

# METHADONE HYPERALGESIA

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- ▶ Our results help to reconcile the apparent discrepancies in the literature. They partly support the findings of Ho and Dole (1979) who found that pain threshold (detection) values of methadone-maintained patients were significantly lower than those of controls. However, with regard to pain tolerance values, our results are very different in that methadone-maintained patients were substantially intolerant of cold pressor-induced pain compared with control subjects, whereas Ho and Dole (1979) found no significant difference. Our finding of pain intolerance in methadone patients is similar to that reported by Compton (1994), who also using a cold pressor model found that methadone patients were pain intolerant compared with cocaine abusers. Using electrical stimulation, our results concur with those of Dyer et al. (1999) who reported that at the time of trough plasma methadone concentrations patients had similar threshold (pain detection) values to controls, whereas at the time of peak plasma methadone concentrations patients were less pain-sensitive than controls

# Aims

- ▶ Our study aims were to (i) compare the nociceptive responses (pain detection and tolerance) within and between methadone maintenance patients and matched controls, (ii) determine whether the method of pain induction results in different responses, and in methadone maintenance patients, (iii) determine if nociceptive responses are different at trough and peak plasma methadone concentrations.

# Abstract

- ▶ Methadone patients were tested over an inter-dosing period: at the time of trough plasma methadone concentration (0 h), and 3 h after their daily dose.
- ▶ Control subjects were tested twice 3 h apart.
- ▶ Blood samples were collected to determine plasma methadone concentration.

# Methadone concentrations

- ▶ R-(-)- and S-(+)-methadone were quantified in plasma using high-performance liquid chromatography (HPLC) as described by Foster et al. (2000). The method had a limit of quantification of 15 ng/ml of each enantiomer and inter- and intra-day precision and accuracy data of low, medium and high quality control concentrations as assessed by the coefficients of variation were less than 12%.

# Plasma methadone concentrations

	R	S
0h	118 ± 12	138 ± 20
3h	185 ± 18	259 ± 31

# Abstract

- ▶ This study compared nociceptive responses between 16 patients on stable, once daily, doses of methadone and 16 matched control subjects.
- ▶ 2 types of nociceptive stimuli were used: 1. electrical stimulation  
2. A cold pressor test.

Two parameters were measured: detection for onset of pain, and pain tolerance.

# Methods

- ▶ 1. patients and control subjects
- ▶ 2. procedures and measures
- ▶ 3. pain induction (electrical stimulation-cold pressor test)
- ▶ 4. methadone concentration
- ▶ 5. statistical and other analysis



