BRIEF COMMUNICATION

Loperamide: From antidiarrheal to analgesic

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ABSTRACT

Loperamide, an antidiarrheal drug has been observed to produce analgesia in animal models of pain. However, the exact mechanism underlying loperamide analgesia needs further studies.

Loperamide is a piperidine derivative opioid ligand that selectively activates peripheral opioid receptors without entering the CNS. Loperamide is commonly used as antidiarrheal agent to treat nonbacterial diarrhea (resulting from gastroenteritis or inflammatory bowel disease). It acts on the μ-opioid receptors in the myenteric plexus of the large intestine and inhibits peristalsis of intestinal muscles and reduces gastrocholic reflex.[1] In the last 10 years, experiments involving animal models of pain report loperamide analgesia after systemic[2-5] or intraspinal administration.[6-10]

In the clinical setting, oral route of drug administration is highly desirable. To eventually reach opioid receptors in peripheral tissues, orally administered loperamide must first permeate the intestinal epithelium and enter the blood stream. However, its low absorbance rate from the gut prevents the same. Similarly, it does not cross the blood-brain barrier and even if does cross this barrier, it is immediately pumped out by P-glycoprotein into non-central nervous system (CNS) circulation.[11] Loperamide produces antinociception after systemic and intraspinal administration.[2-10] In the experiments involving animal as a model of acute pain, loperamide is preferentially administered through systemic route. It does not cross the blood brain barrier; therefore, systemic administration does not produce pleasurable side effects like euphoria, which can lead to addiction. Thus, loperamide appears as one of the choice as opioids. However, its analgesic potential needs to be further examined. Loperamide could produce mild physical dependence during preclinical studies, specifically in mice, rats, and rhesus monkeys after systemic administration.[12,13] Also, the systemic administration requires higher dose, which can invite adverse drug reactions (ADRs). ADRs associated with loperamide include abdominal pain and bloating, nausea, vomiting, and constipation.[14] Furthermore, loperamide may produce rare side effects like paralytic ileus, dizziness, and rashes. Similar effects, if any, after intraspinal administration needs future attention.

The use of regional analgesic technique is associated with lower pain scores than are seen with systemic opioids. Intrathecal drug administration is one such technique where drug is delivered into subarachnoid space, close to the spinal cord. The advantage of intraspinal administration of a drug is to obtain maximum effect with even little quantity of drug.[15] Many studies document the antinociceptive action of loperamide after intraspinal administration.[6-10] Also, studies have shown that a single intrathecal injection of loperamide produced a higher analgesic effect than an equal amount of morphine.[8-10] When administered directly into the CNS, being a lipophilic substance,[16] loperamide would rapidly infiltrate the neighboring nervous

tissue at the site of injection with limited spread of the drug to cranial and caudal levels, which is responsible for the occurrence of side effects like respiratory depression and urinary retention. Loperamide analgesia after intraspinal administration has primarily been observed in animal models of acute pain; however, its potency in chronic pain conditions remains to be examined.

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