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Administration of Nalbuphine to Heroin Addicts. Feasibility and Short-Term Effects

Michael Voronkov¹, Daria Ocheret², Svetlana Bondarenko², Yuriy Ivanov
Yu³, and Sergey Koren⁴

¹ Clinical Research Department "Moschimpharmpreparaty", Moscow, Russia

² Community Based Organization "Kolodets", Moscow, Russia

³ Tver Drug Treatment Clinic, Tver, Russia

⁴ AIDS Foundation East-West, Moscow, Russia

Summary

Kappa-opioid agonists attenuate some of the neurochemical and behavioural effects of opiates and are under consideration as potential treatments for opiate dependence. We have shown that mixed kappa-agonist mu-antagonist nalbuphine (0.25 mg im b.i.d.) was effective in reducing opiate consumption in 29 patients with a broad range of ages (29.4±6.4 years) and with a long history of substance abuse (9.3±3.6 years). Administration of nalbuphine for at least 14 days, up to at most 6 months, on an outpatient basis, led to a dramatic fall in the consumption of heroin and other totally illicit substances, along with a decline in criminal behaviour, as well as a higher level of retention of patients in the study, but also to improvements in patients' quality of life. Nalbuphine was safe, effective and highly compatible with the traditional therapy used to combat opiate addiction in Russia. Nalbuphine can also be used to stabilize HIV-positive patients. The study showed that both the current Russian medical infrastructure and medical professionals themselves could successfully contribute to the long-term agonist-antagonist treatment of patients with opiate addiction. We believe that our study warrants the further investigation of nalbuphine in treating opiate addiction.

Key Words: Nalbuphine, Heroin Addiction, Short-Term Treatment

1. Introduction

Although the current heroin addiction epidemic is becoming more and more daunting, together with the associated problem of HIV-infection, no adequate medical tools are available in Russia to face the worsening situation. In fact, methadone and buprenorphine maintenance treatment [1,2], which represent highly effective medical interventions against narcotic addiction and the spread of HIV infection among IDUs, are not allowed by Russian law.

As a result, only detoxification followed by naltrexone treatment is available for IDUs; this combined

therapy requires recourse to heavily sedating medication and hospitalization to ensure patients' compliance, even in the short-term. Hence, there is an increasingly urgent need to find safe alternatives for the treatment of opiate addiction and to combat the related spread of HIV infection in Russia, in the hope that effective agonist treatment will soon become legal and widely applied.

Nalbuphine, a mixed kappa-opioid agonist / mu-opioid antagonist, has been widely used as an analgesic drug in clinical populations [3]. On one hand, according to recent investigations, nalbuphine prevents morphine effects and attenuates the effects of morphine

withdrawal. [4,5,6]. On the other hand, it has been shown to have little or no abuse potential, and does not induce long-term tolerance [7], which makes it a good candidate substance for the treatment of opiate abuse. Furthermore, it is characterized by such a strong “ceiling effect” that dose increases above 30 mg do not produce any aggravation of respiratory depression or other side-effects. The safety window is wide: toxic effects only become significant at 160mg, which is roughly eight times higher than both the doses used in this study and generally recommended analgesic doses.

Aim: To determine the feasibility of nalbuphine among opiate-dependent injectors, and register the course of heroin use and related behaviours, in order to support the hypothesis of effectiveness against narcotic addiction. To our knowledge, this is the first reported study of nalbuphine administration to patients with opiate addiction.

2. Method.

2.1 Study Design

We performed an open-label, 2-week feasibility study including 29 participants recruited at two different sites. Study completers were included in a further 6-month observation period under nalbuphine treatment. Due to limited supplies of nalbuphine, only eight patients were allowed to proceed with nalbuphine maintenance, on a ‘first come, first served’ basis. After three months, all three HIV-positive patients included in the longer-term programme were excluded from follow-up, due to the potential risks of combining nalbuphine with antiretroviral drugs.