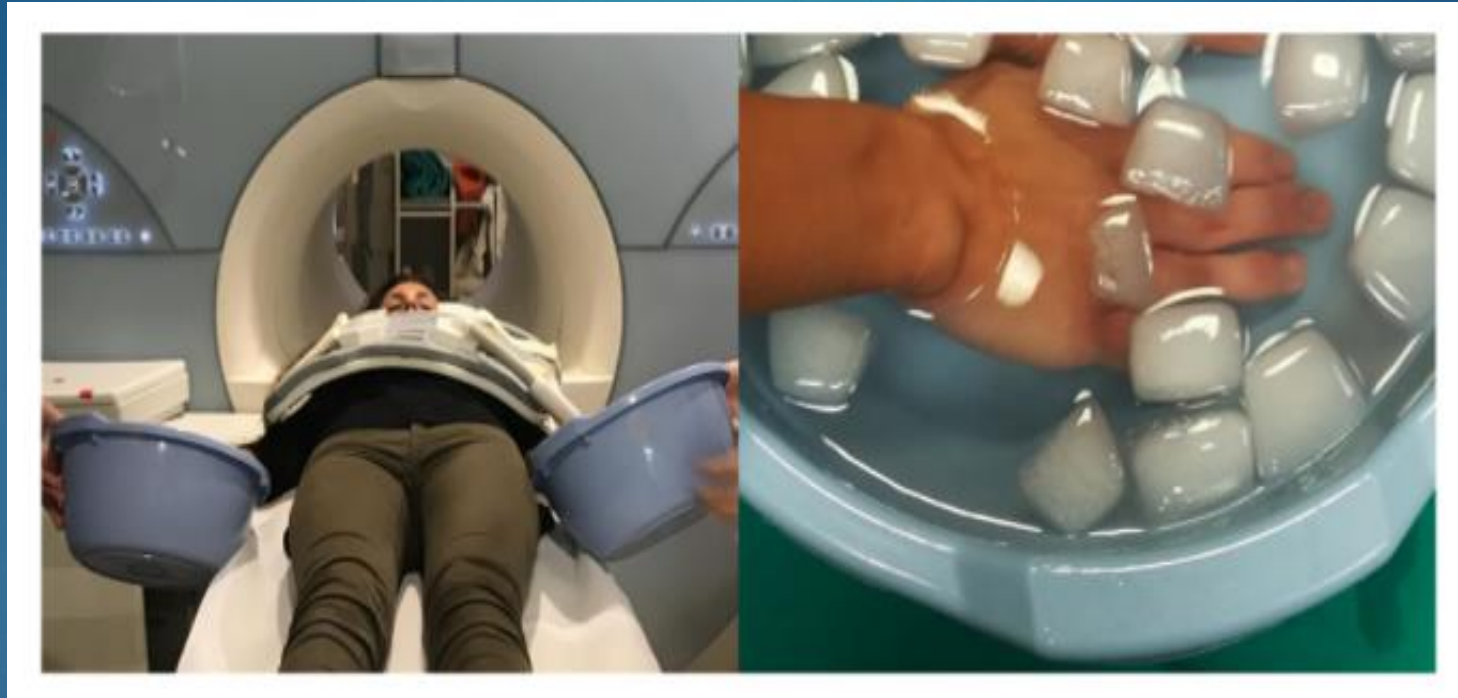
# Pain induction

- ▶ Electrical stimulation
- ▶ Cold pressor test

# Electrical stimulation



# Cold pressor test



# Statistical and other analyses

Data are presented as the mean  $\pm$  SEM (with 95% confidence intervals (CI)). Within-group comparisons were made using Student's t-test (paired) and between-group comparisons were made using Student's t-test (independent). These tests were also used to determine order effects. Pain tolerance to pain detection ratios were also calculated. All data were analyzed using SPSSe for Windows (version 9) which carried out tests for homogeneity of variance and adjusted the P value accordingly.

# Electrical stimulation

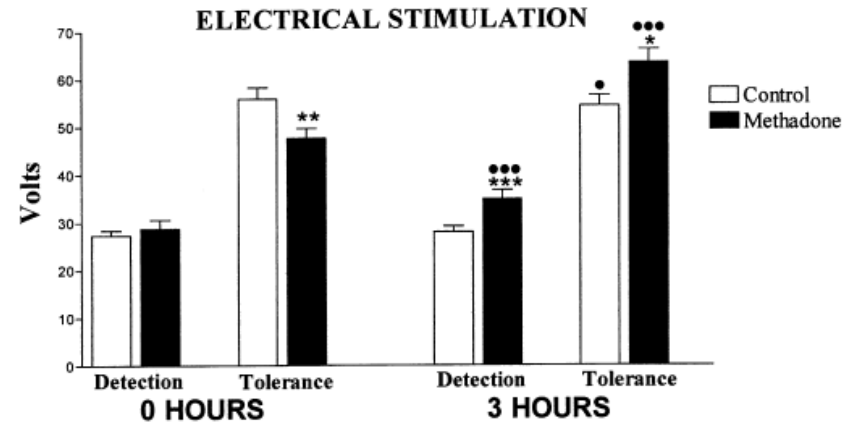


Fig. 1. Electrical stimulation. Comparison of mean ( $\pm$ SEM) pain detection and pain tolerance values at 0 and 3 h in 16 methadone maintenance patients and 16 matched controls. Methadone versus controls: 0 h, detection  $P = 0.744$ , tolerance  $**P = 0.013$ ; 3 h, detection  $***P = 0.002$ , tolerance  $*P = 0.015$ . 0 versus 3 h: methadone, detection  $***P < 0.0001$ , tolerance  $***P < 0.0001$ ; controls, detection  $P = 0.096$ , tolerance,  $*P = 0.018$ .

# Cold pressor test

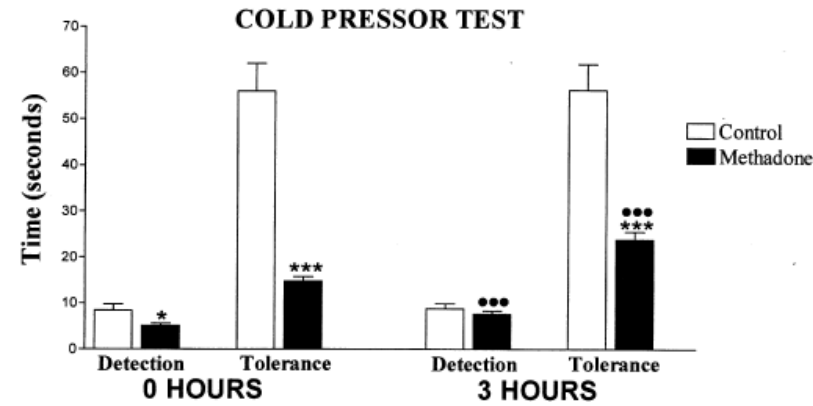


Fig. 2. Cold pressor test. Comparison of mean ( $\pm$ SEM) pain detection and pain tolerance values at 0 and 3 h in 16 methadone maintenance patients and 16 matched controls. Methadone versus controls: 0 h, detection  $*P = 0.023$ , tolerance  $***P < 0.0001$ ; 3 h, detection  $P = 0.369$ , tolerance  $***P < 0.0001$ . 0 versus 3 h: methadone, detection  $***P < 0.0001$ , tolerance  $***P < 0.0001$ ; controls, detection  $P = 0.211$ , tolerance  $P = 0.857$ .

