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Safety profile of injectable hydromorphone and diacetylmorphine for long-term severe opioid use disorder

Eugenia Oviedo-Joekes[a,b,*], Suzanne Brissette[c], Scott MacDonald[d], Daphne Guh[a], Kirsten Marchand[a,b], Salima Jutha[a], Scott Harrison[d], Amin Janmohamed[a], Derek Z. Zhang[a], Aslam H. Anis[a,b], Michael Krausz[a,e], David C. Marsh[f], Martin T. Schechter[a,b]

[a] Centre for Health Evaluation and Outcome Sciences, Providence Health Care, St. Paul's Hospital, 575- 1081 Burrard St., Vancouver, BC, V6Z 1Y6, Canada
[b] School of Population and Public Health, University of British Columbia, 2206 East Mall, Vancouver, BC, V6T 1Z3, Canada
[c] Centre de recheche du Centre Hospitalier de l'Université de Montréal, (CRCHUM), 900 St-Denis, Montréal, QC, H2X 0A9, Canada
[d] Providence Health Care, Providence Crosstown Clinic, 84 West Hastings Street, Vancouver, BC V6 B 1G6, Canada
[e] Department of Psychiatry, Faculty of Medicine, Detwiller Pavilion 2255 Wesbrook Mall, Vancouver, BC V6T 2A1, Canada
[f] Northern Ontario School of Medicine, 935 Ramsey Lake Road, Sudbury, ON P3E 2C6, Canada

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ABSTRACT

Aims: To review the safety profile of injectable hydromorphone and diacetylmorphine and explore if adverse events (AEs) or serious adverse events (SAEs) were associated with dose and patterns of attendance.
Methods: This was a non-inferiority randomized double-blind controlled trial (Vancouver, Canada) testing hydromorphone (n = 100) and diacetylmorphine (n = 102) for the treatment of severe opioid use disorder. Medications were delivered under the supervision of trained Registered Nurses up to three times daily. AEs were described using MedDRA codes.
Results: Most common related AEs included immediate post-injection reaction or injection site pruritus reactions, somnolence and opioid overdoses. Adjusted analysis indicated that participants in the hydromorphone group were less likely to have any related AE or SAE compared to the diacetylmorphine group. Related somnolence and opioid overdose events were distributed throughout the six months treatment period. In the diacetylmorphine group, five of the eleven related SAE opioid overdoses (requiring naloxone) occurred in the first 30 days since most recent treatment initiation. Analysis of somnolence and opioid overdose (AEs and SAEs) event rates by received dose suggested a non-linear relationship. However, in the diacetylmorphine group higher event rates per person days were recorded at lower doses.
Conclusions: When injectable hydromorphone and diacetylmorphine are individually dosed and monitored, their opioid-related side effects, including potential fatal overdoses, are safely mitigated and treated by health care providers. In the midst of an opioid overdose epidemic, injectable options are timely to reach a very important minority of people who inject street opioids and are not attracted to other treatments.

1. Introduction

Opioid dependence continues to be a major public health concern worldwide. This chronic illness (Cami and Farre, 2003), characterized by patterns of continued drug use and intervening periods of treatment, abstinence, and relapse, poses great harms to the individual, her/his family and the community (Gowing et al., 2008; Hser et al., 2007). Opioid-dependent people often suffer from poor mental and physical health, as well as poor psychosocial functioning, especially after long-term use (Galai et al., 2003; Hser et al., 2001; March et al., 2006b). Although effective treatments and public health approaches exist, the global burden of disease attributable to opioid dependence has increased over time (Degenhardt et al., 2014).

Opioid substitution treatment (OST) is effective at retaining people with opioid dependence in treatment and has been shown to reduce illicit heroin use, illegal activities, and decrease the risk of HIV infection and mortality among other benefits (Mattick et al., 2009; Mattick et al., 2014). However, not all individuals are attracted or retained into oral methadone or buprenorphine, even when delivered following best practices (Strang et al., 2010). Long-term injection of heroin and other illicit opioids exposes individuals to many associated risks (e.g., overdoses, infections), particularly when they are not retained to OST, thus

* Corresponding author at: St. Paul's Hospital, 575-1081 Burrard St, Vancouver, BC V6Z 1Y6, Canada.
E-mail address: eugenia@cheos.ubc.ca (E. Oviedo-Joekes).

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we require alternative treatments tailored to patients' differential capacities for overcoming opioid use problems.

There are several opioids licensed for analgesia; however, few countries offer opioids beyond methadone and buprenorphine for OST. This is particularly relevant given that, despite opioids being quite similar, there are important inter-individual differences that could have an impact on patient safety as well as treatment retention (Eap et al., 2002; Hammig et al., 2014; Kourounis et al., 2016; Saxon, 2015). For example, dose thresholds, and side effects may vary among patients receiving the same treatment (Drewes et al., 2013). Thus, expanding the list of opioids for OST could reduce some of the barriers related to individual variations in the medication response.

For a small but important minority of individuals with severe opioid use disorder, studies in Europe and Canada have shown that injectable diacetylmorphine (i.e., pharmaceutical-grade heroin), prescribed and delivered under supervision is more effective than offering patients another attempt of methadone maintenance (Bell, 2014; European Monitoring Centre for Drugs and Drug Addiction, 2011). This treatment is aimed at attracting and retaining individuals who otherwise remain outside of the health care system, and thus continue to be exposed to harms associated with illicit opioid use.

