

## Changes in Oxygen Saturation Rate in Opioid-Dependent Patients on Heroin-Assisted Treatment

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**Abstract:** High doses of pharmaceutical graded heroin in combination with methadone are prescribed nowadays in a Dutch trial with methadone treatment refractory heroin addicts. Heroin is prescribed either through intravenous injection or inhalation. One of the major risks of using opioids is ventilatory depression. In this study, the effect of heroin on oxygen saturation rate (SpO<sub>2</sub>) in a group of opioid tolerant patients was investigated. SpO<sub>2</sub> was measured in 22 patients on heroin treatment (12 injectors, 10 inhalers) during 4 consecutive days. Heroin dosages were varied double-blindly from 67% to 150% of the regular dose. Methadone dosages remained unchanged and took place 120 minutes after heroin intake. SpO<sub>2</sub> assessments took place till 250 minutes after heroin administration. From 20 subjects, heroin plasma concentrations could be obtained. At the first measurement 13 minutes after heroin administration, the average SpO<sub>2</sub> dropped from a pre-dose level of 96.9% to 93.8% (difference 3.1%; 95% CI: 2.4-3.8%; p<0.0001). This decline in SpO<sub>2</sub> was not related to heroin dose or plasma concentrations, and there were no significant differences between intravenous heroin users and heroin inhalers. Co-administration of benzodiazepines in 10 patients, however, caused a significant additive reducing effect on the SpO<sub>2</sub> levels (p<0.0001). Three patients who used both promethazine and diazepam beside heroin showed the lowest SpO<sub>2</sub> (p<0.01). In conclusion, heroin administration causes statistically significant but relative small reductions in SpO<sub>2</sub> with no clinical signs of acute hypoxia in heroin addicted patients on a stable dose of methadone and medically prescribed heroin. The observed reductions in SpO<sub>2</sub> were not heroin dose related, suggesting that dose elevations up to 50% are safe from a respiratory point of view in the tested dose range (150-450 mg heroin). Any co-prescription of benzodiazepines or promethazine should be monitored carefully due to the additive effect of these medicines on the ventilatory depression.

In several European countries clinical trials are performed to test the feasibility, effectiveness and safety of heroin (diacetylmorphine) on medical prescription, in heroin addicts. The aim of this treatment is harm reduction, i.e. reduction of illegal drug use, and prevention and reduction of the medical and social consequences of illicit drug use. In the Netherlands, a heroin-assisted treatment trial is currently performed that takes into account

the specific characteristics of the heroin-addicted population in The Netherlands. The vast majority of the Dutch heroin addicts (80-90%) predominantly uses heroin by inhalation (“chasing the dragon”), and only a small proportion predominantly uses heroin via intravenous injection (Van den Brink *et al.*, 2003). Therefore, heroin base for inhalation is prescribed in one study arm and heroin hydrochloride for injection in the other study arm. Methadone is co-administered with heroin in this study, to prevent withdrawal and craving symptoms when a participant would not attend one or more heroin administration occasions. Heroin and methadone administration takes place in special

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outpatients' clinic under constant supervision of a nurse team. The maximal heroin dosage is 400 mg for a single dose and 1000 mg for the total daily dose. Based on clinical experience, the prescribed heroin doses are titrated carefully with a maximal dose increase of 50% per day.

One of the major concerns in the prescription of opioids like heroin or methadone is the occurrence of ventilatory depression. The respiratory stimulant action of a high carbon dioxide level is inhibited by opiates (Weil *et al.*, 1975). Tolerance for the effects of opioids on respiration is build up during long term use. However, when in a Swiss heroin prescription program pulse oximetry was performed after intravenous administration of heroin in tolerant patients, the oxygen saturation rate dropped considerably in over 50% of the chronic opiate users. This fall in oxygen saturation rate also occurred in methadone injectors, although to a much lesser extent (Dürsteler *et al.*, 2000).

No scientific data are however available on the effects of high doses of heroin on the oxygen saturation rate when heroin is taken by inhalation. In addition, very little is known about the effects of the combined treatment of heroin and methadone on oxygen saturation rate, and about the influence of common co-medication in these patients. It is also not known to what extent the in clinical practice applied dose increase of 50% would influence the oxygen saturation rate in patients treated with heroin.

The present study aims to investigate these effects of different and changing dosages of medically prescribed heroin in combination with methadone on oxygen saturation rate (SpO<sub>2</sub>) by means of pulse oximetry, among injecting and inhaling heroin users. The relationship between heroin induced changes in SpO<sub>2</sub> and plasma exposure of heroin were investigated as well. In addition, the study explores the effects of additionally non-opioid co-medication on the SpO<sub>2</sub>.