2.2 Sample

29 active injection heroin-addicted patients over a broad range of ages (29.4 ± 6.4 years, 22-46 years of age), 16 males and 13 females, with long histories of narcotic abuse (9.3 ± 3.6 years, from 5 to 16 years), and three or more unsuccessful treatment attempts (detox, outpatient detox, Christian rehab centres, etc.), were recruited from a community involved in case management project (primarily dealing with requests for HIV treatment, job placement, legal help, and other social services besides drug treatment). The average individual reported that his/her heroin dose before the study was 0.67 ± 0.35 g/day. The combined reported heroin consumption for the entire sample ($n=29$) before the study was 19.50 ± 2.24 g/day, while the frequency of injection was 1.41 ± 0.61 a day.

Five IDUs with HIV infection were included in the study. Changes in viral loading, immune status, and compliance with ARVT were also monitored for these patients.

2.3 Treatment Regimen

Subjects were required to abstain from opiates and alcohol for two days prior to nalbuphine administration, in order to avoid nalbuphine-induced acute withdrawal, and possible withdrawal was managed by standard symptomatic treatment. On this basis, nalbuphine treatment began on the third day after the previous heroin injection, along a 0.25 mg/Kg im b.i.d. schedule.

All these patients also received case-management and risk-reduction counselling. The counselling was delivered individually by staff who had undergone specific training for addictive diseases and HIV prevention; it was focused on achieving and maintaining

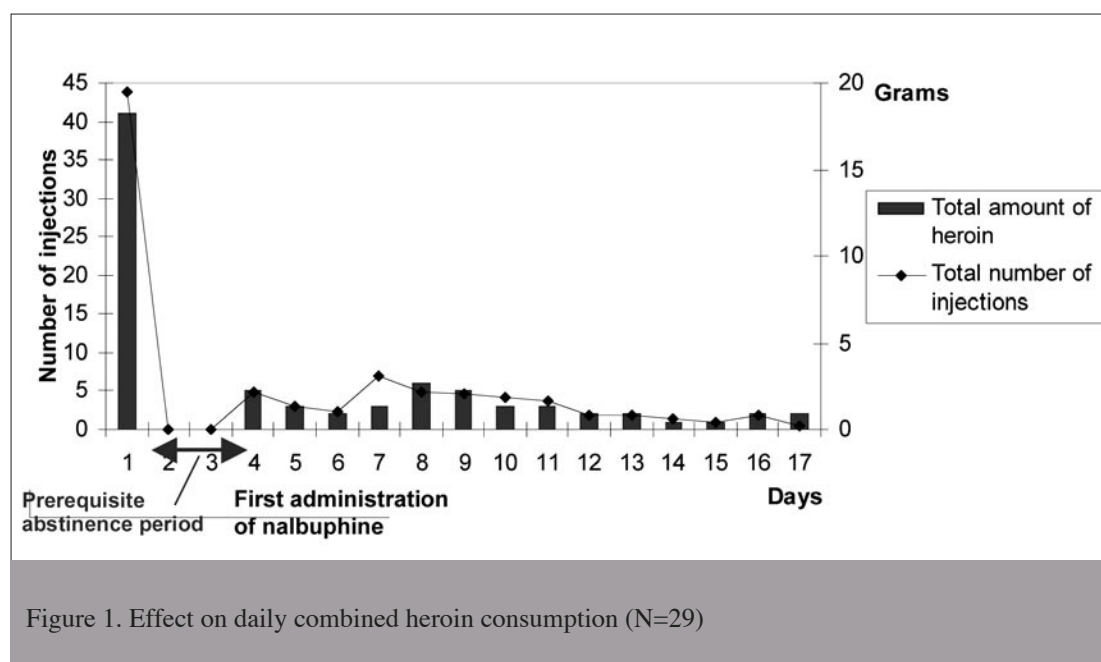


Figure 1. Effect on daily combined heroin consumption (N=29)

