Methadone and buprenorphine maintenance therapies for patients with hepatitis C virus infected after intravenous drug use

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Abstract

Heroin addiction is a chronic relapsing disease that is difficult to cure, but stabilisation and harm reduction can importantly increase the life time expectancy and the quality of life of the patient, his immediate vicinity and society in general. Currently, no proven effective pharmacological interventions are available for cocaine addiction, and treatment has to rely on existing cognitive behaviour therapies combined with contingency management strategies. Substitution therapy, however, is effective in caring for heroin addicts. Methadone is a synthetic opioid that counteracts withdrawal symptoms of heroin. Buprenorphine is a derivative of the morphine alkaloid, thebaine, and is a partial opioid agonist at the μ opioid receptor in the nervous system. A substitution treatment program effectively reduces and often eliminates heroin injection behaviour, rendering patients more socially stabilised. Reduction in the number of viral co-infections can be observed. Methadone undergoes oxidative biotransformation in the liver, but is also stored in the liver and released into the blood in unchanged form. The usual dose can be continued in patients with stable chronic liver disease, including advanced cirrhosis. In acute liver disease or acute decompensation of chronic liver disease, close clinical observation for signs of narcotic overdose or withdrawal is necessary. A modest alteration in methadone dose may be appropriate for some patients. Buprenorphine can cause liver dysfunction after sublingual and even more after intravenous administration. It is advised to follow the liver function during buprenorphine treatment and to warn the clients for intravenous use of buprenorphine. Neither methadone nor buprenorphine do influence the effect of interferon and ribavirin during the treatment of chronic hepatitis C patients. It may be necessary to increase the dosage of methadone during interferon treatment. (Acta gastroenterol. belg., **2005**, 68, **81-85**).

Key words : chronic hepatitis C, substitution therapy, antiviral treatment, maintenance therapy, methadone, buprenorphine.

Management of chronic hepatitis C patients infected after substance use is more complicated than in other patient groups. Both, treatment regimens for substance abuse (1) and hepatitis C infection are complex and evolving. Therefore, there is a need for hepatologists to become knowledgeable regarding the management of substance use and abuse and they have to participate in caring for hepatitis C virus (HCV) infected substance users.

1. Aims of detoxification

The first treatment objective in substance dependent patients remains to 'cure' the patient of addiction, i.e. to achieve stable abstinence. However, it is usually not possible to obtain this goal in the short term. One mostly has to accept that the patient remains abusing substances and then the aim is to 'care' for the patient, i.e. to improve his physical health, mental and social well-being, and to minimise the damage by having the patient minimise and stop supplementary intravenous substance use.

Ultimately, for patients who are totally unable to stop substance use, 'palliation' of the drug user is aimed at, i.e. to lighten the pain as in a severe and long-lasting disease with a modest life expectancy.

In order to cure the patient, he first has to detoxify and resist his abstinence symptoms. Next, relapse has to be prevented by decreasing the positive effects of addictive substances and by decreasing craving.

Although extensive literature on the subject is currently available (2), no evidence helps clinicians when deciding which medication has to be given to which patient at which moment. The best moment to achieve abstinence depends on the presence of social, personal and medical circumstances.

To detoxify from opiates, the short working heroin is substituted by an equivalent dosage of long working methadone (3). This dosage is decreased very slowly. Despite a high initiating dose and a progressive decreasing dose, deprivation symptoms are possible and symptomatic treatment can be appropriate. Most problems occur when the dose of methadone reaches 40 mg a day (1). Alternatively, after an opiate free period of more than six hours, heroin can be substituted by an equivalent dose of a long working partial agonist buprenorphine as soon as deprivation symptoms become apparent (4-6), also to be decreased progressively. Although good results are reported after a decrease period of ten days to three weeks, the relapse rate is lower when the reduction period lasts for several months. If the patient is using higher doses of heroin, it can also initially be substituted with methadone followed by buprenorphine.

A relapse mostly occurs in the first two to ten days after the detoxicification period. There is currently no

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first choice of medication to prevent this relapse. Reuse of the previous dosage of heroin after stopping for a month or longer can cause overdose as a result of loss of tolerance. It is only possible to prevent relapse for motivated patients. Informal self-help groups and non-professional support can also be helpful (7).

A maintenance medication can be prescribed to prevent abstinence symptoms and craving in order to optimise the clients' physical and mental health and to prevent diseases such as hepatitis, tuberculosis and HIV-viral infections. It is possible to help patients with social problems such as finances, housing and day planning. Acute intoxication due to overdosage can be prevented (1).

In randomised clinical trials, methadone seems effective in a maintenance treatment program. Patients on higher doses of methadone (60-100 mg a day) use less opiates. There is no influence on the use of other substances such as cocaine or benzodiazepines. Trying to decrease the methadone dosage may cause relapse in illegal drug use. Buprenorphine in higher doses (16-32 mg 3 times a week) is also efficient. In case of low dosage of methadone the supplementary use of substances is diminished. The drop out ratio under methadone is expected to be lower than under buprenorphine. Comparing a methadone and a buprenorphine maintenance program, there is no difference in the use of illegal opiates and cocaine. The schedule for buprenorphine is only two to three times a week. However this is not an advantage for patients who are not stable and who don't benefit from daily contact and supervision (1). In Belgium the price of buprenorphine is much higher in comparison to methadone.