### Materials and Methods

*Subjects* Twenty-two relatively healthy male patients, 12 intravenous heroin injectors and 10 heroin inhalers, who participated in the Dutch heroin on medical prescription trial were enrolled. Both heroin injectors and inhalers had been treated with heroin in combination with methadone for a period of at least 12 months. It was expected, that heroin injectors would have higher heroin plasma concentrations than heroin inhalers. In prior studies, the bioavailability of heroin inhalation method applied in this study was estimated to be approximately 50% of intravenous heroin application (Hendriks *et al.*, 2001). Therefore, no crossing-over between heroin inhalation and injection was planned for safety reasons.

At the start of this study, all subjects were on a twice-daily heroin-dosage scheme and on a once daily methadone dosage scheme. The maximal single dose for

inclusion in this study was 300 mg for heroin and 100 mg for methadone. Heroin and methadone doses were kept constant for a period of at least 4 weeks before entering the study. Patients with anaemia were excluded. Patients who used ritonavir, cimetidine or moclobemide were excluded from this study because of the possible interactive effects of these medications. Other co-medication that was prescribed by physicians at least one month before the start of this study could be continued. The use of other substances, beside heroin and methadone on medical prescription, was not allowed during this study, except for tobacco. This study took place in a closed ward of a CRO under constant supervision of a nurse team. Luggage was checked for alcohol and illicit drugs like cannabis and cocaine at arrival in the CRO. Alcohol breath tests were taken before each heroin administration session. Patients with positive alcohol test were not allowed to take heroin until the test turned negative. Blood samples of the patients were controlled for cocaine use afterwards the study. Patients with positive cocaine tests were excluded from statistical analyses.

The study was performed according to Good Clinical Practice regulations, after approval of relevant Medical Ethics Committees. Informed consent had to be signed by all participants before start of the study.

*Materials* Pharmaceutical prepared heroin base for inhalation and heroin hydrochloride for injection were produced under Good Manufacturing Practice regulations (for production of heroin base see Klous *et al.*, 2004). Heroin inhalation occurred by a method called "chasing the dragon" (Strang, Griffiths & Gossop, 1997). By this method, heroin base is heated by the patients on tin foil with a lighter underneath. The thus heated heroin base will sublime and the resulting fumes are inhaled by a straw in the mouth. "Chasing the dragon" is also applied in the regular Dutch heroin on medical prescription trial. The participating patients needed on average 15 minutes (range 10-30) to finish the offered heroin base dosages.

In this trial, heroin was administered twice daily under strict supervision of a trained nurses' team. The heroin evening dose was taken eight hours after the morning dosage. Methadone was administered orally once daily, two hours after the heroin morning administration. At day one, the heroin morning dose remained unchanged for each participant. At the following days, heroin morning doses varied double-blindly from 67%-100%-150% of the regular heroin morning dose in random order. The heroin evening dose and the methadone dose remained unchanged throughout this study. Other co-medication beside heroin and methadone originated from community pharmacies.

The peripheral oxygen saturation rate was recorded by the Datex-Ohmeda S/5 Light Monitor with a FingerSat™ SAS-F sensor, which was placed on the index finger tip (Datex-Ohmeda Inc. Tewsbury, MA, USA). The light diode emitted light with wavelengths of 660 and 910 nm. Assessments of SpO<sub>2</sub> were taken one hour before heroin morning administration and 13, 28, 70, 113, 145 and 250 minutes after heroin administration.

Blood samples were taken 10 minutes before start of heroin administration and at 2, 5, 10, 15, 30, 45, 60, 115, 180, 240 and 480 minutes after heroin administration. For

inhalers, an additional sample was collected after 40% of the heroin dose was used. Blood samples were put in ice water immediately after sampling. Within 15 minutes after sampling, the blood samples were centrifuged in order to obtain plasma. Plasma samples were kept at  $-30^{\circ}\text{C}$  till analysis. Plasma samples were analysed for heroin by LC-MS-MS (Rook et al., 2005). Maximal plasma concentrations ( $C_{\text{max}}$ ) were derived from plasma-concentration-time curves. Area under the curves ( $\text{AUC}_{0-\text{inf}}$ ) were calculated by the Applicant by the log-linear trapezoidal method and non-compartmental analysis, using WinNonlin version 3.0 (Pharsight, Mountain View, CA, USA, 1999).

