Refining Drug Delivery: Behavioral and Pharmacokinetic Validation of MDA in Mice

Olga Krzyzaniak [1], Frida Nilsson [2], Sarah Steiner [1], Laura Kämpfen [3], Paulin Jirkof [3], Pål Johansen [3], Urs Meyer [1]
[1] Institute of Veterinary Pharmacology and Toxicology, University of Zürich
[2] Department of Dermatology, University of Zürich and University Hospital Zürich
[3] Office for Animal Welfare and 3R, University of Zürich

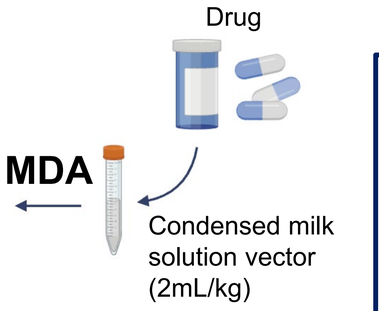
Introduction

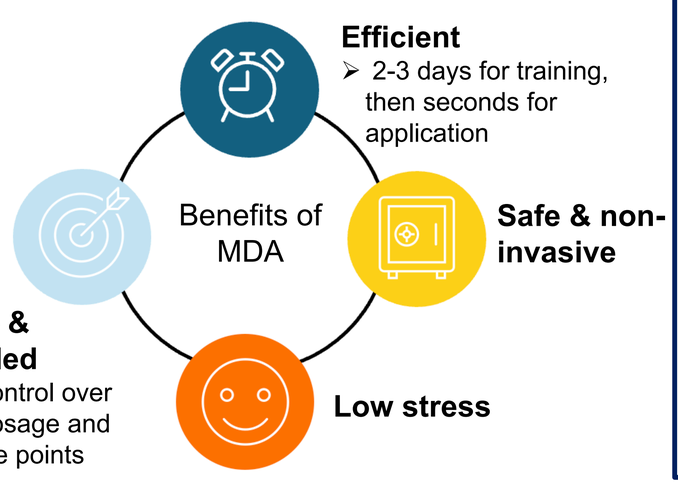
Precise and low-stress drug delivery is essential for reliable outcomes in neuroscientific research, especially in behavioral & **pharmacological** studies.

This project aims to validate the micropipette guided drug administration (MDA) method in mice using pharmacokinetic analyses of carprofen and buprenorphine.

Primary objectives

- Assess if MDA achieves therapeutic carprofen and buprenorphine exposure in mice.
- Compare drug exposure after MDA versus subcutaneous injection.





MDA Oral Drug Administration

Micropipette-guided **D**rug **A**dministration (MDA) is a stress-reducing oral delivery method in mice that enables precise dosing without restraint.

The mice learn to drink the drug, formulated in a palatable solution, over 2-3 training days (Fig. 1).

Day 1: Mice are restrained and introduced to the milk solution via pipette.

Day 2: Mice are loosely restrained by the tail base and fed the milk.

Day 3: Mice voluntarily drink the milk solution without restraint.

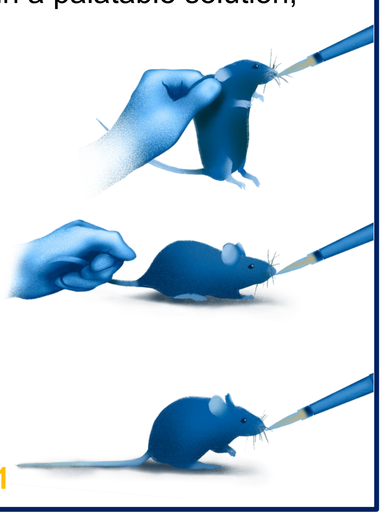


Fig. 1

METHODS

1 Pharmacokinetic Study: Buprenorphine

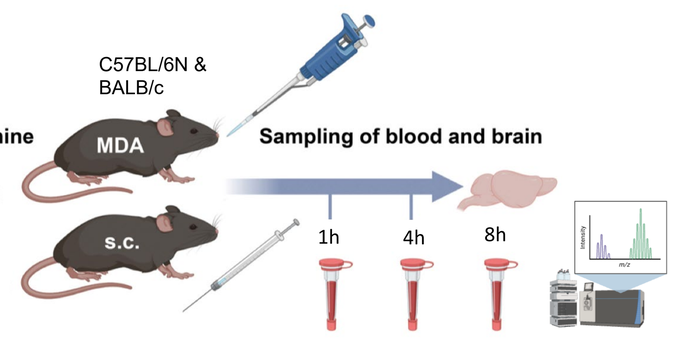


Fig. 3

Mice received **buprenorphine** via **MDA** (0.5, 1.0 or 2.0 mg/kg) **or subcutaneous injection (SC)** (0.05, 0.1 or 0.2 mg/kg). The MDA dose was adjusted to account for the hepatic first-pass effect. Plasma and brain levels were measured by LC-MS.

