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A PROSPECTIVE EVALUATION

EVALUATION OF ABUSE OF PRESCRIPTION AND ILLICIT DRUGS IN CHRONIC PAIN PATIENTS RECEIVING SHORT-ACTING (HYDROCODONE) OR LONG-ACTING (METHADONE) OPIOIDS

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Background: Multiple studies have documented the incidence of illicit drug use and abuse of opioids. Over the years, several hypotheses have been proposed. Short-acting opioids such as hydrocodone are generally considered to predispose patients to poor pain management, dependency, misuse, or abuse; whereas long-acting opioids such as methadone are thought to provide sustained pain management without dependency or abuse.

Objectives: To evaluate and identify the prevalence of illicit drug use and prescription drug abuse or misuse in patients receiving hydrocodone or methadone.

Study design: A prospective, comparative evaluation.

Methods: A total of 200 patients from an interventional pain management setting, divided into two groups of 100 consecutive patients receiving either hydrocodone (Group I) or methadone (Group II) were evaluated with urine testing for illicit drug use, and/or misuse or abuse of opioids.

Drug testing was carried out by Rapid Drug Screen®.

Results: Results of this study showed that 22% (95% CI, 13% - 30%) of Group I patients receiving hydrocodone used illicit drugs as compared with 24% (95% CI, 15% - 32%) of those in Group II who were receiving methadone. The misuse or abuse of a prescription opioid was seen in 3% (95% CI, 0% - 6%) of the patients in Group I and 12% (95% CI, 5% - 18%) in Group II. In a significant proportion of patients in both groups, the drug prescribed for them was not detected on testing.

The combined use of illicit drugs and misuse of prescription drugs was noted in 24% (95% CI, 15% - 32%) in Group I and 33% (95% CI, 23% - 42%) in Group II.

Conclusions: There were no significant differences as to illicit drug use and/or misuse of opioids in patients treated with hydrocodone or methadone. These findings suggest that the use of a long acting opioid formulation by patients with chronic pain does not reduce the risk of drug abuse or improve compliance with medical therapy.

Keywords: Controlled substance abuse, illicit drug use, abuse, misuse, drug dependence

An increasing number of studies have documented the relatively high incidence of controlled substance abuse and illicit drug use among patients undergoing treatment for chronic pain (1-10). Manchikanti et al (3, 4) showed an 18% to 24% incidence of controlled substance abuse among patients in interventional pain management practice settings. Manchikanti et al (1, 5) also identified illicit drug use in patients without controlled substance abuse in 14% to 16% of patients, and illicit drug use in patients with controlled substance abuse in 34% of patients. Katz et al (10), reporting the results of behavioral monitoring and urine toxicology in patients receiving long-term opioid therapy, reported that 43% presented with either a positive urine toxicology or one or more aberrant drug-taking behaviors. However, recent studies (11, 12) that utilized an instrument identifying controlled substance abuse were able to identify only controlled substance abuse, but were unable to identify illicit drug use. Misuse of prescription-controlled substances and the use of illicit drugs individually, or in combination with opioids leads to serious health consequences with increased healthcare costs, drug dependence, overdose, and death (13, 14).

Among the various methods described to help prevent opioid dependency, the administration of long-acting opioids around the clock is the foremost (13-16). It is presumed that short-acting opioids not only provide inadequate pain management but also cause drug abuse and dependency. By contrast, long-acting opioids are thought to provide adequate pain management without dependency, abuse, or diversion.

In chronic pain management, the goal of therapy is to provide sustained, around-the-clock analgesia that includes prevention of breakthrough pain (16). Pharmacotherapy for moderate to severe pain often begins with a non-opioid analgesic and progresses to fixed-dose opioid combinations of hydrocodone or oxycodone with acetaminophen (17). These agents are appropriate for the management of moderate pain with an episodic pattern but are not suitable for more severe, continuous pain; at higher doses their use is constrained by the analgesic ceiling effect and by potential toxicities of the non-opioid component.