# Pain tolerance/pain detection ratios

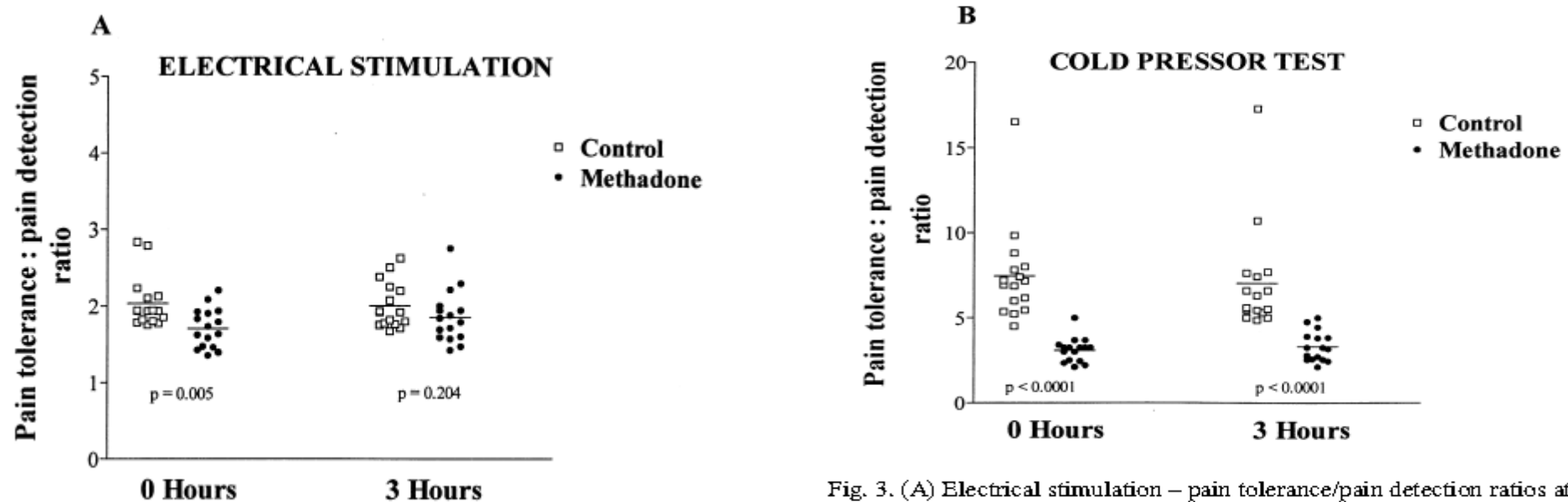


Fig. 3. (A) Electrical stimulation – pain tolerance/pain detection ratios at 0 and 3 h. Methadone versus controls (mean ratios): 0 h, 1.7 versus 2.0 ( $P = 0.005$ ); 3 h, 1.9 versus 2.0 ( $P = 0.204$ ). 0 versus 3 h: methadone  $P = 0.022$ , controls  $P = 0.444$ . (B) Cold pressor test – pain tolerance/pain detection ratios at 0 and 3 h. Methadone versus controls (mean ratios): 0 h, 3.1 versus 7.4 ( $P < 0.0001$ ); 3 h, 3.3 versus 7.0 ( $P < 0.0001$ ). 0 versus 3 h: methadone  $P = 0.220$ , controls  $P = 0.071$ .

# Discussion

- ▶ This study sought to compare pain detection and pain tolerance responses between methadone maintenance patients and controls using different methods of pain induction. Furthermore, in methadone maintenance patients, we sought to determine the association between nociceptive responses and plasma methadone enantiomer concentrations. There were marked differences in pain tolerance responses between methadone maintenance patients and controls using the cold pressor test, with methadone patients exhibiting a hyperalgesic response. Using electrical stimulation, differences for pain tolerance between methadone patients and controls were less marked. Nociceptive responses of methadone maintenance patients were attenuated by the increase in the plasma methadone concentration irrespective of the method of pain induction.



# Discussion

- ▶ In summary, the relative pain sensitivity of methadone maintenance patients is determined by the nature of the nociceptive stimulus (e.g. cold pressor test versus electrical stimulation), the concentration of methadone (trough versus peak plasma concentration), and whether thresholds are determined for the detection of pain or pain tolerance. Methadone maintenance patients are hyperalgesic to pain induced by the cold pressor test.