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Bioavailability *in vivo* of naltrexone following transbuccal administration by an electronically-controlled intraoral device: A trial on pigs

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ABSTRACT

Naltrexone (NLX), an opioid antagonist, is widely used in the treatment of opiate addiction, alcoholism and smoking cessation. Its current peroral administration induces various adverse side effects and has limited efficacy since bioavailability and patient compliance are poor. The development of a long-acting drug delivery system of NLX may overcome the current drawbacks and help in the improvement of treatment of addiction. The primary endpoints of this study were: a) to compare the NLX bioavailability and pharmacokinetics after delivering a single transbuccal dose, released by a prototype of intraoral device, *versus* an intravenous (I.V.) bolus of the same drug dose; b) to verify the functioning of a prototype of a new intraoral device *in vivo*; c) to evaluate the permeation enhancement effect of iontophoresis; d) to assess any histomorphological changes in the buccal mucosa after transbuccal delivery. The system was tested on 6 pigs in a cross-over trial. Venous blood samples were drawn at a fixed timetable from the beginning of drug administration and analyzed for the presence of NLX, using an LC/MS/MS method. A punch biopsy was performed for histological analysis after the final experiment. The administration of I.V. NLX induced a sharp increase in blood levels after 5 min and then a steep decrease. In contrast, transmucosal delivery resulted in a gradual increase in blood NLX levels, reaching its peak after 90 min, followed by a slow decrease. After 6 h the blood levels of NLX delivered through the buccal mucosa were higher as compared to I.V. administration. No signs of flogosis or tissue damage were histologically highlighted. These results suggest that buccal delivery by an intraoral electronic device could potentially induce long-lasting, continuous and controlled blood levels of NLX, avoiding at the same time spikes of drug plasma levels typical of the I.V. administration route.

1. Introduction

Consumption of alcohol and heroin dependence are modulated by opioid receptor activity, and clinical data have indicated that they could be reduced by pharmacological treatment with opioid antagonists. NLX is a highly specific opioid antagonist with a high affinity for opiate receptor sites, used as an adjunct to the maintenance of an opioid-free state in detoxified, opioid-dependent individuals [1]. Recently, NLX has also been authorized for the treatment of alcoholism and smoking cessation [2,3]. Clinical pharmacological studies have demonstrated that NLX following peroral administration at 50, 100 and 150 mg effectively blocks the physiological and subjective effects of parenterally-administered heroin, hydromorphone or morphine for 24, 48 and 72 h respectively [4]. Studies have demonstrated that the lowest effective plasma NLX levels of 2 ng/ml provided an average of 86.5% blockade of 25 mg intravenous heroin effects [5]. Thus, in controlled-release therapy for opiate antagonist activity, the plasma level of NLX should be kept above 2 ng/ml. Unfortunately, following peroral administration in humans, NLX is rapidly and quite completely absorbed (about 96%) from the GI tract but the drug undergoes a significant first-pass effect [6]. Accordingly,

Abbreviations: NLX, naltrexone; I.V., intravenous; GI, gastrointestinal; PMMA, poly (methyl methacrylate); LC–MS, liquid chromatography–mass spectrometry; MS, Mass spectrometry; HPLC, High performance liquid chromatography; MS/MS, Tandem mass spectrometers.

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hepatic metabolism (>98% metabolized) could cause an inadequate drug level in the brain, so higher drug concentrations than needed are required [1]. Furthermore, clinical experience using NLX for treating opiate addiction has been replete with data regarding poor medication compliance, in part due to the need of almost daily visits at the rehabilitation centres [7]. In addition, current methods of medication administration limit its effectiveness and give rise to adverse side effects. Peroral NLX administration is often associated with a range of gastrointestinal and neuropsychiatric adverse reactions. It was recently shown that ultra-low-dose NLX blocks the adverse effects of withdrawal, which can result from chronic treatment with this drug [8]. Hence, there is an interest in developing a long-acting drug delivery system which may help in the improvement of narcotic antagonist treatment using NLX [9]. Recently, a depot formulation of NLX, which releases drug for up to 30 days to minimize patient decision making, has been proposed. This dosage form consists of a suspension containing drug loaded polymeric microspheres administered by intra-muscular injection. The typical NLX unwanted effects associated with the use of conventional oral formulations appear to be quite low, but a direct comparison between the oral and depot formulation within the same clinical trial has yet to be made [10]. Nevertheless, some adverse events associated with the depot preparation (eg, erythema, induration, and injection site reactions) seem to negate its apparent advantages over oral NLX. Furthermore, their use requires that many health care providers be trained, seen that injections must be administered properly to decrease the possibility of local site reactions, which could, in turn, diminish compliance [11].

The transbuccal delivery of NLX could be a suitable means for the slow and constant administration of low drug doses, due to various advantages as: ease of administration; avoidance of hepatic first-pass metabolism; avoidance of possible drug degradation in GI tract; reduction of dose-dependent unwanted effects observed with peroral NLX [12].