Since a partial opiate antagonist as buprenorphine has fewer side effects, it is an interesting product to start a detoxification treatment and in patients who use a relative low dosage of opiates. Methadone remains a good treatment for addicts who use opiates during a long time at a high dosage (1). Heroin may be the ultimate medication for severe addicts in whom all other drugs have failed.

2. What is a maintenance program ?

A maintenance program tries to reintegrate the drug user in the society on an ambulatory base. The aims of a maintenance program are :

- to decrease and minimise the harmful effects of illegal substance abuse and to improve the quality of life of drug abusers and their environment
- to promote the social reintegration process
- to support and increase the motivation for 'change'
- to increase access to social facilities and to adjust social facilities to substance users
- to refer the patient to other health care facilities if necessary
- to decrease mortality and morbidity among substance users

In maintenance program psychiatrists, general practitioners, psychologists, social workers, nurses and street workers are collaborating. Local meetings are organised on a monthly basis.

Within the Limburg methadone maintenance program, during the intake the patient is seen by a social worker or a psychologist or both. He performs a psychological and social review and helps to formulate individual aims of treatment. The physician performs a medical history and physical examination and screens for hepatitis B, C, HIV and tuberculosis. The urine is tested for the presence of substances. The patient can enter the methadone maintenance program only if both the social worker and the medical doctor agree.

Most substance abusers are polydrug users. Additional use of alcohol, cannabis, tranquillizers and cocaine is frequent. They are used to live only to obtain and to use drugs. The first aim of the program is to reduce the abuse to a mono substance abuse : opiods. This enables the patient to solve the problems of the past (justice, debts, family ties and other relationships…), to build a new future (relationships, education and profession) and to be liberated from dependence. This program takes a lot of time with many ups and downs. One of the most difficult moments is the moment when that the client himself wants to decrease the methadone dosage. If he feels stressed, it is difficult to resist the physical dependency. It may take a lot of time before the person is substance free. Urine screening is only performed on indication of the team or the physician to evaluate the clients evolution or for evaluation of the program in its totality.

At the present time, methadone treatment programs can accommodate only 15-20% of the estimated heroin users in the United Sates (8).

3. Pharmacological characteristics of methadone/buprenorphine

Methadone is a synthetic opiate-analogue that counteracts the deprivation symptoms of heroin without tolerance. Methadone causes no euphoria and does not remove the desire for heroin. Patient should be informed about the characteristics before the start of the treatment in order to prevent disillusion.

In comparison to heroin, methadone has multiple advantages : It is effective after oral administration (the effect of oral heroin is only minimal). It should be administered once a day only (heroin three to four times a day). Methadone is cheap while heroin is expensive. Methadone will be provided as syrup and has to be taken immediately on the site of distribution. It can not be injected intravenously. The 24 hours rhythm reinforces social reintegration (3,9).

Methadone undergoes oxidative biotransformation in the liver (10) but it is also stored in the liver and released into the blood in unchanged form (11). The usual dose can be continued in patients with stable chronic liver disease, including advanced cirrhosis. In acute liver disease

or acute decompensation of chronic liver disease, close clinical observation for signs of narcotic overdose or withdrawal is necessary. A modest alteration in methadone dose may be appropriate for some patients (11).

Methadone can thus be continued during the different stages of liver disease (chronic hepatitis, cirrhosis, decompensated cirrhosis) (12). Treatment continuation over years or decades causes no liver function alteration or liver disease (13).

It was suggested that methadone is associated with normalisation of cellular immunity which had become abnormal during injection drug use (12,14).

Buprenorphine is a derivative of the morphine alkaloid, thebaine, and is a partial opioid agonist at the μ opioid receptor in the nervous system. It is also a μ opioid receptor agonist. It is administered sublingually. It is principally metabolised by two hepatic pathways : conjugation with glucuronic acid and N-de-alkylation. The metabolites are excreted in the biliary system, with enterohepatic cycling of buprenorphine and its metabolites. Most of the drug is excreted in the faeces and the urine (1).

A lot of literature compares the effects of methadone and buprenorphine (1,15-17). Thirteen randomised clinical trials compared the effect of methadone and buprenorphine in a maintenance therapy (1). All but one were double-blinded. Buprenorphine may be an effective intervention for use in a maintenance treatment of heroin dependence, but it is not more effective than methadone at adequate dosages (15). Buprenorphine did not differ from methadone in its ability to suppress heroin use, but retained approximately 10% fewer patients (16). In Iranian heroin-dependent patients 30 mg of methadone is superior compared to 1 mg dose of buprenorphine to increase their retention in treatment (17).