For continuous analgesia, controlled-release opioid formulations offer the advantage of a convenient dosing schedule (16). Controlled-release formulations of morphine, oxycodone, and methadone are considered as long-acting opioids. In contrast to general assumptions, oxycodone given four times daily is equivalent in efficacy and safety to controlled-release

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oxycodone given every 12 hours (18). In fact, in a systematic review of seven randomized trials (16, 18-21), Chou et al (22) concluded that the trials showed no consistent trends that demonstrated a difference in effectiveness between long-acting and short-acting opioids.

However, thus far no controlled study has evaluated the abuse of prescription-controlled substances, or the use of illicit drugs, among patients receiving either short-acting or long-acting opioids. Hydrocodone is the most commonly utilized short-acting opioid in chronic pain management. Among the multiple long-acting opioids, OxyContin® is most commonly used, although with significant diversion and abuse (13). Methadone is an inexpensive alternative to other long-acting opioids (controlled-release morphine or oxycodone) with a better safety profile with respect to abuse and diversion than controlled-release oxycodone. It is more cost effective than controlled-release morphine and has significant mortality related to abuse and misuse (14).

This evaluation was undertaken to compare abuse or misuse of controlled substances and the use of illicit drugs in two groups of patients: those receiving hydrocodone and those receiving methadone.

METHODS

A total of 200 consecutive patients were evaluated, with 100 in each of two groups (Group I – hydrocodone, Group II – methadone); all patients were considered to be stable at their prescribed dosages. Hydrocodone (7.5 mg or 10 mg) with acetaminophen was administered three or four times daily. Methadone was administered two or three times daily at a total daily dose of 20 mg to 60 mg.

All patients were in treatment in a pain management setting, receiving or having received interventional techniques along with opioids. All were considered to be in stable condition with their pain reasonably controlled for at least six months, with stable or improving functional status and with no clinical evidence of abuse or misuse of opioids. Opioid therapy was not the mainstay of treatment, but was used only as supplemental therapy. With the understanding there would be no identification of individuals, all patients signed an informed consent for random drug monitoring and the publication of results. Appropriate precautions were taken to protect the privacy and identity of study participants.

Drug abuse or misuse was considered if a patient tested positive for methadone (i.e., all opioids are identified on drug screening as opioids – not as individual drugs such as morphine, codeine, hydrocodone, etc.), or for oxycodone. In Group II, the presence of any opioid other than methadone was considered a positive result. Further, a potential misuse was considered if the prescribed drug was not detected in the urine test. Positive drug screen for cocaine was considered conclusive by Rapid Drug Screen. Those patients on drugs that could potentially cause a false-positive screening for methamphetamine, amphetamines, or marijuana were also checked with a follow-up laboratory evaluation. The results confirmed by laboratory evaluation were considered positive.

Rapid Drug Screen is a one-step, lateral flow immunoassay for the simultaneous detection of up to nine abused drugs by urine analysis. Each analysis occupies a separate channel intended for use in the qualitative detection of the various drugs.

Statistical analysis

Data were recorded in a database using Microsoft® Access® 2000. Statistical Package of Social Sciences (SPSS) software, Version 9.0, was used to generate descriptive tables. Demographic data were analyzed by means of the student's t test and the chi-squared test. Fischer's exact test was used wherever the expected value was less than five. Results were considered statistically significant if the *P* value was less than 0.05. The prevalence and 95% confidence intervals (CI) were calculated.

RESULTS

A total of 200 patients receiving either hydrocodone or methadone (Groups I and II) were evaluated with a Rapid Drug Screen. Urine samples from each patient were tested for the following drugs: cocaine, opiates, methadone, amphetamines, cannabinoids, barbiturates, benzodiazepines, methamphetamine, and phencyclidine.

Patient flow

From December 2003 to February 2004, 200 consecutive patients from a total of 765 patients were evaluated. While 212 patients were judged eligible for participation in the study, 12 patients were unable to provide a urine sample.

Demographic characteristics

There were no significant differences between Groups I and II. Both groups had approximately 45% male patients (Group I - 45%, Group II - 46%). Age was (mean ± SD) 49 ± 12 years in Group I and 48 ± 11.7 in Group II. Age range was 22 - 75 in both groups.

Illicit drug use

As illustrated in Table 1, 22% (95% CI, 13% - 30%) of the patients in Group I and 24% (95% CI, 15% - 32%) of the patients in Group II were using illicit drugs. There were no significant differences noted between the groups with regard to the use of each illicit drug or combination of illicit drugs.

