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α-l-ACETYLMETHADOL AND ITS N-DEMETHYLATED METABOLITES HAVE POTENT OPIATE ACTION IN THE GUINEA PIG ISOLATED ILEUM

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Summary

α-l-Acetylmethadol (LAM) and its N-demethylated metabolites α-l-noracetylmethadol (NAM) and α-l-dinoracetylmethadol (NNAM) exhibited opiate-like actions *in vitro* by depressing the electrically induced twitch of the longitudinal muscle of the guinea pig ileum. These effects were reversed by the opiate antagonist naloxone. The effect of both NAM and NNAM was approximately 15 times greater than LAM. The 50 percent inhibitory concentrations of the metabolites were well below those levels in plasma reported for man. The long duration of action of LAM as an opiate substitute is most likely due to the conversion to its metabolites.

The l-isomer of α-acetylmethadol, commonly called LAM or l-methadyl acetate, is presently under extensive study as an alternative to methadone for the treatment of heroin addiction (1-4). LAM has a longer duration of action than methadone in suppressing narcotic withdrawal (1,2,3,5).

In man (6) and animals (7,8) the delayed onset of action and long duration suggested an active metabolite. LAM is N-demethylated to α-l-noracetylmethadol (NAM) (9) and then, to α-l-dinoracetylmethadol (NNAM) (10). Billings and coworkers (11) recently reported that patients receiving LAM exhibited significant and sustained plasma levels of both NAM and NNAM. α-dl-Noracetylmethadol is an active analgesic in man (12) and both α-dl-noracetylmethadol and α-dl-dinoracetylmethadol are

active analgesics in rodents comparable in potency to α-dl-acetylmethadol (13) but the opiate-like effects of the l-isomers, α-l-noracetylmethadol and α-l-dinoracetylmethadol, were unknown. It was important to know what NAM and NNAM contributed to the long duration of action of LAM.

In 1957 Paton (14) demonstrated that the depression of twitch of the electrically stimulated guinea pig ileum by morphine-like substances was the result of a reduced acetylcholine output from cholinergic nerve endings. He and other workers (14,15) have shown that these depressant effects correlated well with analgesic potencies in man. Kosterlitz and Watt (15) demonstrated that these effects were reversed with the opiate antagonist naloxone. This method provides a convenient *in vitro* model for the study of opiate action without a significant contribution from metabolites. Using a modification (16) of the Paton method we observed that each of the three racemic compounds, α-dl-acetylmethadol, α-dl-noracetylmethadol and α-dl-dinoracetylmethadol, produced opiate-like agonist effects (17). The present report shows that the l-isomers, NAM and NNAM are potent opiate-like agonists, but LAM itself is much less active *in vitro* and probably owes its prolonged *in vivo* effects to metabolic conversion.

Methods

Tissues were bathed in Kreb's solution containing 0.125 μM pyrilamine. The longitudinal muscle strip of the guinea pig ileum was prepared as described by Paton and Vizi (16). It was separated from the underlying circular muscle by stroking it away from mesenteric attachment along the whole length of the