

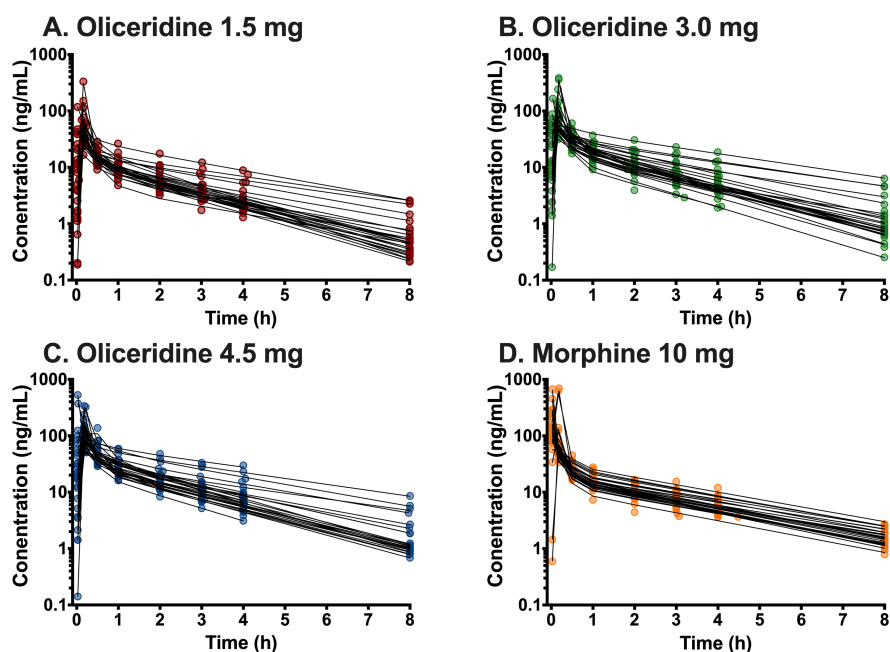
**Supplemental document: Results of the pharmacokinetic and pharmacodynamic modeling analyses: pharmacokinetic parameter estimates and pharmacokinetic and pharmacodynamic fits and goodness-of-fits plots.**

**Pharmacokinetic analysis**

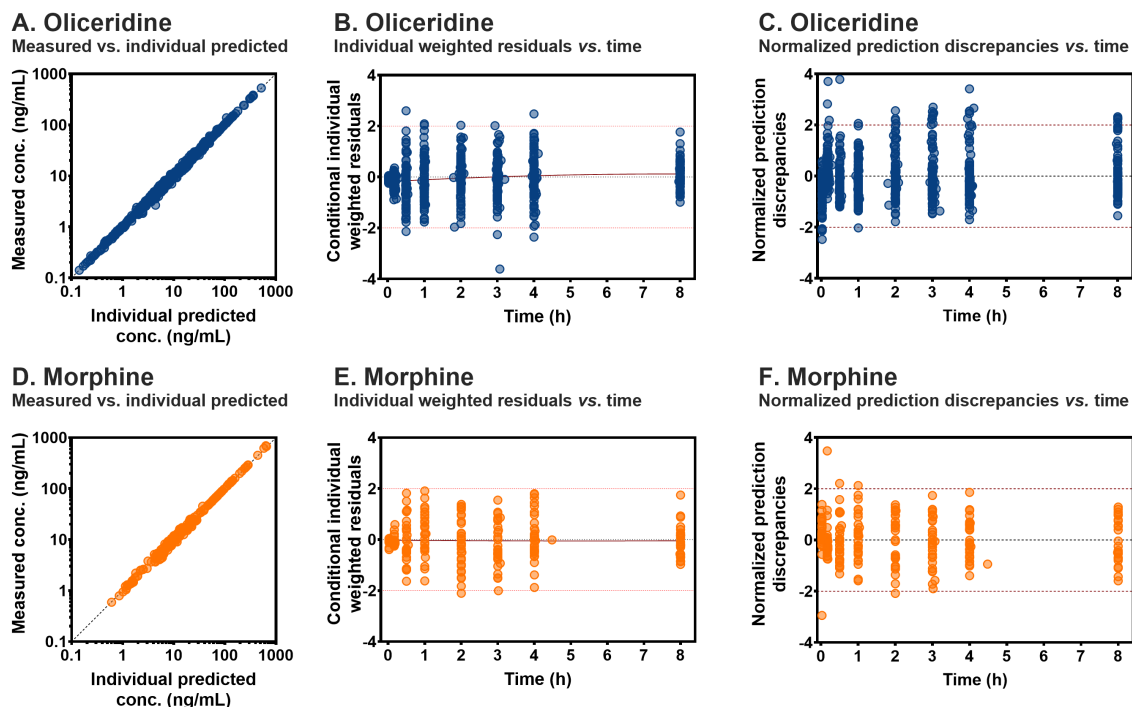
**Supplemental Table 1.** Pharmacokinetic parameter estimates