In a recent randomized clinical trial, injectable hydromorphone was demonstrated to be as effective as injectable diacetylmorphine for long-term, severe opioid use disorder, with participants in both treatments achieving similar reductions in street opioid use, illegal activities, health outcomes and retention to treatment (Oviedo-Joekes et al., 2016a). During this study, participants received both medications under identical conditions, double-blinded. An unexpected finding was that hydromorphone had significantly less related adverse events (AEs) compared to diacetylmorphine. However, all drug reactions were expected as part of the opioids profile (Oviedo-Joekes et al., 2016a).

There are risks associated with injecting a medication (compared to oral) (Oviedo-Joekes et al., 2016b), as well as taking a short-acting potent opioid, such as overdoses and seizures (European Monitoring Centre for Drugs and Drug Addiction, 2011). The present study examines the safety profile of injectable hydromorphone and diacetylmorphine by exploring if related AEs were associated with dose and patterns of attendance. Clinically, these results could support decision making to minimize the impact of potential AEs for patient safety and treatment retention.

2. Material and methods

2.1. Study design, setting and participants

Conducted from December 2011 to December 2013 in the Greater Vancouver area, British Columbia, Canada, SALOME (Study to Assess Longer-term Opioid Medication Effectiveness) was a double-blind randomized clinical trial. SALOME examined the non-inferiority of injectable hydromorphone compared with injectable diacetylmorphine, as a treatment option for long-term opioid users who were not sufficiently benefiting from other treatments (e.g., oral methadone). The SALOME trial design (Oviedo-Joekes et al., 2016a), participant recruitment and eligibility criteria (Oviedo-Joekes et al., 2015b), baseline characteristics (Oviedo-Joekes et al., 2015a) and main results on treatment efficacy and safety for both hydromorphone and diacetylmorphine treatment arms (Oviedo-Joekes et al., 2016a) can be found in previous publications. Briefly, to be eligible for the study, individuals were at least 19 years old, had a minimum of five years of illicit opioid dependence, regular injection of illicit opioids in the prior year and at least one prior episode of opioid maintenance treatment. Volunteers were excluded if, for example, they had severe medical conditions contraindicated for treatment with diacetylmorphine or hydromorphone (e.g., respiratory problems, stage II or greater hepatic encephalopathy).

SALOME received ethical approval from the Providence Health Care/University of British Columbia Research Ethics Board and is registered with ClinicalTrials.gov (NCT01447212). The clinical trial followed the good clinical practice guidelines as well as guidelines that have their origins in the Declaration of Helsinki (World Medical Association, 2016). Informed written consent was obtained from all participants before administration of any study treatment.

2.2. Procedures and measures

Injectable hydromorphone and diacetylmorphine were self-administered in a controlled setting under the supervision of Registered Nurses (RN) at the study clinic. All doses of hydromorphone were prescribed and dispensed double-blind with diacetylmorphine, and participants did not guess their treatment beyond what was expected by chance (Oviedo-Joekes et al., 2016a). For participant and public safety reasons, medications could only be taken in the supervised clinical setting. Self-administered intravenous injection was only allowed in the upper extremities but intramuscular injections were also allowed in thighs and gluteals. Each participant underwent pre- and post-injection assessment periods, lasting 5 and 15 min, respectively. During this time, RN's monitored participants to ensure their safety both before (e.g., no signs of intoxication) and after (e.g., no signs of over-sedation, respiratory depression) taking the medications.

Participants could receive up to three doses of injectable medications per day: up to 200/400 mg per dose and up to 500/1000 mg per daily-total of hydromorphone or diacetylmorphine respectively. Doses were presented in diacetylmorphine equivalents. Doses in the study were titrated individually in order to achieve a safe and effective dose for each participant. Initial doses were determined over a 3-day titration phase (see SALOME protocol for titration and methadone dose equivalence conversion procedures (Oviedo-Joekes et al., 2016b) jointly by the attending RN and the participant (a lower starting dose or a slower titration process was used if medically indicated). Participants, in consultation with and under the guidance of their prescribing physician, could adjust the dose and frequency of daily injection sessions (up to 3). Such adjustments were considered after a meeting between the physician and the participant, upon reviewing the dose used history and consulting with at least one nurse. Doses that were not tolerated, as per assessment by a nurse during either the pre- or post-injection assessment periods, were reduced by pre-wasting the drug in the pre-filled syringes and could be increased by session or day as the situation improved. Patients could also lower their prescribed dose. Differences between daily-total dose prescribed and daily-total dose received reflect missed days of treatment (when having an active prescription), unattended sessions, and adjustments to a single dose in a given session either by the RNs or by the participants themselves.

All participants were granted full autonomy regarding their participation in the study, and could choose to withdraw from treatment/follow-up at any time. Participants were allowed to re-enter their treatment program within the study period after discontinuation (e.g., hospitalizations, jail, personal reasons, not abiding by clinic rules, etc.). In such an event, clinic staff and doctors always offered participants an opportunity to discuss appropriate treatment options, both within and outside the study clinic.

2.3. Safety assessments

An AE was defined as any temporary untoward medical occurrence in a participant administered a pharmaceutical product that did not necessarily have a causal relationship with the treatment. A serious adverse event (SAE) was any AE that was life threatening, required hospitalization, or medical intervention to prevent a severe outcome. At each visit to the clinic, nurses, coordinators, physicians and/or other clinic workers assessed all study participants for AEs, SAEs, drug reactions or changes in health status. The independent research staff could also report possible SAEs (mainly hospitalizations) if regular