It is advisable to carry out liver function tests during a buprenorphine maintenance treatment. An increase in aspartate aminotransferase (ASAT) is reported in a dose-dependent way (18). Also after intravenous injection of buprenorphine a significant increase in ASAT was seen in 4 patients, and jaundice in three of them (19). Interruption of buprenorphine injections was associated with prompt recovery, even though two of these patients continued buprenorphine by the sublingual route. A fifth patient carrying the hepatitis C and human immunodeficiency viruses, developed jaundice and asterixis with panlobular liver necrosis and microvesicular steatosis after using sublingual buprenorphine and small doses of paracetamol and aspirin. Although buprenorphine hepatitis is most uncommon even after intravenous misuse, addicts placed on buprenorphine substitution should be repeatedly warned not to use it intravenously. Higher drug concentrations could trigger hepatitis in a few intravenous users, possibly those whose mitochondrial function is already impaired by viral infections and other factors (19). Another case with serious hepatitis was reported after ingestion of 112 mg of buprenorphine, 48 hours earlier (20).

Narcotic substitution may result in asymptomatic bile duct dilatation not requiring invasive diagnostic procedures (21).

4. Influence of a maintenance program on drug use and prevalence of hepatitis viruses and HIV

It is generally accepted that **methadone maintenance treatment** (MMT) effectively reduces and often eliminates heroin injection and thus should reduce virus transmission (22,23). MMT has been used for more than 35 years and has proven to be safe even when administered for 15 years or longer (12). Indeed, in a follow-up study of patients who were originally included in a methadone treatment program, subjects who continued the methadone treatment were less likely to inject at follow-up compared to patients who left methadone treatment. In Seattle, WA, among 468 (65%) subjects who continued injecting, those who continued treatment injected less frequently, were less likely to pool money to buy drugs and inject with used needles compared to those who left treatment. The results of this study suggest that drug use risk reduction is more likely to be achieved by those who remain in maintenance treatment and by those who stop injecting. This supports the role of consistent drug treatment in an overall harm-reduction strategy (24).

This may influence the incidence of viral infections in a methadone maintenance program. However, at this moment it seems that the effect is more important for HIV and HBV than for HCV (24-28).

Injection drug users not infected with HCV, who enter a methadone program and do not use other drugs or alcohol, are very likely to remain HCV-negative. However, it is likely that the high seroprevalence of anti-HCV in injection drug users, coupled with the ability of HCV to be transmitted by a small numbers of injections, will result in ongoing seroconversions to HCV (23-26).

Higher doses of methadone lead to less ongoing heroin use during treatment and to greater treatment retention (30,31).

Also in **buprenorphine maintenance programs** a beneficial effect on drug use and viral infection status was reported. In a two-year follow-up study of 909 opioid users nearly 70% of the patients remained within the healthcare system. Patients in maintenance treatment with high-dose buprenorphine (more than 80%) had a significantly improved social status, a significant decrease in drug intake and a significant improvement in their social adaptation and severity of drug abuse. Among the other patients, 13.5% were lost to follow-up (2.6% had moved, 2.6% were incarcerated, 1.2% had successfully discontinued drug usage and 0.8% had died). The HBV, HCV and HIV seroconversion rates were low in this high-risk population (2.7%, 4.1% and 0.8% respectively) (32). Also in another study, after two years of follow-up, a reduction of drug-related harm (seroconversions for hepatitis B, hepatitis C and HIV) was observed (33).

5. Interaction between substitution therapy and treatment with interferon

Methadone does not influence the effect of interferon and ribavirin (34). Methadone patients have the same drop-out rate (24%) as seen in interferon/ribavirin trials (20-21%) (12). Pegylated interferon and methadone do not mutually influence their pharmacokinetics. Biologic response, as assessed by 2', 5'-oligoadenylate synthetase activity, was similar to that in healthy subjects. HCV RNA decline was similar to that seen in chronic hepatitis C patients not receiving methadone maintenance therapy (34).

6. Additional therapies in HCV infected substance abusers

Caring for drug users with hepatitis C can be optimised with information and education concerning hepatitis C, harm reduction (education and support for safe injection practices, needle exchange programs) and giving information concerning the antiviral treatment (35,36). This can be organised in **hepatitis networks,** optimally organised **in collaboration with multidisciplinary teams**. A multidisciplinary team, with input from primary care physicians, hepatologists, nurses, psychiatrists, social workers, drug counsellors, psychologists, and infectious disease specialists (especially in HIV/HCV co infected patients) may be the optimal approach to manage substance use and viral infection with hepatitis C virus (37-40).

Conclusion

Substitution therapy with methadone and buprenorphine is effective in caring for heroin addicts. A substitution treatment program effectively reduces and often eliminates heroin injection behaviour. Patients become more socially stabilised. Reduction in the number of viral co-infections is seen, especially of HIV and hepatitis B. Neither methadone nor buprenorphine do influence the effect of interferon and ribavirin during the treatment of chronic hepatitis C patients. It may be necessary to increase the dosage of methadone during interferon treatment. Hepatitis networks, optimally organised in collaboration with multidisciplinary teams are of benefit in the treatment of the management of HCV infected substance users.

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