Parameter	Estimate $\pm$ SEE	$\omega^2 \pm$ SEE	$v^2 \pm$ SEE
<b>Oliceridine</b>			
$V_1$ (L)	$28.0 \pm 5.92$	$0.52 \pm 0.08$	$0.04 \pm 0.05$
$V_2$ (L)	$29.1 \pm 1.91$	-	$0.04 \pm 0.02$
$CL_1$ (L/h)	$31.7 \pm 2.80$	-	$0.01 \pm 0.003$
$CL_2$ (L/h)	$37.5 \pm 2.42$	-	$0.12 \pm 0.10$
$\sigma^2$	$0.10 \pm 0.04$		
<b>Morphine</b>			
$V_1$ (L)	$69.6 \pm 14.5$	-	
$V_2$ (L)	$209 \pm 11$	-	
$CL_1$ (L/h)	$113 \pm 7$	$0.02 \pm 0.01$	
$CL_2$ (L/h)	$241 \pm 29$	-	
$\sigma^2$	$0.13 \pm 0.02$		

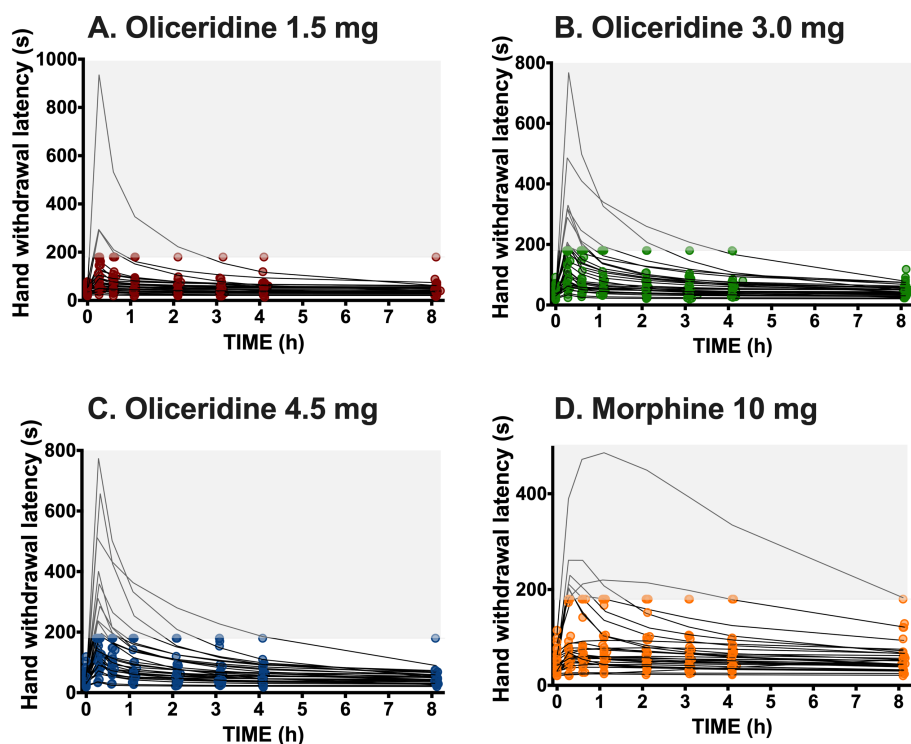
$\omega^2$  and  $v^2$  are between-subject and between-occasion variances (on the log scale);  $\sigma^2$  the within-subject proportional error variance; SEE the standard error of the estimate; - not included in the statistical model. Overall between-subject variance on all parameters was  $0.08 \pm 0.03$  for the oliceridine data and  $0.04 \pm 0.01$  for the morphine data.