*Statistics* Paired students T tests were performed to compare SpO<sub>2</sub> values obtained pre- and post-heroin or methadone administration. Univariate analyses were performed to study the relationship between SpO<sub>2</sub> and heroin dose and plasma levels, the method of heroin administration (intravenous versus inhalation), methadone dose level and the use of other co-medication beside heroin and methadone. Only significant covariates were included into the multivariate ANOVA model, with backwards elimination from the full model. Analysis of variance by the GLM repeated measures ANOVA was performed for SpO<sub>2</sub>, with scheduled time points of measurements and study day as fixed within factors. When Mauchly's test of sphericity was violated, adjusted degrees of freedom were used according to the Huynh-Feldt correction. When more than two subgroups existed, Bonferroni post-hoc multiple comparisons were made to explore the differences between these subgroups.

All statistics were performed with SPSS for Windows, version 13.0 (Statistical Package Service and Solutions Inc., Richmond, CA, USA; 2004). P-values below 0.05 were considered significant throughout statistical analyses.

## Results

### *Patients and substance use*

Fourteen heroin injectors and ten heroin inhalers were enrolled. Two heroin injectors were excluded due to protocol violations (cocaine abuse and misbehaviour). The remaining 22 participants completed the whole study. The mean age ( $\pm$  SD) was  $39.9 \pm 3.7$  and  $42.8 \pm 4.3$  years in the heroin injectors and inhalers group, respectively.

The prescribed heroin dose was similar in heroin inhalers and intravenous heroin users. The mean methadone dose was however slightly higher in the heroin injectors than in the inhalers (see Table 1). Beside heroin and methadone, benzodiazepines and promethazine were prescribed in some subjects. Ten subjects used benzodiazepines (Table 1), in 9 cases diazepam and in one case oxazepam was prescribed. The mean diazepam dosages were significantly higher in the intravenous using patients (30 mg, SD 8.2) than in the heroin inhalers (15 mg SD5.8,  $p < 0.01$ ). Three subjects also used

the antihistamine promethazine (25 mg bid) in addition to diazepam, heroin and methadone.

Plasma samples could only be obtained from 20 subjects, due to serious venous sclerosis. The mean (SD) of  $C_{\text{max}}$  and  $\text{AUC}_{0-\text{inf}}$  was 3.4 (1.2)  $\mu\text{g/ml}$  and 3.6 (1.1)  $\mu\text{g/ml}\cdot\text{h}$  after heroin injection and 0.6  $\mu\text{g/ml}$  and 1.8 (0.8)  $\mu\text{g/ml}\cdot\text{h}$  after heroin inhalation, respectively.

### *Oxygen saturation rate*

The mean SpO<sub>2</sub> dropped from an average of 96.9% to 93.8% at the first measurement, 13 minutes after heroin intake (95% CI 2.4-3.8%;  $p < 0.0001$ , see Figure 1). SpO<sub>2</sub> dropped below 90% after heroin administration in 12.5% of the heroin administration occasions in this study. The mean SpO<sub>2</sub> recovered gradually after the first post-heroin intake measurement, although complete recovery to the pre-heroin administration level was still not achieved after 250 minutes (Figure 1,  $p < 0.001$  compared to baseline). The oral methadone administration seemed to interfere with the recovery of the oxygen saturation rate to pre-dose levels (Figure 1a). However, the decline in SpO<sub>2</sub> after methadone intake was marginal and did not reach significance.

In univariate analyses, SpO<sub>2</sub> was not significantly related to heroin dose or method of heroin administration (in this trial by injection or by inhalation). Neither was SpO<sub>2</sub> related to  $C_{\text{max}}$  or AUC of heroin. SpO<sub>2</sub> was however significantly related with benzodiazepine use, promethazine use, and methadone dose at several time points before and after heroin administration. The fall in SpO<sub>2</sub> was significantly associated with the diazepam dose in linear regression analysis (regression constant  $\beta$  0.9% (SE = 0.06) per 10 mg diazepam,  $p < 0.0001$ ). The mean SpO<sub>2</sub> was lowest in the group of 3 patients using promethazine and diazepam concomitantly (figure 1b).

