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Review

Development of pharmaceutical heroin preparations for medical co-prescription to opioid dependent patients

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Abstract

Presently, there is a considerable interest in heroin-assisted treatment: co-prescription of heroin to certain subgroups of chronic, treatment-resistant, opioid dependent patients. In 2002, nine countries had planned (Australia, Belgium, Canada, France, Spain) or ongoing (Germany, The Netherlands, Switzerland, United Kingdom) clinical trials on this subject. These trials (and the routine heroin-assisted treatment programs that might result) will need pharmaceutical heroin (diacetylmorphine) to prescribe to the patients. Research into the development of pharmaceutical forms of heroin for prescription to addicts can benefit from the large amount of knowledge that already exists regarding this substance. Therefore, in this paper we review the physicochemical and pharmaceutical properties of diacetylmorphine and the clinically investigated routes of administration, as well as routes of administration utilised on the street in the context of developing pharmaceutical heroin formulations for prescription to addicts. Patient acceptability of the formulation is essential, because heroin-assisted treatment is aimed at treatment-resistant addicts, who often have to be encouraged to participate (or to maintain participation) in a treatment program. This means that the most suitable products would have pharmacokinetic profiles mimicking that of diacetylmorphine for injection, with rapid peak concentrations of diacetylmorphine and 6-acetylmorphine, ensuring the 'rush effect' and the sustained presence of morphine(-6-glucuronide) creating the prolonged euphoria. Diacetylmorphine for inhalation after volatilisation (via 'chasing the dragon') seems to be a suitable candidate, while intranasal and oral diacetylmorphine are currently thought to be unsuitable. However, oral and intranasal delivery systems might be improved and become suitable for use by heroin dependent patients.

Keywords: Heroin; Prescription; Addiction; Pharmaceutical technology

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1. Introduction

Heroin (3,6-diacetylmorphine, diamorphine) is a di-ester of morphine that was introduced into medicine by Bayer in 1898, as a cough suppressant to assist breathing in patients with severe lung disease (Sneader, 1998). It was known to be twice as potent a cough suppressant as morphine, but its analgesic potency (two to three times that of morphine (Moffat et al., 1986)) was only recognised decades later, when it had been banned from prescription in many countries due to its addictive properties (Sneader, 1998). Heroin is now considered a drug of abuse that it is included in the United Nations list of Narcotic drugs under international control (International Narcotics Control Board, 2004). However, heroin was not banned from medical practice completely, the drug and its preparations are still included in the British Pharmacopoeia today (British Pharmacopoeia, 2004).

Nowadays, addiction has been accepted as a psychiatric disorder and several pharmacological treatments have been developed to treat addiction to opioids. In the last decade, attention has also turned to heroin-assisted treatment: co-prescription of heroin to certain subgroups of chronic, treatment-resistant, opioid dependent patients. In 2002, nine countries had planned (Australia, Belgium, Canada, France, Spain) or ongoing (Germany, The Netherlands, Switzerland, United Kingdom) clinical trials (Fischer et al., 2002; March et al., 2004). Most heroin-assisted treatment programs involve methadone with co-prescribed injectable heroin, although heroin tablets (UK, Spain) and cigarettes (UK, Switzerland) are also used. Street heroin is most commonly injected, snorted or smoked. The first route of administration poses little problems in heroin-assisted treatment programs, because parenteral use of diacetylmorphine is well established in the UK. However, it has proven more difficult to provide addicts that are used to snorting or smoking their street heroin with a suitable pharmaceutical alternative. In addition, alternative dosage forms could prove useful, even in countries where these routes of administration are unpopular compared to injecting, because they could be used by patients who wish to change their route of administration in order to avoid the risks associated with injecting or because of damaged veins. For the same reasons, non-injectable pharmaceutical dosage forms of diacetylmorphine could be stimulated in heroin-assisted treatment programs.

Research into the development of pharmaceutical forms of diacetylmorphine for prescription to addicts can benefit from the large amount of knowledge that already exists regarding this substance. Therefore, in this paper we review the physicochemical and pharmaceutical properties of diacetylmorphine and the clinically investigated routes of administration as well as routes of administration utilised on the street in the context of developing pharmaceutical heroin for prescription to addicts.

2. Properties of diacetylmorphine

2.1. Physicochemical properties

Diacetylmorphine is a morphine ester, its synthesis involves replacement of the two hydroxyl groups at the 3 and 6 position of the morphine molecule by acetyl groups. A base form exists, but the hydrochloride monohydrate salt is much more common in pharmaceutical dosage forms. Diacetylmorphine is a lipophilic substance with a partition coefficient (P(octanol/water) = 52) between that of morphine ($P = 6$) and fentanyl ($P = 955$). As the pK_a of diacetylmorphine (7.6 (Moffat et al., 1986)) is close to physiological pH, a large proportion is present in the lipophilic non-ionised form, favouring absorption, while it also has excellent water solubility in the ionised form. The melting point of diacetylmorphine base (173 °C (The Merck Index, 1996)) is lower than that of the hydrochloride salt (243–244 °C (The Merck Index, 1996), 229–233 °C (British Pharmacopoeia, 1990; Hays et al., 1973; Moffat et al., 1986)), favouring its use in smoking or ‘chasing the dragon’ (see Section 3.3).

Since researchers and patients will tend to compare safety, efficacy and toxicity of pharmaceutical heroin for prescription to addicts with that of street heroin, it is important to address the properties of the latter. Street heroin varies in chemical composition: generally about 35–45% of a sample of brown heroin is identified as diacetylmorphine (hydrochloride) (Darke et al., 1999; de la Fuente et al., 1996; Huizer et al., 1977; Huizer, 1983; Kaa and Bent, 1986), while white heroin