SLOW-RELEASE ORAL MORPHINE (SROM) AS FURTHER MEDICATION IN OPIOID SUBSTITUTION TREATMENT (OST): RESULTS FROM A REGISTRATION STUDY

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Abstract

Since 50 years oral methadone is the gold standard in OST. However, some of the heroin dependent patients refrain from this kind of treatment due to different reasons (e.g. no injections, limited well-being, excessive sweating). Additionally the prolongation of the QTc poses a clinical problem in double diagnosed patients as many medications that are necessary in the treatment of these patients, add to the QTc prolongation. Unconfirmed reports from different countries suggested that SROM could be a useful addition to the in Switzerland already registered medications methadone, diamorphine, and buprenorphine. In order to test this assumption a prospective, multi-dose, open label, non-inferiority, cross-over study in a bi-national, multicenter setting over 11 weeks, in which methadone and SROM were compared (ITT population n = 276). Beyond this time-point, the participants were observed another 25 weeks. Main results were: The proportion of heroin-positive urine samples and retention rates under SROM was equal to the ones under methadone. The mean QTc-interval under methadone was significantly longer than that under SROM. Higher treatment satisfaction, fewer cravings for heroin, and lower mental stress were reported by patients under SROM. More Details will be presented. SROM is now registered in Switzerland as an OST medication.

Introduction

History of opioid substitution treatment (OST)

The British doctor Francis E. Anstie suggested in 1871 the long term prescription of opioids for opioid dependent patients and thus was the first to advocate an opioid substitution treatment. In the early 20th century this form of treatment was widely applied, and the reasons were the same as today (stopping the use of street drugs, stabilization of the patients, and reduction of criminality). However, in the US this kind of treatment was stopped by 1923 as a consequence of stricter drug control, which was finally also imposed internationally (only the UK resisted with their “British system”). In the “narcotic farm” Lexington, Kentucky, methadone was instituted in the management of detoxification already in 1948, but only in 1964 Dole & Nywander could start their trials with methadone as a maintenance medication. Due to political reasons a number of constraints, how the substance should be used (indication, dosage, counselling, take-home doses, urine tests) were established. MMT was restricted to specialized clinics. These rules were written down in the Narcotic Addict Control Act (NATA), which is an amendment of the Controlled Substance Act (CSA). These laws are enforced by the Drug Enforcement Agency (DEA). The restrictions served as a model for regulations in many other countries.

The Swiss situation

In Switzerland methadone maintenance treatment (MMT) was available since the 1970ies. However, according to the narcotic law physicians need a license by the In Switzerland the gold standard for OST, but many patients complain about disabling excessive sweating and insufficient well-being. Additionally patients in MMT show a high comorbidity and medications needed to treat these conditions may add to the prolongation of QTc induced by methadone, thus raising the risk for cardiac arrhythmias. In the view of the street-heroin epidemic of the early 1990ies, when large groups of heroin user could not be reached by MMT, the authorities agreed to conduct trials with injected heroin [1994-1996]. The positive trial results allowed a proper registration of diacetyl-morphine (“heroin”) as a substitution medication (heroin-assisted treatment HAT), but HAT is only possible in specialized clinics with a number of further restrictions (minimal age, treatment history, mandatory psychosocial treatment, no take-home etc.). In 2000 unilingual buprenorphine got based on existing data and an already existing European registration as substitution medication. Buprenorphine is listed in Switzerland as a narcotic, so the licensing as for methadone is applied. After the peak of the heroin epidemic in the early 1990ies more and more heroin users switched from i.v. to nasal and smoked applications. So the i.v.-program of the HAT was not suitable for them and the HAT centers started off-label prescriptions of slow release oral morphine (SROM). An additional reason was that morphine prescription is subject to less restriction than diacetyl-morphine (possible take-home of SROM). However, existing data on SROM in opioid substitution treatment (OST) were despite positive reports from neighboring Austria not sufficient for a registration as a 4th substitution medication. That’s why it was decided to conduct a study.

References


Disclaimer:

The author of this poster had mandates as expert in addiction for Roche-Benckiser, Lundbeck, and Orpha, He declares no conflict of interests with this work.

The study on SROM as OST medication

The study was planned as a comparison between oral methadone and SROM in maintenance treatment for opioid dependence. The study design was a multiple-dose, open-label, randomized cross-over, non-inferiority study. Patients were recruited at 4 outpatient treatment centers in Switzerland, and those for inclusion were adult patients with an opioid dependence (DSM-IVTR), who were participating in a stable MMT for at least half a year and a daily dose of methadone of 50mg or more. Exclusion criteria were severe comorbidity (psychiatric and somatic), pregnancy and QTC >450ms. Protocol and written informed consent forms were approved by national and regional ethics committees and national health authorities and complied with the standards of the Declaration of Helsinki, ICH Guideline for Good Clinical Practice, the European Union Clinical Trials Directive and national narcotic laws.

The study consisted of 2 phases. At the beginning of phase 1 patients were randomized in 2 groups. Group 1 was switched from methadone to SROM with a ratio methadone:morphine of 1.6 – 1.8 for 11 weeks. After this they were switched back to methadone for another 11 weeks. Group 2 stayed on methadone for the first 11 weeks and was then switched to morphine.

At the end of phase 1 at 22 weeks, 198 of the 211, who completed phase 1, entered in the extension phase 2 that was then additional 25 weeks. In this phase everybody received SROM.

Results from phase 1

Primary endpoint was the number of heroin positive urine samples. Urine was tested on 6-Mono-Acetyl-Morphine (metabolite of heroin) and 6-O-Acetyl codeine (by-product of illegal heroin production). The non-inferiority margin was pre-defined at 10%. Overall the slight differences in positive urines were within the pre-defined non-inferiority margin and showed a negative correlation with the substitution dose.

The number of adverse events showed no difference between the substances.

Results from phase 2

There was a reduction of hyperhidrosis on SROM, both in frequency and severity (p<0.001). QTC was lower on SROM by approx. 10msec. Craving for heroin declined over the 25 weeks. Also dysthyemic symptoms in SCL-27.

Conclusion

The results showing no inferiority of SROM were sufficient for an official registration of SROM™ for the indication of OST in opioid dependent patients and SROM is since May 2013 available, for substitution, also in office-based treatment by general practitioners.

References


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** The brand name of the registered SROM is Sreve-Long®