The therapeutic efficacy of a drug, delivered via a transmucosal route, mainly depends on its ability to penetrate the tissue fast enough to provide the required plasma concentrations which result in the desired pharmacological effect. Recently, *in vitro* and *ex vivo* studies have clearly demonstrated that NLX permeates through mucosal models resembling human buccal mucosa, without any significant cytological or architectural changes [13,14]. These studies include researches performed as a part of the IntelliDrug Project (supported by the European Commission under the 6th Framework Programme) which was aimed to develop a controlled intraoral drug delivery device equipped with an electronic- and software-driven system. The device consists of a stainless steel, two molar-sized intraoral module containing an osmotic membrane, a drug reservoir, an actuation mechanism for pushing the drug solution, a drug level sensor, a flow sensor, and a power source. The device contains also electrodes for possible iontophoretic delivery enhancement [15].

The aim of this study was to evaluate: a) the NLX bioavailability and pharmacokinetics after delivering a single transbuccal dose, released by a prototype of intraoral device, compared with an intravenous (I.V.) bolus of the same drug dose; b) the functioning of a prototype of a new intraoral device *in vivo* on pigs; c) permeation enhancement effect of iontophoresis; and, finally, d) potential histomorphological changes in the buccal mucosae after transbuccal delivery.

2. Materials and methods

2.1. Drug delivery system

The drug delivery prototype tested in this study consists of two parts (one intraoral and the other extra-oral), connected by a Teflon hose for fluid passage and by an electrical line for iontophoresis (Fig. 1a–c). The intraoral part consists of an outlet system embedded

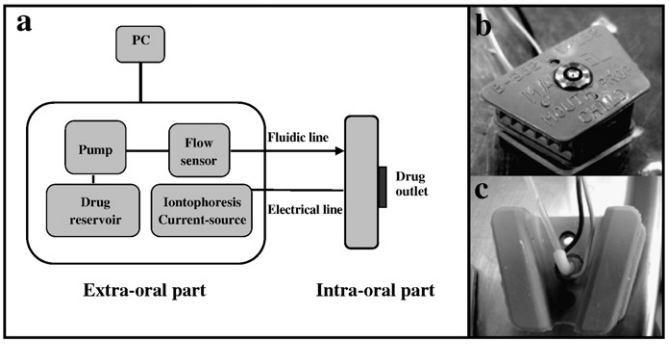

Fig. 1. a–c. a) Scheme of the IntelliDrug prototype and b–c) Intraoral part of the system: the drug outlet is composed of an outer ring made of steel and a concave-shaped, inner nozzle made of silver, which is fixed inside the former with a silicone tubing.

in a silicone-made mouth prop (Becker-Parkin, T152), whereas the extra-oral part contains a drug reservoir, containing the drug solution, a syringe pump (Aladdin AL 1000-220®, World Precision Instruments) for the drug solution withdrawal from the reservoir, a flow sensor with a full-scale sensitivity of about 20 µl/min (Hahn-Schickard Gesellschaft - Institut für Mikro-und Informationstechnik, Villingen-Schwenningen, Germany), and a power source for the sensor. The control pump mechanism and the iontophoresis electrodes are provided by a PC and a control program (TestPoint), connected to a controllable power source. The sensor signal is received by an AD-card (Keithley KUSB 3102) inside the PC and analyzed by the TestPoint program.

Secured in the mouth prop, the drug outlet is composed of an outer ring made of steel (Sandvik Bioline 316LVM) and a concave-shaped, inner nozzle made of silver, which is fixed inside the former with a silicone tubing. The two electrodes (silver anode and steel cathode) inside the mouth prop were used for iontophoretic transmucosal delivery. The intraoral part is fixed by clamping two mouth props (one with the intraoral part, the other unchanged) between the lower and the upper jaw (Fig. 2).

2.2. Test animals

Six healthy female pigs, each weighing approximately 35 kg, were used and treated as prescribed in the Guide for the Care and Use of Laboratory Animals, Institute for Laboratory Animal Resources (ILAR;

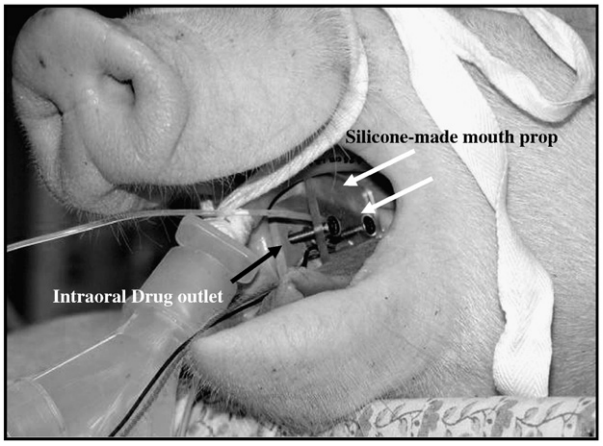

Fig. 2. Location of the drug outlet. The intraoral part (black arrow) is fixed by clamping two mouth props (white arrows) (one with the intraoral part, the other untreated) between the lower and the upper jaw. See the text.