2 Pharmacokinetic Study: Carprofen

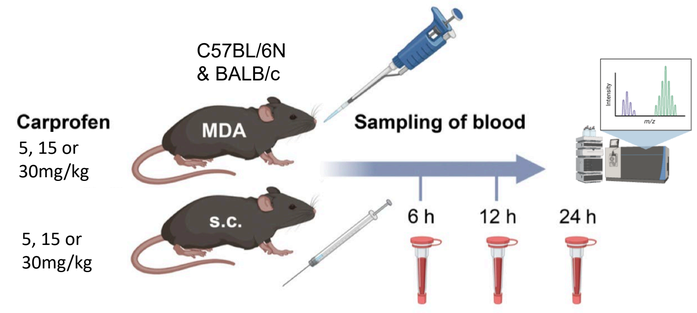


Fig. 2

Mice received **carprofen**(5, 15 or 30mg/kg) via **MDA or subcutaneous injection**. Plasma levels were measured by LC-MS to evaluate the suitability of MDA for systemic drug delivery.

RESULTS & CONCLUSIONS

1 MDA Ensures Therapeutic Brain Buprenorphine Despite Low Plasma Levels

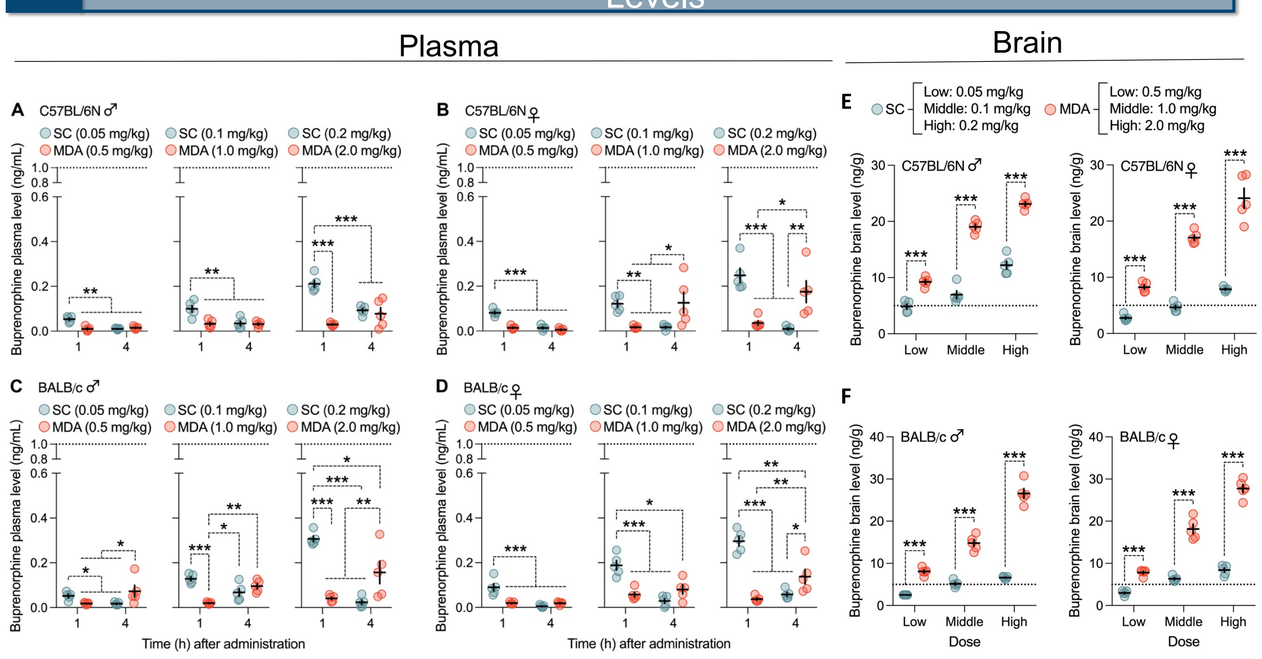


Fig. 4 **Plasma and brain tissue concentrations of buprenorphine in C57BL/6N and BALB/c mice following administration via micropipette-guided delivery (MDA) or subcutaneous (SC) injection.** (A-D) Plasma; (E-F) Brain. SC treated mice received 0.05, 0.1, or 0.2 mg/kg buprenorphine, while doses for MDA administration were adjusted to 0.5, 1 and 2mg/kg in order to compensate for the metabolism through the hepatic first-pass effect. Plasma samples were collected 1, 4, and 8 hours post-administration; at the final time point, brain tissue was collected as well. Buprenorphine was quantified by LC-MS. Krzyzaniak et al., Neuropsychopharmacology, accepted (in press).