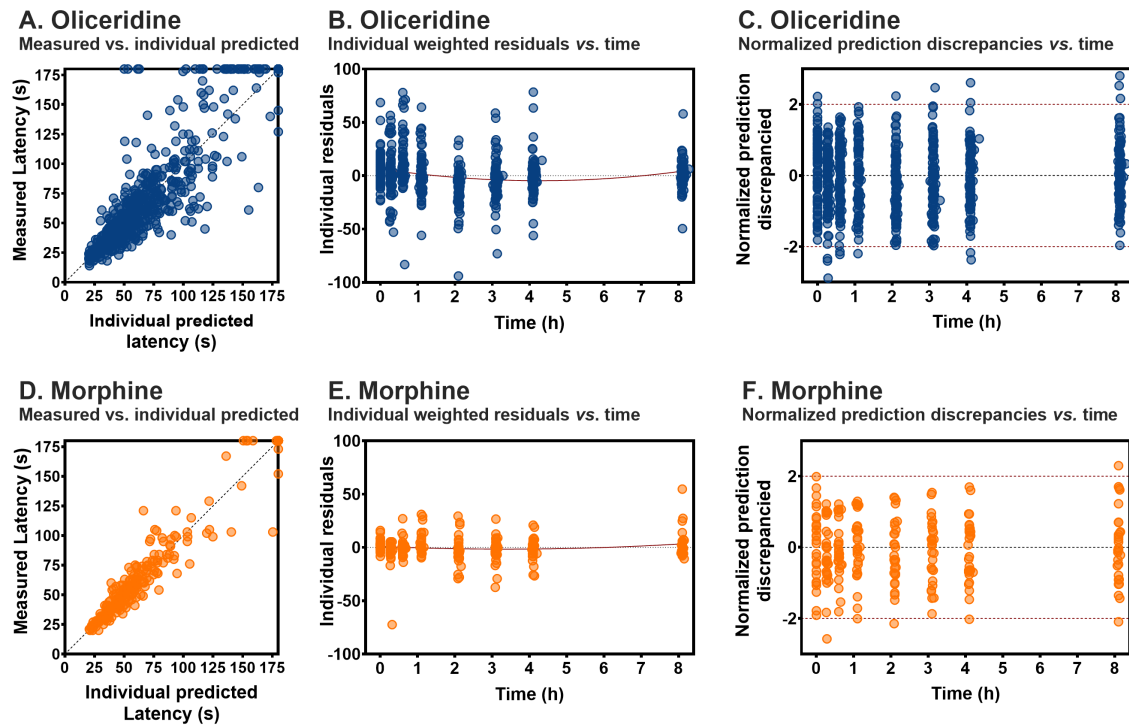
**Supplemental Figure 1.** Pharmacokinetic data fits of all subjects receiving and intravenous dose of oliceridine 1.5 mg (A), 3.0 mg (B), and 4.5 mg (C) and morphine 10 mg (D). The circular data points represent the measured data, the lines through the symbols the estimated values (data fits).



**Supplemental Figure 2.** Pharmacokinetic goodness-of-fit plots. **A.** Oliceridine measured pharmacokinetic data *versus* individual predicted pharmacokinetic data. **B.** Oliceridine conditional individual weighted residuals *versus* time. A smoothed line is plotted through the data points (continuous red line), the broken red lines are the 95% confidence interval. **C.** Oliceridine normalized predicted discrepancies (NPD) *versus* time. NPD = 0 is the median, the red broken lines are the 95% confidence interval. **D.** Morphine measured pharmacokinetic data *versus* individual predicted pharmacokinetic data. **E.** Morphine conditional individual weighted residuals *versus* time. A smoothed line is plotted through the data points (red line), the broken red lines are the 95% confidence interval. **F.** Morphine NPD *versus* time; NPD = 0 is the median, the red broken lines are the 95% confidence interval.

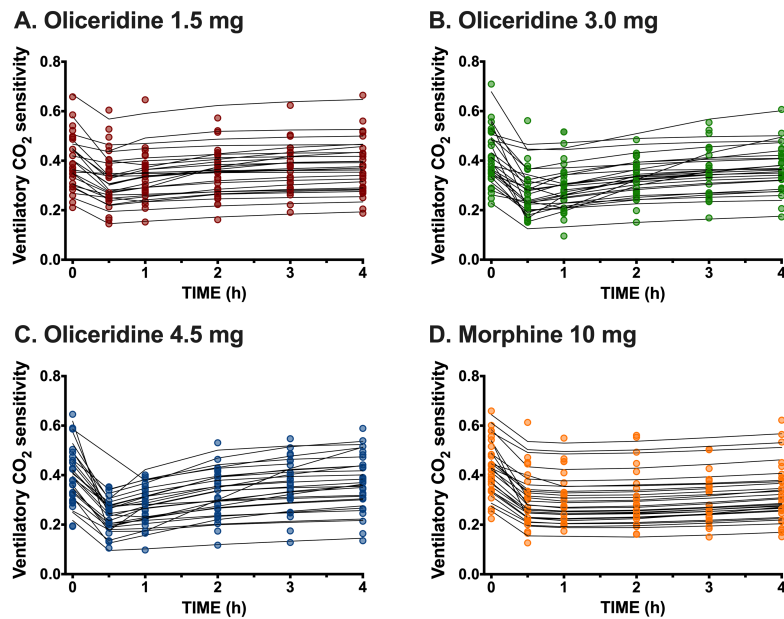


**Supplemental Figure 3.** Individual oliceridine (A-C) and morphine (D) induced antinociceptive responses and corresponding data fits. The subjects received intravenous dose of oliceridine 1.5 mg (A), 3.0 mg (B), and 4.5 mg (C) and morphine 10 mg (D). The circular data points represent the measured data, the lines through the symbols the estimated values (data fits). The grey areas depict the latencies above the 180-s cutoff.