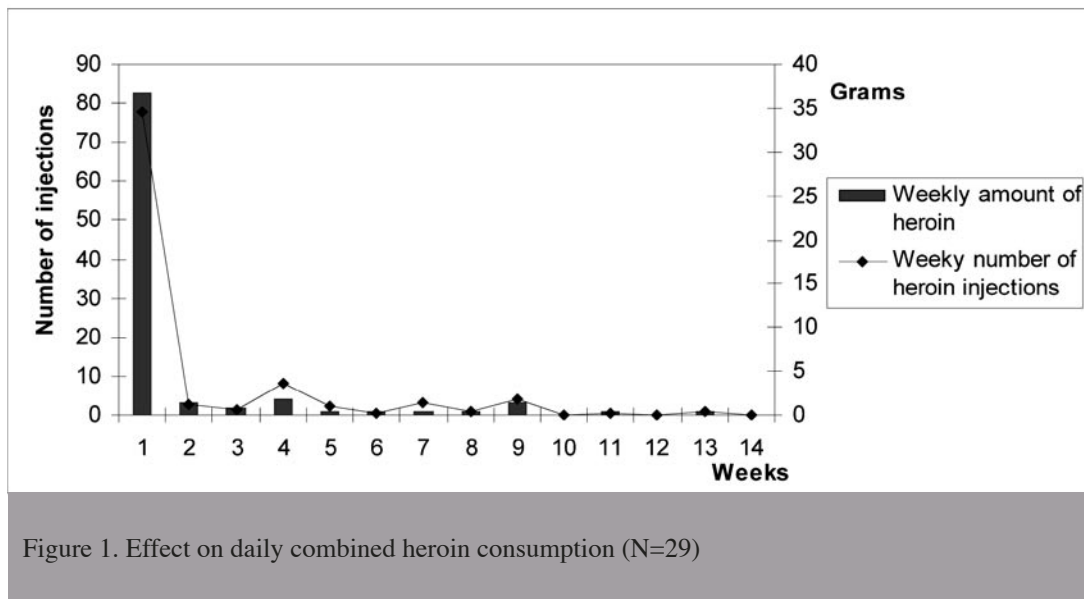


Figure 1. Effect on daily combined heroin consumption (N=29)

the goals of drug use reduction and avoidance of HIV infection.

2.4 Measures

Patients were asked to estimate their daily dose of illicit drugs before and during the study. Assessments took place at baseline and twice a week during the observation period: self-reporting on daily use, number of injections, heroin dosages and polyabuse were all recorded. Claims about not using heroin were verified by urinalyses.

3. Results

The effect of 2-week administration of nalbuphine on heroin consumption ($n=29$) is shown on Figure 1. The average level of consumption was reduced to under one thirteenth of the previous level, to 0.05 ± 0.02 g/day, while overall consumption by the entire sample fell to 1.35 ± 0.69 g/day, with nine patients abstaining completely. The number of heroin injections during the observation period fell to just one fifteenth of the previous figures, to 0.09 ± 0.05 injections a day. As was to be expected, a majority of patients (20/29) did use heroin during the study on at least one occasion, while 7 patients used it more than once. Heroin use peaked on day 4 (the second day on nalbuphine) with 17% of use episodes, and on day 7 (the fourth day on nalbuphine), with 21% of use episodes.

All the patients successfully completed the two-week study and expressed interest in receiving further treatment. Two chose to switch to naltrexone maintenance, while 8 patients were allowed to proceed with nalbuphine. Of these, five remained in treatment for six months, and the other three for three months.

Figure 2 shows data for eight patients receiving

nalbuphine for at least 3 months. An average individual heroin dose for these patients fell from 0.62 ± 0.17 g/day to 0.02 ± 0.02 g/day, and the overall heroin consumption for the entire sample fell from 4.94 ± 1.17 g/day to 0.13 ± 0.10 g/day. The individual number of heroin injections fell from an average of 1.48 ± 0.53 to 0.19 ± 0.17 injections a day. Six out of eight patients actually became abstinent during the last five weeks, and two patients had a stably sporadic pattern of consumption (1-2 times a month) with no dose or frequency peaks.