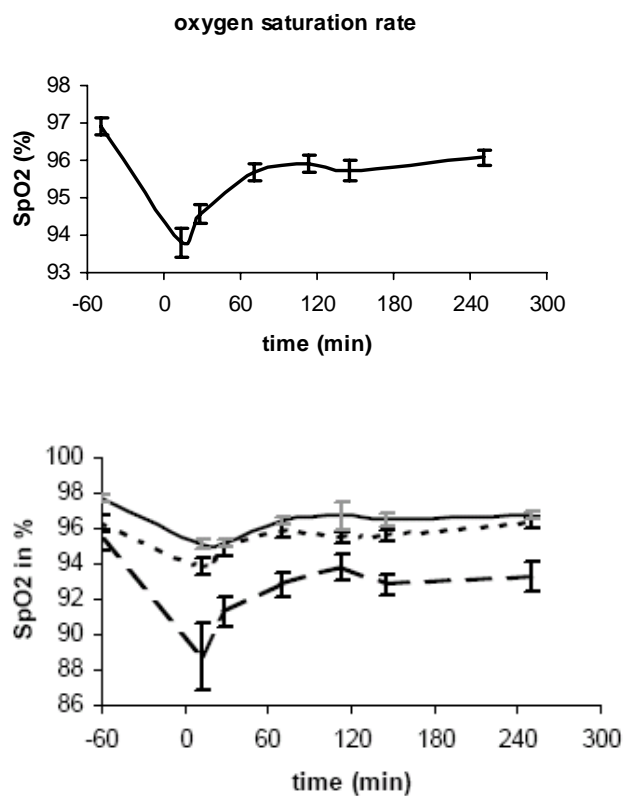
In repeated measures ANOVA analysis without co-variables, oxygen saturation rates differed significantly over time ( $F=19.21$ ,  $p < 0.0001$  with Huynh-Feldt correction). Co-variables that were significantly related to SpO<sub>2</sub> in univariate analyses, *in casu* methadone dose and the use of benzodiazepines, were included in the ANOVA model. In backwards analyses, the methadone dose factor turned out to be non-significant. The significant interactive effect of the use benzodiazepines, with or without promethazine, was however confirmed in ANOVA analysis ( $F=8.538$ ,  $p=0.002$ ). Post-hoc tests confirmed that SpO<sub>2</sub> of the patients who used diazepam in combination with promethazine ( $n=3$ ) differed significantly from those who used benzodiazepines as a single co-medication or no co-medication at all ( $n=19$ ).

**Table 1. Medication on medical prescription in intravenous heroin users and heroin inhalers**

	intravenous group (n=12)	inhalation group (n=10)	p-value
heroin dose (mg) , mean (SD)	289 (24)	285 (33.7)	ns
methadone dose (mg) , mean (SD)	71 (15)	57 (14)	<0.05
benzodiazepine use , n(%)	6 (50%)	4 (40%)	ns
promethazine use, n(%)	2 (17%)	1 (10%)	ns

ns= non-significant

**Figure 1a and 1b. Oxygen saturation rate (mean, 95% CI) in both heroin inhalers and injectors.** At t=0 heroin was administered, at t=120 m methadone was administered. In figure 1b, the data are stratified over the patients who used no co-medication (n=12, continuous line), benzodiazepine (n=7, interrupted line) or benzodiazepines + promethazine (n=3) beside heroin and methadone on medical prescription



## Discussion

There is a growing international interest in prescribing pharmaceutically prepared heroin to heroin addicts, who are otherwise treatment resistant. Methadone, heroin and its metabolite morphine, all  $\mu$ -opiate receptor agonists, are known to suppress respiration in several ways. Interaction of  $\mu$ -receptor agonists with aortic and carotid chemoreceptors would blunt the compensatory reaction of the body to increase of carbon dioxide levels (Weil *et al.*, 1975). In addition, central breathing regulation centres in the brain stem could be inhibited by opiates, which may result in ventilatory depression (Lao, 1997; White & Irving, 1999). In the Dutch heroin-assisted trial, heroin is prescribed in combination with methadone. Uniquely in this trial, heroin is also administered by inhalation. Not much is known what would be the effect of combined methadone-heroin use on ventilatory functioning. Neither was known, what would be the effect of heroin inhalation on oxygen saturation. In this study, the influence of heroin use on oxygen saturation rate (SpO<sub>2</sub>) was investigated in 10 heroin inhalers and 12 heroin injectors, who were on long-term treatment with a combination of heroin and methadone. Methadone was administered orally with maximal dose of 100 mg. The regular heroin dosages were varied at random by a reduction of 33% and an increment of 50%, whereas the methadone dosages remained stable. These changes in heroin dosing resemble the titration schedule that is applied in the Dutch heroin-assisted trial. The maximal up-titrated single heroin dose was 450 mg. It was investigated whether SpO<sub>2</sub> was related to heroin and methadone doses, heroin plasma levels and the use of non-opioid co-medication (benzodiazepines and promethazine) beside heroin and methadone.