Misuse or abuse of opioids

As illustrated in Table 2, hydrocodone was absent at the time of testing in 35% (95% CI, 26% - 44%) of the Group I patients, whereas methadone was absent in 29% (95% CI, 20% - 39%) of the Group II patients. Further, 3% (95% CI, 0% - 6%) of the patients in Group I had evidence of methadone in their urine samples, and 12% (95% CI, 5% - 18%) of the patients in Group II had a non-prescription opioid in their urine. There were no significant differences noted between the groups, either with regard to the absence of the pre-

Table 1. *Prevalence of Illicit Drug Use*

	Group I (Hydrocodone)	**Group II (Methadone)**
Cocaine	7% (95% CI, 2% - 12%)	4% (95% CI, 0% - 8%)
Marijuana	16% (95% CI, 8% - 23%)	20% (95% CI, 12% - 28%)
Total proportion of patients using illicit drugs*	22% (95% CI, 13% - 30%)	24% (95% CI, 15% - 32%)

CI = Confidence Intervals; differences between groups not significant
*Totals may not correlate as some patients used combination of drugs

Table 2. *Misuse or Abuse of Opioids*

	Group I (Hydrocodone)	Group II (Methadone)
Absence of prescribed drug in urine	35% (95% CI, 26% - 44%)	29% (95% CI, 20% - 39%)
Presence of non-prescription opioid in urine	3% (95% CI, 0% - 6%)	12% (95% CI, 5% - 18%)

CI = Confidence Intervals; differences between groups not significant

Table 3. *Combined use of illicit drugs and misuse of prescription drugs*

	Group I (Hydrocodone)	Group II (Methadone)
Illicit drug use	22% (95% CI, 13% - 30%)	24% (95% CI, 15% - 32%)
Non-prescription opioid use	3% (95% CI, 0% - 6%)	12% (95% CI, 5% - 18%)
Combined use and misuse	1% (95% CI, 0% - 3%)	3% (95% CI, 0% - 6%)
Total* use and misuse	24% (95% CI, 15% - 32%)	33% (95% CI, 23% - 42%)

CI = Confidence Intervals; differences between groups not significant
*Totals may not correlate as some patients used combination of drugs

scribed drug in the urine or the presence of non-prescription opioid in the urine.

Combined use of illicit drugs and misuse of prescription drugs

As illustrated in Table 3, total use and misuse was noted in 24% (95% CI, 15% - 32%) of the patients in Group I and 33% (95% CI, 23% - 42%) in Group II.

Discussion

This evaluation of illicit drug use, with or without prescription-controlled substance abuse or misuse, showed no significant differences between patients receiving hydrocodone and those receiving methadone. There was confirmed use of illicit drugs in 22% of patients in Group I and 24% of patients in Group II. Further, misuse or abuse of opioids was confirmed in 3% of patients in Group I and 12% in Group II. There was a total use of illicit drugs and/or misuse of prescription drugs in 24% of the patients in Group I and 33% of the patients in Group II. Additionally, 35% of the patients in Group I and 29% of the patients in Group II presented with negative screening for the prescribed drug. The results of this study are similar to previous publications (1-10). However, this is the first study to evaluate illicit drug use and opioid abuse in patients receiving two diverse opioids.

Results from the 2002 National Survey on Drug Use and Health (23) showed that an estimated 19.5 million Americans, or 8.3% of the population aged 12 or older, were current illicit drug users. An estimated 6.2 million persons, or 2.6% of the population aged 12 or older, were current users of psychotherapeutic drugs taken non-medically, with 4.4 million people using pain relievers, 1.8 million using tranquilizers, 1.2 million using stimulants, and 0.4 million using sedatives. In addition, an estimated 11 million persons reported driving under the influence of an illicit drug during the previous year, which corresponds to 4.7% of the population aged 12 or older. Approximately 1.9 million persons aged 12 or older had used OxyContin non-medically at least once in their lifetime, an increase from 957,000 such uses in 2001. OxyContin's psychotherapeutic use for non-medical purposes was second only to marijuana. For the first time, OxyContin use for non-medical purposes was the same as for the use of cocaine; abuse and deaths have been reported with OxyContin and methadone with prescription use (13, 14).