2 MDA Achieves Therapeutic Carprofen Levels Comparable to Subcutaneous Administration

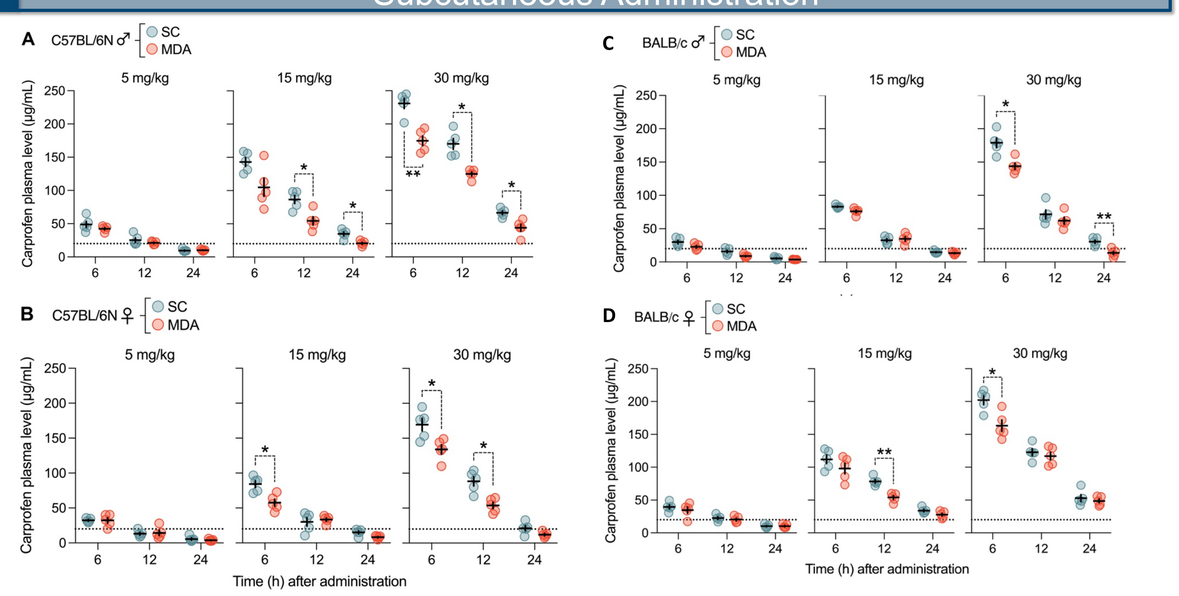


Fig. 5 **Plasma concentrations of carprofen metabolites in C57BL/6N and BALB/c mice following administration via micropipette-guided delivery (MDA) or subcutaneous (SC) injection.** (A) Male mice; (B) Female mice. Mice received 5, 15, or 30 mg/kg carprofen, and plasma samples were collected at 6-, 12- and 24-hours post-administration. Krzyzaniak, et al. Neuropsychopharmacology. Accepted (in press)

MDA enables low-stress, precise oral dosing in mice and yields carprofen plasma exposure comparable to SC injection, while producing higher buprenorphine brain levels despite lower plasma concentrations. These findings support MDA as a reliable, welfare-conscious refinement consistent with the 3Rs.

Contact:
olgaiwona.krzyzaniak@uzh.ch, +41 79 475 21 48

MDA illustrations:
Jean Kesselring, Zürich 8055
Jean.Kesselring@gmx.ch, +41 78 880 33 41

Universität Zürich[UZH]
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