Despite the fact that the participating patients in this study were on steady state treatment with a combination of heroin and methadone, the use of heroin still caused a small but statistical significant decline in SpO<sub>2</sub> levels in this tolerant population. It should however be noted, that the first SpO<sub>2</sub> measurement was only taken 13 m after the last heroin dose, due to the intensive blood sampling schematic of this study. Heroin is a fast acting drug, and the impact of heroin use would probably have been larger immediately after heroin administration. In a Swiss heroin trial with comparable doses of intravenous heroin, SpO<sub>2</sub> levels were measured with continuous pulse oximetry instead. In that study, SpO<sub>2</sub> dropped below 90% in 56% of all subjects instead of 12.5% of all measurements in this study (Dürsteler *et al.*, 2000).

In our study, heroin doses were varied within each subject with a dose reduction of 33% and a dose increment of 50%. Remarkably, the magnitude of

the decline in SpO<sub>2</sub> was not related to various heroin dose levels. The decline in SpO<sub>2</sub> was neither dose related in the study by Dürsteler, though heroin dosages were not varied in that study (Dürsteler *et al.*, 2000). For the first time, SpO<sub>2</sub> levels were measured in heroin inhalers. Remarkably, the change of SpO<sub>2</sub> was similar in heroin injectors and inhalers in this study, despite the fact that the C<sub>max</sub> plasma levels were considerably lower in heroin inhalers than injectors. However, it should be mentioned that the duration of heroin administration and exposure was considerably longer in heroin inhalation than in heroin injection. In our study, the administration of oral methadone two hours after the last heroin administration seemed to interfere with the recovery of the SpO<sub>2</sub> after heroin intake, although the decline of SpO<sub>2</sub> after methadone intake did not reach statistical significance.

In clinical settings, supportive oxygen administration is commonly recommended when the SpO<sub>2</sub> drops below 90%. In a considerable number of heroin dosing occasions in our study SpO<sub>2</sub> dropped below this threshold value. However, the participating patients did not show any serious clinical sign of hypoxia and SpO<sub>2</sub> recovered spontaneously without oxygen support.

It is however not known whether repeated periods of hypoxia following heroin use may be harmful on the long term. In autopsies, lesions of ischemic brain damage, resembling neuropathology that is typically seen in systemic hypoxia, were found in a large percentage of intravenous using heroin addicts (Oehmichen *et al.*, 1996; Andersen & Skullerud, 1999). However, the causality of these lesions is difficult to interpret, because polydrug use is very common in heroin addicts. Moreover, injection of impurities of "street" heroin may also have contributed to cerebrovascular damage.

In this study, co-administration of benzodiazepines and promethazine caused a significant additive reducing effect on the oxygen saturation rate. To our knowledge, this is the first study that shows that a combination of benzodiazepines and promethazine causes lower levels of SpO<sub>2</sub> in opioid tolerant patients who were treated with high doses of pharmaceutical grade heroin.

Sedatives like benzodiazepines are known to suppress respiration, but in a much milder way than most opioids (Mak *et al.*, 1993). Inhibition of the brain stem respiratory centres by benzodiazepines is not  $\mu$ -opiate receptor mediated, but occurs by GABA<sub>A</sub> receptor binding (Paakkiri *et al.*, 1993). The first generation antihistamine promethazine is also known for its sedative effect. It is reported that promethazine alone can cause respiratory failure (Simons, 1994). Promethazine is often co-

administered with morphine to prevent opioid-related itching. However, the combination of promethazine with diazepam, without opioids, did not result in clinically relevant hypoxemia in other studies (Bergeron *et al.*, 1995). In contrast to a study by Tramer & Walder, where a combination of small doses of opioids with promethazine did not lead to extra hypoxia, the concomitant use of promethazine seemed to induce hypoxia in this study with extreme doses of heroin (Tramer & Walder 1999). Since all promethazine treated participants also received diazepam in this study, no clear conclusions can be drawn however with regard to the effects of promethazine alone on heroin-induced hypoxia.

Although this trial revealed that heroin administration could give rise to mild hypoxemia in chronic opiate users, clinical experience showed that, even at high dosages of heroin, hypoxemic incidents very rarely happen in the daily practice of heroin substitution programs. In addition, the current study provides an empirical support for the safety of heroin dose increments up to 50% till within the dose ranges tested. However, some considerations have to be made when benzodiazepines and/or promethazine are concomitantly prescribed with heroin and methadone, and these medications should be carefully introduced.

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