthesia, oral analgesics have been the primary means of treating pain, and the frequency of the use of oxycodone sustained-release tablets is the first in the treatment (Aminoshariae *et al.*, 2016). The bioavailability of oxycodone hydrochloride prolonged-release tablets was 60% to 90%, and the drug showed a biphasic absorption peak in the body, and 38% of the release part could quickly take effect in 1 hour (Fallon *et al.*, 2017). The sustained release part of 62% could maintain the blood concentration of the patient and sustained the analgesic effect of 12h (Garth *et al.*, 2016). The analgesic

Table 3: DDC and sequencing of narcotic analgesics in inpatients

Drug name	Specifications	2015		2016		2017	
		DDC	Sort	DDC	Sort	DDC	Sort
Pethidine Hydrochloride Injection	0.1 g	11.2	9	12.3	9	12.3	9
Pethidine Hydrochloride Injection	50 mg	20.8	6	22.3	6	22.3	6
Morphine Hydrochloride Injection	10 mg	17.5	7	19.1	7	19.1	7
Morphine Sulfate Sustained-release Tablets	30 mg	32.7	4	35.6	4	35.6	4
Fentanyl Transdermal Patch	8.4 mg	45.1	3	48.2	3	48.2	3
Fentanyl Transdermal Patch	4.2 mg	14.3	8	16.2	8	16.2	8
Morphine Hydrochloride Tablet	5 mg	8.4	10	9.1	10	9.1	0
Oxycodone ER	20 mg	274.3	2	278.3	2	278.3	2
Oxycodone ER	10 mg	298.2	1	305.7	1	305.7	1
Bucinnazine Hydrochloride Tablets	30 mg	6.3	11	7.5	11	7.5	10
Bucinnazine Hydrochloride Injection	0.1 g	5.1	12	6.3	12	6.3	11
Tramadol Hydrochloride Sustained Release Tablets	100 mg	27.5	5	29.6	5	29.6	5

Table 4: Statistics of B/A value of narcotic analgesics in inpatients

Drug name	Specifications	Particular year		
		2015	2016	2017
Pethidine Hydrochloride Injection	0.1 g	1.20	1.35	1.1
Pethidine Hydrochloride Injection	50 mg	1.10	1.18	1.15
Morphine Hydrochloride Injection	10 mg	1.30	1.25	1.00
Morphine Sulfate Sustained-release Tablets	30 mg	1.75	1.75	1.75
Fentanyl Transdermal Patch	8.4 mg	0.80	1.20	1.20
Fentanyl Transdermal Patch	4.2 mg	1.50	2.00	1.70
Morphine Hydrochloride Tablet	5 mg	0.90	1.00	
Oxycodone ER	20 mg	0.30	0.35	0.40
Oxycodone ER	10 mg	0.45	0.45	0.50
Bucinnazine Hydrochloride Tablets	30 mg	1.20	1.10	1.00
Bucinnazine Hydrochloride Injection	0.1 g	1.80	1.65	1.80
Tramadol Hydrochloride Sustained Release Tablets	100 mg	1.10	1.00	1.10

effect was 2 times that of morphine. The related literature suggests that the incidence of ADR in constipation and nausea and vomiting is significantly lower than that of morphine, which is a better choice for the titration of moderate to severe cancer pain, so it is the first choice in the treatment of oxycodone tablets, and the frequency of morphine and morphine sustained-release tablets has gradually decreased (Ganswindt *et al.,* 2003).

In the treatment of pain relief, the fentanyl transdermal patch is used in second places, and the transdermal patch is a noninvasive skin paste. It avoids the first effect of the liver. It is not affected by the gastrointestinal factors and reduces the individual difference of the drug (Goymann *et al.,* 2002). The analgesic effect of fentanyl transdermal patch is sustainable 72h, reduces the number of drug delivery, improves the compliance of the patient, has the characteristics of convenient use and small adverse reactions, and is especially suitable for the patients with cancer pain, severe vomiting or constipation. Because of its unique analgesic activity and unique dosage form, it has become one of the first choice for clinical treatment of severe pain (Helin, 1999; Hunt *et al.,* 2004). The analgesic effect of bucinnazine hydrochloride injection is about 1/3 of morphine, and its addiction is lower than morphine. It has become the first choice in clinical emergency analgesia (Hierbert *et al.,* 2000). It is mainly used in migraine, trigeminal neuralgia, inflammatory and traumatic pain, joint pain, dysmenorrhea and advanced cancer pain (two-ladder analgesic medication), and its DDDs was placed in the front of morphine injection. Morphine is a strong opioid analgesic, but it is tolerated for 3~5 days in a continuous use, and is dependent on more than 1 weeks (Johnson *et al.,* 1993; Ostojic *et al.,* 2015). It is used only for acute and acute pain with clear pain and short term use, cardiogenic asthma, myocardial infarction, or advanced cancer pain. The advantage of DDDs in the treatment of pain relief and the superiority of oxycodone tablets in the treatment of severe pain are all in the form of morphine.

From table 2 and table 4, throughout the year 2015-2017 fentanyl transdermal patch (8.4, 4.2mg) DDDs are located in first, second. The B/A value in 2017 is 1.20 and 1.70 respectively. The sales amount is in good sync with the DDDs and the drug use is more reasonable. The characteristics of this drug use are related to the characteristics of fentanyl itself: fentanyl has a selective

high affinity for the receptor, and 75~100 times the analgesic effect of morphine (Millspaugh *et al.,* 1996). The transdermal patch is a noninvasive skin paste. The drug is released slowly through the skin to avoid the liver's first effect. It is not affected by the gastrointestinal factors and reduces the individual difference in the drug use (Mcdonald *et al.,* 1980). The analgesic effect of Fentanyl transdermal patch sustainable 72 h, reduce the number of drug delivery, easy to use, small adverse reaction characteristics, especially suitable for food difficulties, severe vomiting or constipation of cancer patients (Negus *et al.,*2015).

