

Pharmacology of methadone and its isomers

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Methadone is a synthetic opioid analgesic that is used as an alternate to morphine and hydromorphone for patients with severe pain. It is increasingly being used in opioid rotation schedules. Methadone has an asymmetric carbon atom resulting in 2 enantiomeric forms, the d and l isomers. The racemic mixture (dl-methadone) is the form commonly used clinically. Recent studies have revealed the pharmacological activity of the d-methadone isomer. We found that the d isomer of methadone has N-methyl-D-aspartate (NMDA) receptor antagonist activity both *in vitro* and *in vivo*. Studies were designed to examine the ability of d-methadone to attenuate the development of morphine tolerance and to modify NMDA-induced hyperalgesia in rats. Repeated dosing with intrathecal morphine produced a 38-fold increase in the morphine ED₅₀ value. This decrease in the potency of morphine was completely prevented by the coadministration of intrathecal d-methadone at 160 µg/rat. In addition, the decrease in thermal paw withdrawal latency induced by the intrathecal administration of 1.64 µg/rat NMDA was completely blocked by pretreatment with 160 µg/rat d-methadone. Thus, the same dose of intrathecal d-methadone that attenuates the development of spinal morphine tolerance blocks NMDA-induced hyperalgesia in rats. These results support the conclusion that d-metha-

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done affects the development of morphine tolerance and NMDA-induced hyperalgesia by virtue of its NMDA receptor antagonist activity.

Key words: Methadone - d-methadone - NMDA receptor - Morphine, tolerance - Hyperalgesia.

Methadone is a synthetic opioid analgesic that has long been viewed as an alternate to morphine and hydromorphone for patients with severe pain.¹ Its bioavailability is 85% and from single dose studies its oral to parenteral potency ratio is 1:2. Its plasma half-life averages 24 h but may range from 13 to 50 h, whereas the duration of analgesia is often only 4 to 8 h.¹ Repetitive analgesic doses of methadone lead to drug accumulation because of the discrepancy between its plasma half-life and the duration of analgesia. Sedation, confusion and even death can occur when patients are not carefully monitored and the dosage adjusted during the accumulation period which can last from 5 to 10 days.¹

A recent surge of interest in the use of methadone appears to be related, in part, to

Supported in part by NIH grants, DA001457 and DA000198.

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the observation in animals that methadone has N-methyl-D-aspartate (NMDA) receptor antagonist activity. Ebert *et al.*² found that methadone exhibited NMDA receptor antagonist activity in a ligand binding assay and a neonatal rat spinal cord electrophysiological preparation.

Methadone has an asymmetric carbon atom resulting in two enantiomeric forms, the d and l isomers. The racemic mixture (dl-methadone) is the form commonly used clinically and in laboratory studies. The l isomer possesses analgesic activity while the d isomer is inactive or weak as an opioid.³ Gorman *et al.*⁴ reported that both the d and the l isomers bind, with similar affinities, to the noncompetitive site of the NMDA receptor in rat forebrain and spinal cord synaptic membranes. Shimoyama *et al.*⁵ found that while intrathecal d-methadone is inactive in the tail-flick test, it is antinociceptive in the rat formalin test. This antinociception is not affected by the opioid antagonist, naloxone, and appears to be a result of the NMDA receptor antagonist activity of d-methadone. Davis *et al.*³ reported that d-methadone affects the development of morphine tolerance after systemic or intrathecal administration. After intrathecal treatment increasing doses of morphine, there is a shift to the right of the morphine dose-response curve (day 5 saline+morphine).³ The relative potency of morphine was decreased approximately 38-fold on day 5 in the saline+morphine group. In contrast, no significant shift was seen in the dose-response curve or in the morphine ED₅₀ value when intrathecal d-methadone was co-administered with each dose of morphine during the 3 day treatment period. The injection of saline at -10 min did not alter subsequent measures over the 40 min. When the saline injection was followed by the administration of NMDA at time 0, a significant decrease in thermal paw withdrawal (TPW) latency was observed at 5, 10, and 15 min after NMDA. The peak of NMDA hyperalgesia occurred at 5 min after NMDA, the earliest time postdrug we were able to measure the TPW latency. The NMDA-induced decrease in TPW was completely blocked by pretreatment (at -10 min) with d-methadone at

160 µg/rat. The intrathecal injection of d-methadone followed by saline did not alter the TPW latency.

Our results are of particular interest because postinjury hyperalgesic states and the development of tolerance to morphine converge at the cellular level through the activation of the NMDA receptor and common signal transduction events including the activation of protein kinase C.⁶ Chizh *et al.*⁷ report that the antinociceptive effect of d-methadone in the Randall-Selitto model of inflammatory pain is antagonized by naloxone. Carpenter *et al.*⁸ concluded from a study of the effects of d-methadone on noxious and innocuous electrically-evoked responses of dorsal horn neurons, that the effects of d-methadone may reflect a degree of synergy between weak NMDA antagonist and opioid agonist activity. *In vitro* studies indicate that both of the enantiomers of methadone and its metabolites are potent noncompetitive antagonists of alpha₃beta₄ neuronal nicotinic acetylcholine receptors.⁹ Thus, although d-methadone was thought to be an inactive isomer, recent studies have revealed a number of interesting pharmacological properties. It remains to be determined whether d-methadone can affect the development of opioid tolerance or produce antihyperalgesic effects in patients with pain.

Riassunto

Farmacologia del metadone e dei suoi isomeri

Il metadone è analgesico oppiaceo sintetico che viene utilizzato quale alternativa alla morfina e all'idromorfone nei pazienti con grave dolore. Esso viene sempre più usato nei protocolli che prevedono la rotazione di farmaci oppiacei. Il metadone ha un atomo di carbonio asimmetrico che produce 2 forme enantiomere, l'isomero d e l'isomero l. La miscela racemica (dl-metadone) è quella che più comunemente viene utilizzata nella pratica clinica. Studi recenti hanno evidenziato l'attività farmacologica dell'isomero d. Abbiamo osservato che l'isomero d del metadone ha un'attività antagonista sul recettore per l'N-metil-D-aspartato (NMDA) sia *in vitro* che *in vivo*. Gli studi erano stati disegnati per valutare la capacità del d-metadone di attenuare lo sviluppo di tolleranza alla morfina e per modificare l'iperlgesia NMDA-indotta nei ratti. Ripetute somministrazioni intratecali di mor-

fini hanno provocato un aumento di 38 volte del suo valore ED50. Questa diminuzione dell'attività della morfina veniva completamente prevenuta dalla somministrazione intratecale di d-metadone alla dose di 160 mg in ogni ratto. Inoltre, nei ratti la diminuzione del periodo di latenza termica a livello della zampa, indotta dalla somministrazione intratecale di 1,64 mg di NMDA, era completamente bloccata dal pretrattamento con 160 mg di d-metadone. Si deve quindi dedurre che la stessa dose intratecale di d-metadone che attenua lo sviluppo di tolleranza alla morfina a livello midollare blocca nei ratti l'iperalgia NMDA-indotta. Questi risultati suggeriscono che il d-metadone influenzi lo sviluppo della tolleranza alla morfina e l'iperalgia NMDA-indotta tramite la sua virtuale attività antagonista per il recettore NMDA.

Parole chiave: Metadone - NMDA recettori - Morfina, tolleranza - Iperalgia.

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