Opioids are analgesics that affect nociception by the modulation of ascending and descending pathways. Traditionally, opioid preparations have been classified into two categories: weak or strong opioid analgesics. Weak opioids include codeine, dihydrocodeine, hydrocodone, propoxyphene, meperidine, and pentazocine. Their effectiveness at higher dosages is limited by an increased incidence of side effects; these include nausea and constipation with codeine, central nervous system excitation with propoxyphene, and dysphoric effects with pentazocine (24, 25). Drugs with a wide therapeutic range and without a ceiling effect for analgesia include morphine, hydromorphone, methadone, oxycodone, and transdermal fentanyl. In this category, higher doses produce an increasing level of analgesia. Thus, all long-acting opioids, including controlled-release morphine, controlled-release oxycodone, and methadone, are considered ideal agents in managing chronic pain.

Hydrocodone undergoes extensive hepatic conjugation and oxidative degradation to a variety of metabolites excreted mainly in the urine. The major excreted metabolites of hydrocodone are conjugates of dihydrocodeine and nordihydrocodeine (both conjugated to approximately 65%) (26). Some of the hydrocodone metabolites (hydromorphone, dihydrocodeine) are pharmacologically active on the opioid receptors and may contribute, in various degrees, to the analgesic activity of hydrocodone, or they may produce unexpected renal dysfunction side effects with impaired excretion. Hydrocodone is the most commonly used opioid analgesic due to its Schedule III controlled substance status as compared to oxycodone, which is Schedule II. Hydrocodone is classified as a mild, weak, or low potency opioid because the maximum daily dose of opiate that can be administered is limited by the maximum safe dose of the nonnarcotic component of the formulation.

Methadone (Dolophine) is a long-acting opioid with a long half-life correlating with its prolonged duration of action. Methadone may offer several advantages over morphine: extended suppression of withdrawal symptoms in opioid-dependent patients, slower development of tolerance and physical dependence, milder withdrawal symptoms after abrupt termination, and lower potential for abuse and diversion (26).

Among all illicit drugs, marijuana is the most widely abused and readily available in the United States, with an estimated 14.6 million users, or 6.2% of the population aged 12 or older. Among marijuana users in 2002, about one-third, or 4.8 million persons, had used it on 20 or more days in the previous month (23). In this study, marijuana was the most commonly abused drug – 16% in Group I and 20% in Group II – as compared with general population usage of 6.2%. These results are similar to multiple previous studies (1, 5, 9-11).

Following marijuana and psychotherapeutic drugs, cocaine is the most common drug abused. In 2002, an estimated 2 million persons (0.9%) were current cocaine users, 567,000 of whom used crack cocaine (23). Cocaine use increased from 0.5% in 2000 to 0.9% of the population in 2002. Compared with the general population, cocaine use in this study was 7% in Group I and 4% in Group II.

The study may be criticized for utilizing rapid drug screening instead of Gas Chromatography/Mass Spectroscopy (GC/MS), or enzyme immunoassay. However, rapid drug screening utilizes enzyme immunoassay and has been shown to be valid. It is a good screening tool providing rapid and inexpensive testing of multiple drugs. Indeed, side-by-side comparison of rapid drug testing with GC/MS yielded over 90% correlation for various drugs. Percent agreement with GC/MS was 91% for THC, 93% for cocaine, over 96% for methadone, over 95% for opioids, 96% for amphetamines and methamphetamines, and 99% for barbiturates. Thus, we believe that the results are reasonably accurate. However, one should exercise caution if the patient is denied future treatment based on these results. They should be accurately confirmed with laboratory testing utilizing GC/MS.

CONCLUSIONS

Similar proportions of patients who received hydrocodone and methadone were shown to use the illicit drugs, cocaine and marijuana. Moreover, nearly one-third of the patients in both groups did not have detectable levels of the prescribed opioid in their urine samples at the time of testing, which implies that they were non-compliant with medical therapy. There were no significant differences in prescription opioid abuse or illicit drug use between patients who received hydrocodone or methadone. These findings suggest that the use of a long acting opioid formulation by patients with chronic pain does not reduce the risk of drug abuse or improve compliance with medical therapy.

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