WHO used morphine as an important ruler to measure the improvement of pain in various countries (Plame *et al.,* 2000). As the first choice for severe pain, long-term oral morphine is the best treatment for cancer pain. As can be seen from table 3, morphine sulfate sustained-release tablets (30 mg) DDDs ranked third in 2015-2017 and the B/A value was 1.75. Because of the analgesic advantage of bucinnazine hydrochloride injection in emergency treatment, Morphine Sulfate Sustained-release tablet's DDDs decreased in 2017. The analgesic time of morphine Sulfate Sustained-release tablets is relatively short (4~ 6h), and the daily dose of medicine is relatively more (4~6 times), while sustained release tablets can reduce the number of taking medicine, which is beneficial to maintain a long time of analgesic effect and more in line with the requirements of the patients. Therefore, in 2015, our hospital reduced the morphine tablets. morphine sulfate injection's annual DDDs ranking is 5, 4 and 5 respectively, and the B/A value is 1.302016 in 2015 and 1 in 1.252017 years. This indicates that morphine injection and sustained-release tablets have gradually achieved the goal of good synchronization between sales sum and DDDs. Due to the inconvenient use of the dosage form, morphine sulfate injection has a relatively low ranking of DDDs, which is in line with the "three ladder guidelines for pain relief", which is the first choice for oral and noninvasive way of administration (Paccez *et al.,* 2014).

It is known from table 1 and table 3 that the amount of pethidine Hydrochloride Injection is declining year by year, the DDDs (50 mg) of DDDs drops to sixth, and the DDDs of pethidine hydrochloride injection (0.1 g) has dropped to ninth. WHO uses pethidine hydrochloride injection as one of the standards to measure the level of malignant tumor treatment, and has listed it as a drug that is not recommended for the treatment of malignant tumor pain because its analgesic time is very short and is easily addicted, and in the long-term application of its metabolite, normethidine will accumulate in the body and cause the nerve toxic symptoms (Sousa *et al.,* 2016). Therefore, it is recommended for trauma, postoperative pain, labor analgesia, colic and renal colic. At the same time, the prescription management method stipulates that the dosage of pethidine is 1 times, and is only used in medical institutions. Therefore, the dosage and DDDs decrease is reasonable.

The national comprehensive cancer network (NCCN) adult cancer pain guidelines recommend oral oxycodone is one of the first choice for the treatment of cancer pain (Shi *et al.,* 2015). The bioavailability of oxycodone hydrochloride prolonged-release tablets is 60% to 90%, and the drug has a biphasic absorption peak in the body, and 38% of the release part can quickly take effect in 1 h. 62% sustained-release part can maintain the blood drug concentration of the patient and continue the 12 h analgesia, and its analgesic effect is 2 times as much as morphine (Lee *et al.,* 2016). From table 2, the 2015-2017 year oxycodone hydrochloride prolonged-release tablets (20 mg) DDDs ranked 7, and oxycodone hydrochloride prolonged-release tablets (10 mg) was ranked in the 10~11 place. From table 3, it is known that the DDC value of oxycodone hydrochloride prolonged-release tablets (10, 20 mg) has been ranked first, second in 4 years, and the B/A value of each year is less than 0.50. The sales amount and DDDs are not in good synchronism, which indicates that the price is relatively high and restricts its use to a certain extent.

Bucinnazine hydrochloride injection ranked 2015-2017 in DDDs ranking in 4-5 years, and DDDs was higher than morphine hydrochloride injection. This is because cinnarizine is a fast acting analgesic, and it is not easy to become addicted to morphine. Although it has a certain degree of tolerance, it is still the first choice for emergency analgesia (Sun *et al.,* 2015). Its B/A value is more than 1.50, which indicates that the frequency of use is high and the price is low. Bucinnazine hydrochloride tablet's DDDs has been 11-12 in the past 4 years, and its B/A value is close to 1, indicating that its DDDs is relatively low, but its sales amount is in good synchronism with DDDs. As a moderate intensity analgesic, the analgesic effect is only 1/3 of morphine. It can be used in migraine, trigeminal neuralgia, toothache, inflammatory pain, neuralgia, traumatic pain, postoperative pain and cancer pain (two ladder analgesics). It is widely used. However, because its dosage form is release tablets, the number of times used is more than that of sustained release tablets, so its DDDs is lower.

CONCLUSION

To sum up, the rational use of narcotic analgesics plays a vital role in clinical treatment, but if the abuse will cause serious harm to the patients, the medical institutions should pay attention to standardized management in the process of use and eliminate the occurrence of drug abuse. To establish and improve the relevant rules and regulations, to implement the responsibility in the human head, only in the various links of the drug use to

standardize and strengthen the management of relevant departments, can the anesthetic analgesics play the most important role in the treatment of patients, reduce or avoid their injuries, and play a positive role in clinical treatment. The use of narcotic analgesics in the hospital is basically reasonable. In recent years, our hospital has paid more and more attention to the standardized use of narcotic analgesics and adopted a variety of measures. For example, doctors in the medical department organize the relevant regulations and regulations on narcotic drugs in the medical department each year. Clinical pharmacists are involved in clinical examination, guidance and supervision.

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