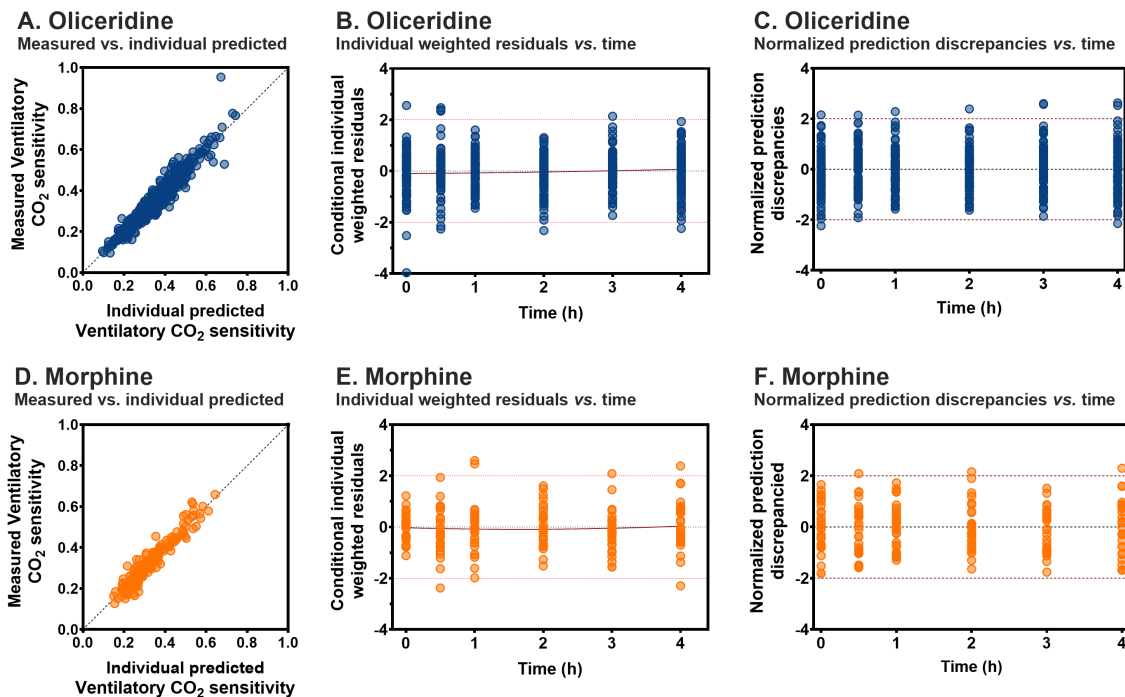


**Supplemental Figure 4.** Goodness-of-fit plots of the data fits of oliceridine- and morphine hand-withdrawal latency responses. **A.** Oliceridine measured latencies data *versus* individual predicted latencies. **B.** Oliceridine individual residuals *versus* time. A smoothed line is plotted through the data points (continuous red line) **C.** Oliceridine normalized predicted discrepancies (NPD) *versus* time. NPD = 0 is the median, the broken red lines, the 95% confidence interval. **D.** Morphine measured latencies data *versus* individual predicted latencies. **E.** Morphine individual residuals *versus* time. A smoothed line is plotted through the data points (continuous red line) **F.** Morphine NPD *versus* time. NPD = 0 is the median, the red broken lines are the 95% confidence interval.

## Pharmacodynamic data analysis: Respiratory depression



**Supplemental Figure 5.** Individual oliceridine (A-C) and morphine (D) induced respiratory responses and corresponding data fits. The subjects received intravenous dose of oliceridine 1.5 mg (A), 3.0 mg (B), and 4.5 mg (C) and morphine 10 mg (D). The circular data points represent the measured data, the lines through the symbols the estimated values (data fits).



**Supplemental Figure 6.** Goodness-of-fit plots of the data fits of oliceridine- and morphine ventilatory responses to  $\text{CO}_2$  (VRH). **A.** Oliceridine measured VRH data *versus* individual predicted VRH values. **B.** Oliceridine conditional individual weighted residuals *versus* time. A smoothed line is plotted through the data points (continuous red line), the broken red lines are the 95% confidence interval. **C.** Oliceridine normalized predicted discrepancies (NPD) *versus* time. NPD = 0 is the median, the broken red lines, the 95% confidence interval. **D.** Morphine measured VRH data *versus* individual predicted VRH values. **E.** Morphine conditional individual weighted residuals *versus* time. A smoothed line is plotted through the data points (red continuous line), the broken red lines, the 95% confidence interval. **F.** Morphine NPD *versus* time. NPD = 0 is the median, the broken red lines are the 95% confidence interval.