Patients with higher baseline levels of heroin use (> 0.8 g/day) were not more likely to consume heroin during the study than those with lower levels (< 0.8 g/day). Overall, we found a statistically significant (Fisher coefficient (F) = 7.02, $p < 0.001$) fall in heroin consumption after two weeks of nalbuphine therapy.

None of the patients reported concurrent consumption of other illicit substances or any increased in alcohol consumption. Even if, significantly, the reported fall in opiate abuse was confirmed by urine analysis, the actual consumption of alcohol or other stimulants was not biochemically monitored. No patient experienced an overdose during the study. A mild abstinent syndrome was observed in cases of patient non-compliance. In approximately one quarter of patients, very mild sedation was noted initially, while other side-effects typical of higher doses of nalbuphine (e.g. dysphoria, vertigo, dry mouth) were not observed.

Among HIV-positive patients, 4/5 displayed better immune status (CD4 counts) and one was unchanged. Patients gained weight (nearly 1 kg on average) and had no increases in viral loading. Three patients received ARVT, with compliance levels of 97% and 100% (Compliance with a treatment regimen, in particular with an ARV regimen, is determined using an 'average adherence' value calculated using the formula: $(A-B) / A \cdot 100\%$, where A is the number of tablets or gel

capsules scheduled by the protocol for administration to a patient over four weeks; and B is the number of tablets or gel capsules which were not actually taken by a patient over the same period of time). One of the patients started ARVT during the study. All these patients expressed interest in harm-reduction training and ARVT, and they regularly visited their doctor's office. The small size of the sample meant that the statistical values of drug consumption for this subgroup were not meaningful, but the actual drug use outcomes appeared to present a coherent picture.

4. Discussion

We found that the recommended analgesic dose of nalbuphine [9] for opiate-naïve patients (0.25mg/Kg i.m. b.i.d.) was effective in reducing heroin consumption among IDUs.

The course of heroin use during treatment was characterized by two peaks. While the first wave of use coincided with discharge from hospitals, the second wave might be explained as the attempt to overcome opiate antagonism. Nevertheless, it was remarkable that no challenge exceeded one's habitual dose, involved multiple injections or was accompanied by consumption of other types of drugs, or alcohol, as typically happens in naltrexone-treated populations [10, 11]. Furthermore, many patients reported that they felt calm while they watched their mates dispensing, preparing the liquid or injecting. As one patient with a eight-year history of heroin abuse put it: "I came to my friend's place [this friend supplied him with heroin] and he was weighing out and packaging heroin right in front of me. It was right in front of me but I felt no excitement. My heart didn't skip a bit. Nothing. It shocked me so much that I just left". In other words, all this evidence points to a successful containment of cravings for opiates.

Similarly, the administration of nalbuphine lead to what could be called a pattern of controlled heroin consumption, in so far as it coincided with some positive event (such as a payday at work, birthday parties, or New Year's Eve). Patients referred to those events as moments "when it was time to relax" or said "there must be something to enjoy in life" or even "that was just for fun because it was under control".

Furthermore, two of the patients with a higher than average heroin dose have had previous experience with MMT outside of Russia. This too may have had an impact on the collected data.

As a mu-opiate receptor antagonist, nalbuphine does not produce euphoric effects; in this study it did not lead to requests from patients to increase their dose or the frequency of administration.

It is worth noting that the medical personnel of both clinics, who conducted the study despite having adopted

initially negative attitudes towards substitution therapy, very quickly 'bought into' the idea of long-term maintenance with agonist-antagonists, even though it put them at odds with some Russian medical officials.

5. Conclusions

Nalbuphine can be used safely in the management of opiate addiction, and can be safely administered to IDUs. Although controlled studies on larger samples are needed now to allow comparison with naltrexone, some self-reported aspects, and its proven effectiveness in successfully treating different levels of heroin consumption, suggest it may turned out to be a viable alternative to full antagonist maintenance treatment.

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Contributors

The authors contributed equally to this work.

Conflict of Interest

The Authors have no conflicts of interest.

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